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Amide bioisosteric replacement in the design and synthesis of quorum sensing modulators

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Abstract: The prevention or control of bacterial infections requires continuous search for novel approaches among which bacterial quorum sensing inhibition is considered as a complementary antibacterial strategy. Quorum sensing, used by many different bacteria, functions through a cell-to-cell communication mechanism relying on chemical signals, referred to as autoinducers, such as *N*-acyl homoserine lactones (AHLs) which are the most common chemical signals in this system. Designing analogs of these autoinducers is one of the possible ways to interfere with quorum sensing. Since bioisosteres are powerful tools in medicinal chemistry, targeting analogs of AHLs or other signal molecules and mimics of known QS modulators built on amide bond bioisosteres is a relevant strategy in molecular design and synthetic routes. This review highlights the application of amide bond bioisosteric replacement in the design and synthesis of novel quorum sensing inhibitors.

Keywords: amide bioisosteres, replacement, quorum sensing, modulator

1 Introduction

1.1 Quorum sensing in Gram-negative bacteria

Quorum sensing (QS), used by many different bacteria, is a cell-to-cell signaling mechanism responsible for coordinating their behaviors, including the production of virulence factors, biofilm formation, and bioluminescence [1-3]. The QS system relies on the biosynthesis of small molecules referred to as autoinducers, their release and diffusion through the bacterial membrane and their perception by cognate receptors. The small molecular signals, namely autoinducers, allow the bacteria to distinguish between a low or high population density. When the autoinducers released by individual cells accumulate and reach a critical concentration, they can bind their cognate receptor and then activate gene transcription. This signaling pathway has become a fundamental process that is wide-ranging in pathogenic bacteria. Therefore, quorum sensing modulation has provided new avenues to decrease virulence and biofilm maturation. It has been stated that Gram-negative bacteria cover a large proportion of resistance threats [4], including several pathogenic ones that pose disturbing threats to humans.

1.2 Role of AHLs and PQS in bacterial quorum sensing

Evolving research on QS has led to the discovery of different chemical structures of autoinducers produced by different bacteria. Each bacterial species responds specifically to its unique autoinducer. Among them, *N*-acyl homoserine lactones (AHLs) are the most well-defined autoinducers (Figure 1) in Gram-negative bacteria. The first quorum sensing system was identified in *V. fischeri*, which regulated the phenotype of bioluminescence [1]. The autoinducer in *V. fischeri* is 3-oxo-C6-HSL produced by LuxI synthase, which then specifically binds to the LuxR transcription factor. For another instance, *C. violaceum* is a Gram-negative bacteria that produces violacein regulated by C6-HSL autoinducer. When the threshold concentration of *C. violaceum* is reached, the CviR transcription factor activates the synthesis of violacein. *P. aeruginosa* is a multi-drug resistance (MDR) opportunistic pathogen, which can cause chronic bacterial infection [5,6]. In *P. aeruginosa*, two interconnected

AHL-mediated quorum sensing systems involve the *Las* and the *Rhl* systems (LasI/LasR and RhlI/RhlR, I for the biosynthesis and R for recognition) [7,8], while a third one referred to as the *Pseudomonas* quinolone signal (PQS), utilizes the 2-heptyl-3-hydroxy-4-quinolone as signal molecule (Figure 1) [9].

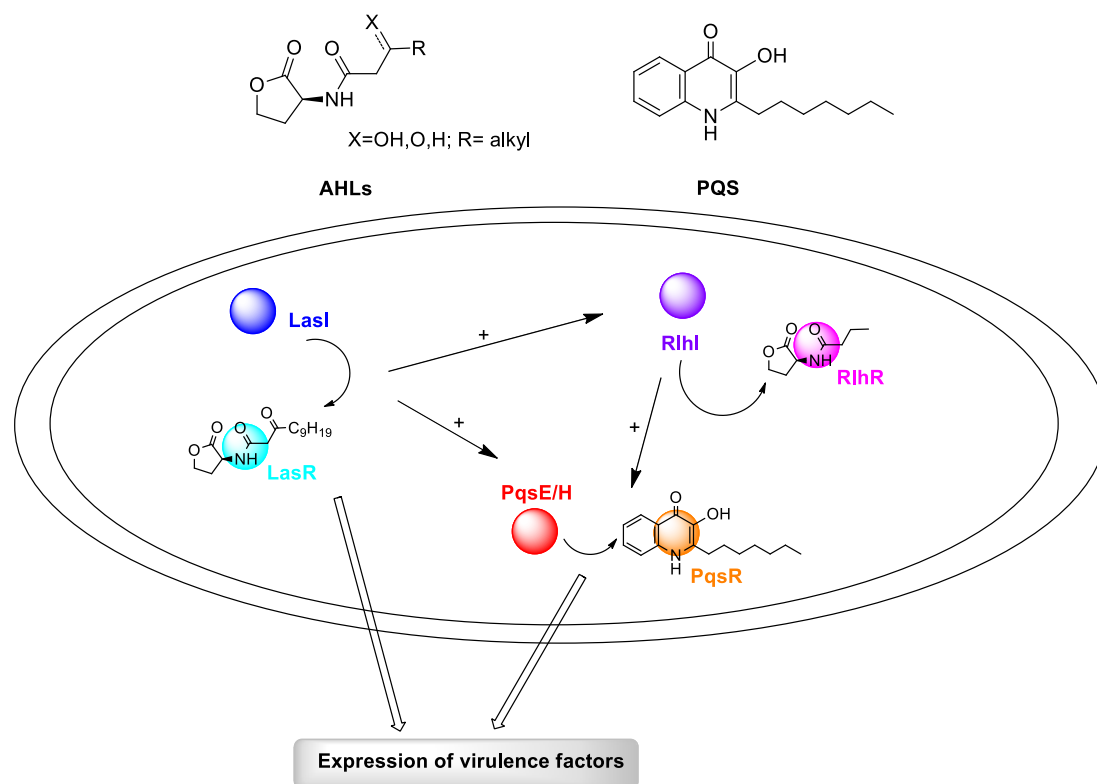


Figure 1. Representative chemical structures of autoinducers and schematic overview of the QS in *P. aeruginosa*.

1.3 Design of synthetic autoinducer analogs for interfering in the QS pathway

To block the quorum sensing circuit, one of the common strategies is to interfere with the ligand-receptor interaction by adding antagonists that mimic the autoinducers. It is suggested that this strategy could slow down or avoid bacterial resistance development as it doesn't affect bacterial growth [10-13]. Contrary to the general opinion, some researchers believed that inhibition of quorum sensing posed selective pressure on bacteria [14,15]. Even if resistance to QS inhibitors is hoped to be less than other types of antibacterial agents, this is still a debated issue. Several strategies

have been pursued for designing QS modulators, resulting in a wide range of possible structures [16-23]. Many QS active compounds possessing an amide function, one approach for extending the scope of potentially active compounds is the application of the bioisostere replacement.

Bioisosteres are functional groups that share physical or chemical properties resulting in similar biological activity in a certain compound, and are thus commonly used in medicinal chemistry for modifying lead compounds [24-30]. Amide bonds being sensitive to enzymatic cleavage by amidases, amide bond bioisosteres that improve chemical stability are of great significance, especially for applications in peptide chemistry [31]. This strategy has also been utilized for the development and structural optimization of novel quorum sensing inhibitors. In the present work, we focus on amide bond bioisosteric replacement in the search for quorum sensing inhibitors designed from existing natural or synthetic QS modulators, discussing both the biological properties and the synthetic approaches. As shown in Figure 2, the most common amide bioisosteres will be discussed in this review.

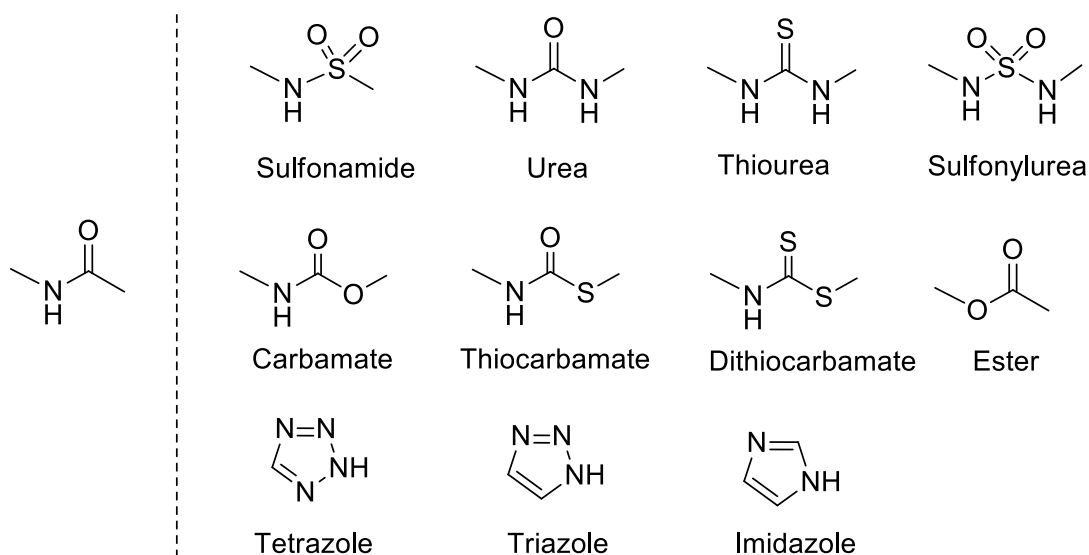


Figure 2. Some common amide bioisosteres used in the design of QS modulators.

2. Amide bioisosteres

2.1 Sulfonamide as amide bioisostere

Isosteric replacement of an amide bond by a sulfonamide moiety is a fundamental pathway for structure optimization in medical chemistry. Structurally, the sulfonamide moiety is similar to the amide in which the carbonyl group is substituted by sulfonyl one. The sulfonamide function possesses unique physicochemical properties, such as higher solubility in water, high polarity and stability, and increasing binding affinity through hydrogen bond interaction as compared to their amide counterparts [32-34]. The main characteristic of this motif is its tetrahedral geometry versus the planar geometry of the *trans* amide functional group. This tetrahedral geometry with an additional oxygen as an H-bond acceptor for the sulfonamide often induces an H-bond network leading to the modulation of the target protein [35].

The first series of sulfonamide AHL analogs was described by Doutheau's group [35] who prepared a series of alkyl- or phenylalkyl-sulfonyl HSLs built on the model of autoinducer 3-oxo-C₆-HSL. These compounds displayed inhibitory activity on quorum sensing in *V. fischeri* (Figure 3) with significant variations in the activity due to chain length and substitution. The pentyl-sulfonamide **1** was found to be the most active compound (IC₅₀ = 2 μM). Compound **2** containing a phenyl group at the terminal of the sulfonyl chain was evaluated for its QS inhibition, achieving an IC₅₀ value of 3 μM almost as active as compound **1**. The introduction of a terminal phenyl functionality on the sulfonyl chain generally provided compounds with antagonistic activity. Further examination of the influence of the chain length or the distance between the sulfonamide and the phenyl group on the activity was conducted. The investigation of the structure-activity relationship revealed the AHL analogs with the acyl chain close in length to native AHL displayed more antagonistic activity. Additionally, a two-carbon space between the sulfonamide moiety and a phenyl group is optimal for inhibition in ligands structurally related to sulfonamide **2**. A key point is the additional H-bond between one of the oxygen atoms of the tetrahedral

sulfonamide group and Ser137 of the LuxR binding site which does not exist neither for the autoinducer 3-oxo-C₆-HSL nor the corresponding amide C₆-HSL as depicted in Figure 3 [35]. It is worth mentioning that the two optically pure enantiomers of sulfonamide **1** were later studied [36] by the same group in a work to examine the possible difference between the biological activities of the two isomers, confirming that only the L one showed significant inhibitory activity while the D-isomer was unable to promote the necessary additional H-bond when complexed in the receptor binding site.

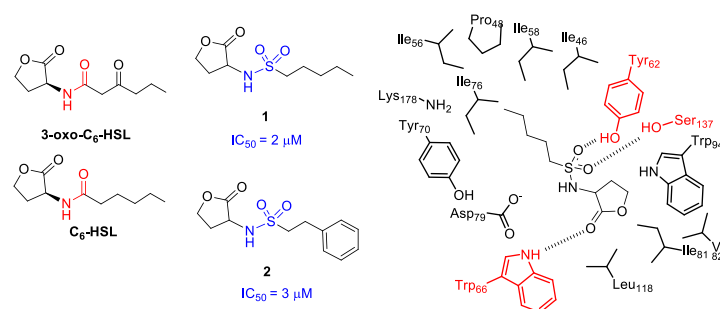


Figure 3. Structure of the natural ligand 3-oxo-C₆-HSL, the C₆-HSL and sulfonamide analogs, schematic diagram showing interactions of compound **1** within the LuxR binding site.

The first collection of enantiomerically pure AHL sulfonamide analogs prepared by combining a solid-phase synthesis with microwave-assisted reactions was reported by Blackwell and co-workers [37,38]. The QS activity of this family of compounds bearing a sulfonamide moiety was systematically evaluated on several Gram-negative bacteria including *A. tumefaciens*, *P. aeruginosa* and *V. fischeri*. Several highly potent synthetic QS inhibitors of TraR and LuxR receptors were revealed (Figure 4). For instance, butyl-sulfonamide **3** and hexyl-sulfonamide **4** exhibited the most antagonistic activity on the TraR receptor with IC₅₀ values down to the nanomolar scale (0.6 and 0.8 μM, respectively). Compounds **5** and **6** with longer chain lengths were determined to be potent and selective inhibitors of the LuxR receptor which were not active against LasR in *P. aeruginosa*. In general, the sulfonyl HSLs with sulfonyl chains of moderate size could antagonize TraR and LuxR. Secondly, TraR

was sensitive to the length of the sulfonyl chain on the sulfonyl HLs, as inhibitory activity dropped off dramatically for sulfonamide AHLs with sulfonyl tails longer than seven atoms. Thirdly, the sulfonyl HLs **3** and **4** in this study were most active against TraR, yet virtually inactive against LasR.

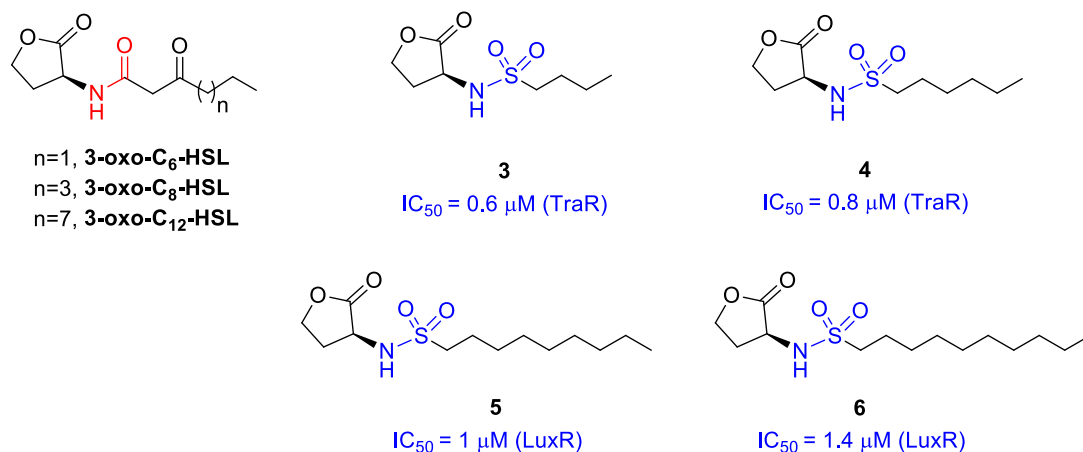


Figure 4. Replacement of an amide bond in natural ligand with sulfonyl moiety leading to enantiomerically pure AHL analogs.

Applying a similar solid-phase synthesis sequence, Lee and co-workers [39] prepared aryl sulfonamide analogs **7** with an unsubstituted phenyl, **8** with *p*-amino substituent and **9** with a *p*-methyl substituent, different from the previous examples involving alkyl sulfonamide chains (Figure 5). A set of enantiomerically pure benzyl sulfonamides bearing various substituents at the *para* position were investigated. The inhibitory activity of these molecules against TraR QS signaling was assayed, revealing sulfonamide **9** with the *p*-methyl substituent as the most active compound with a 65% reduction of QS response at 10 nM (10-fold molar concentration relative to its native ligand). Additionally, sulfonamides **7-9** were also capable of blocking the biofilm formation by *P. aeruginosa*. Very recently, sulfonamide **9** was evaluated to act as a QS inhibitor against violacein pigment in *C. violaceum* [40]. Compared with amide AHL analogs, the sulfonyl group could improve the flexibility of the ligand owing to the distance between the sulfur and the aromatic carbon being longer than that between the carbonyl carbon and the aromatic carbon.

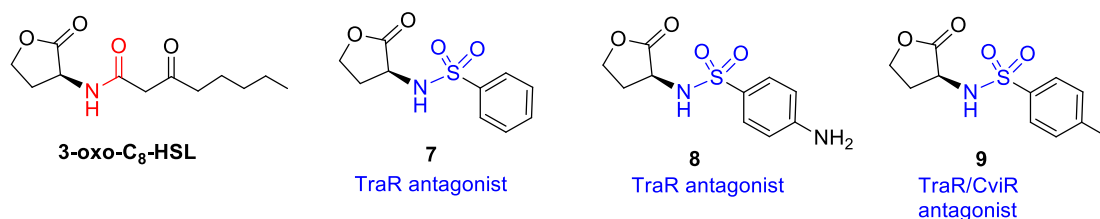


Figure 5. Benzenesulfonamides as QS inhibitors.

Inspired by the above results, Song and Meng [41,42] disclosed quorum sensing antagonistic activity against violacein production by a collection of *N*-(4-aminobenzene)sulfonyl homoserine lactone derivatives (Figure 6). Various aromatic or heteroaromatic groups were grafted on the modified AHL backbone by acylation of the 4-amino group. The resulting compounds displayed high levels of inhibitory activity, the most potent compound being the *ortho*-fluorobenzoyl-substituted derivative **10** with IC₅₀ values of 1.6 μM. The authors ascribed the gain in activity to the increased hydrophobicity resulting from the introduction of a benzene ring moiety. A prominent SAR trend impacting antagonistic activity for this type of compound is that *ortho*-substituted aryl groups bearing electron-withdrawing groups are superior to the corresponding *para* and *meta*-substituted aryl groups. Similar observations were seen in the thiophene substituted series, derivative **11** which was found to be active against CviR (IC₅₀ = 6.2 μM). Docking simulations were conducted and clearly showed that the terminal aromatic or heteroaromatic rings are deeply located in the hydrophobic binding pocket of the C6-HSL alkyl chain additionally to H-bonds with Asp97 and Trp84. For these compounds, it can be hypothesized that the tetrahedral sulfonamide group is also involved in different H-bonds compared to the C6-HSL.

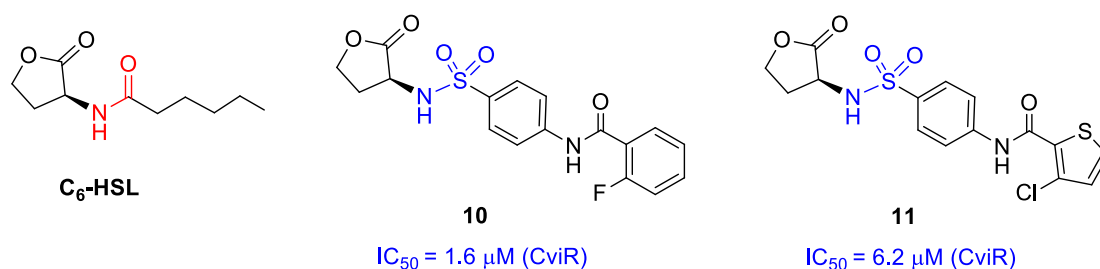


Figure 6. AHL analogs involving a benzoyl-aryl sulfonamide structure.

In all the previous examples, the design of the AHL analogs was based on a move to a sulfonamide and modification of the side chain, though retaining the lactone moiety. The next examples differ by also modifying the lactone ring to some equivalent structure.

One type of such analogs was reported by Taboureau and coworkers [43] who applied a virtual screening and cell-based screening to identify a set of 122 new possible LasR antagonists, which were structurally distinct from the native ligand in *P. aeruginosa*. Among the 122, the screening revealed compounds having a sulfonamide as amide replacement and a thiazole ring as lactone replacement (Figure 7). The biological evaluation showed that sulfonamide **12** and **13** exhibited inhibitory properties, in which sulfonamide **13** ($IC_{50} = 9 \mu M$) displayed 6-fold better inhibition than sulfonamide **12** ($IC_{50} = 60 \mu M$). Investigations on the binding mode by molecular docking simulation with LasR crystal structure revealed that the bioisosteric sulfonamide group maintained the hydrogen bonding interaction with Trp60 and Asp73, and that compound **13** occupied the same space as the native ligand both in the aromatic pocket and hydrophobic pockets with π -stacking interactions with Tyr64 (Figure 7).

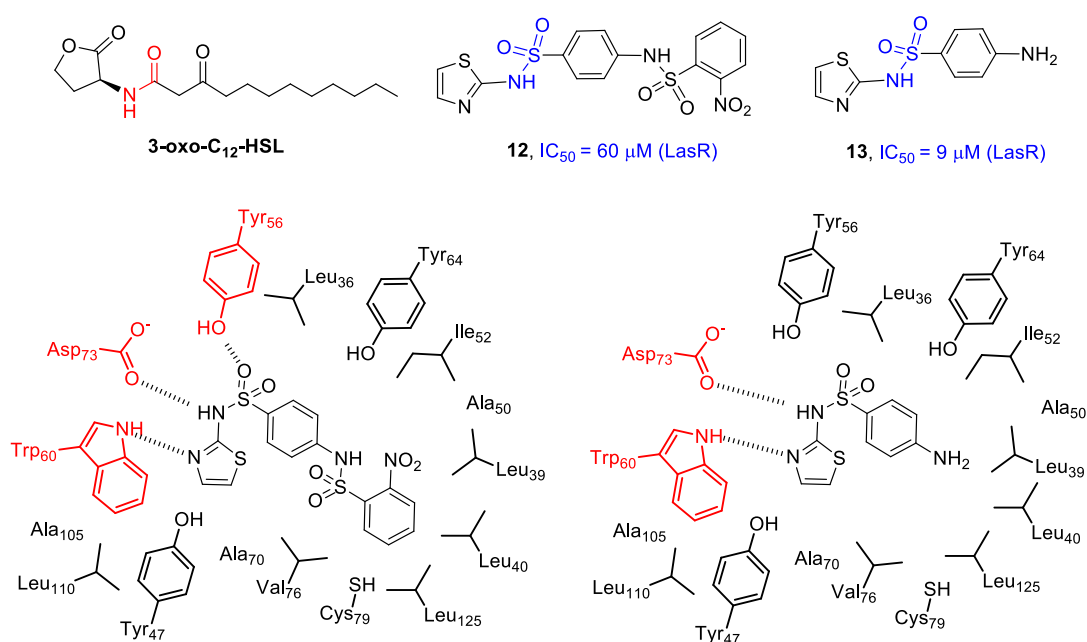


Figure 7. Thiazolylsulfonamides as LasR antagonists and their interactions within the LasR binding site.

Another interesting family was built using a carbohydrate moiety. Actually, *P. aeruginosa* produces two soluble lectins, LecA and LecB, that play key roles in QS-controlled biofilm formation [44], LecB specifically interacting with L-fucosides and D-mannosides [45,46]. This inspired Titz and his colleagues to develop a series of fucose-based or mannose-based QS inhibitors targeting LecB [47-50] that are active against biofilm formation by *P. aeruginosa*. Replacing the amide with a sulfonamide connection in the mannose-derived (**14**) or the fucose-derived (**16**) molecules consistently increased their potency and bioavailability (Figure 8). The biological evaluation revealed that inhibitor **15** ($IC_{50} = 3 \mu M$) exhibited 12-fold better than amide inhibitor **14** ($IC_{50} = 37 \mu M$). And results displayed that sulfonamide **17** ($IC_{50} = 1 \mu M$) had 4-fold better activity than the parent **16** ($IC_{50} = 4 \mu M$). In their further structural modification, a class of fucosyl amides and sulfonamides were designed and synthesized. *N*-linked fucosyl sulfonamide **19** posed moderate antagonistic activity in the micromolar range while the β -fucosyl benzamide **18** was among the most potent LecB inhibitors with an IC_{50} of 88 nM. The sulfonyl chain with larger substituents such as the phenyl group increased the affinity of sulfonamide toward LecB. The influence of linking units between carbohydrate and aromatic moiety targeting the LecB binding potency was investigated. Two factors could explain the dramatic fall in affinity for LecB between the most active β -fucosyl benzamide **18** and the sulfonamides **19**. First, the more acidic sulfonamides group than the carboxamides could influence their hydrogen-bonding properties. Secondly, the substituents of amides or sulfonamides differ in geometry, which leads to an alteration in the orientation of the linked pharmacophore.

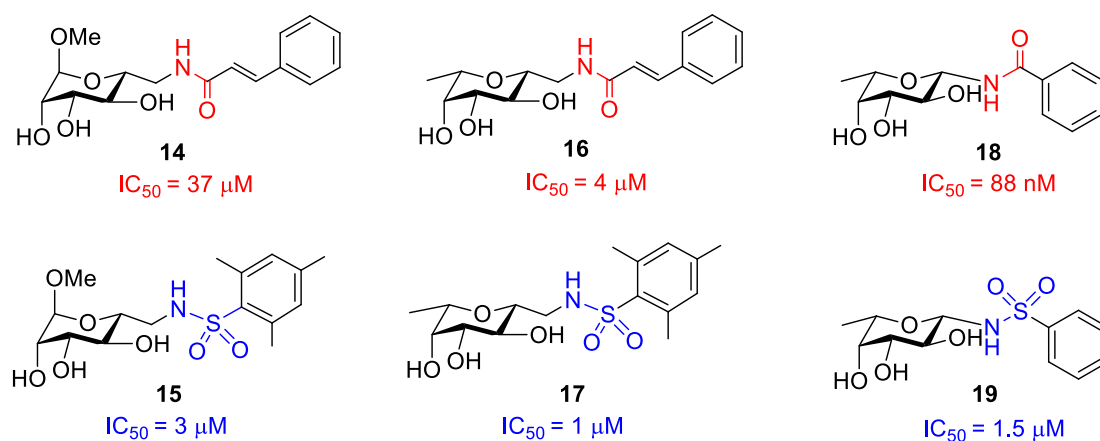


Figure 8. Sulfonamides targeting LecB inhibition.

The replacement of the amide with a sulfonamide was also investigated in the case of the PQS system. Recently, Chen's group [51,52] identified a wide range of 3-hydroxy-pyridin-4(1*H*)-ones as new *Pqs* quorum sensing modulators, able to inhibit biofilm formation by *P. aeruginosa* (Figure 9). Among these compounds, amide **20** was the most active anti-biofilm inhibitor with an IC_{50} value of $4.5 \mu M$. Looking into the biological mechanism, the most active compound was confirmed to inhibit biofilm formation by barricading the biosynthesis of quinolone in the *Pqs* QS. More importantly, the combination of amide **20** with commercial antibiotics produced antibacterial synergism against multidrug-resistant *P. aeruginosa*. When investigating the effect of replacing the amide with a sulfonamide like in 3-hydroxy-pyridin-4(1*H*)-one derivative **21**, a weaker anti-biofilm activity was observed ($IC_{50} = 40.4 \mu M$). Replacement of the amide group with sulfonamide resulted in the loss of the biofilm inhibitory activity in this series. The authors conducted docking and MD simulations with PqsR and they could observe additional H-bonds for the amide group of compound **20** with Gln194 and Arg209 which may not exist for the less active compound **21**.

functional group can preserve the same H-bond network as the amide group with an H-bond of the C=O with Tyr62 and the NH with Asp79 (Figure 10).

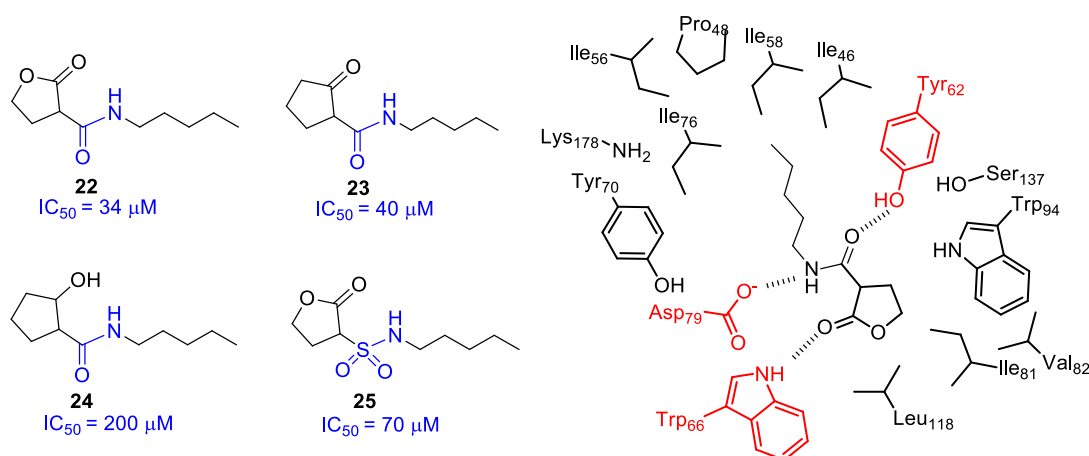


Figure 10. Reverse amides or sulfonamides in LuxR-regulated quorum sensing inhibitors, schematic diagram showing interactions of compound **22** within the LuxR binding site.

The preparation of reverse amide AHL analog **22** was achieved by coupling different alkyl amines with the carboxylic acid derivative prepared from cyclopropane dicarboxylic acid. On the other hand, reverse sulfonamide **25** was obtained by first preparing the chlorosulfonyl derivative from γ -butyrolactone which was later coupled with amines to give the desired products.

The replacement of the amide to a reverse amide was also investigated by Blackwell and coworkers [56] on a series of structurally less related mimics of AHL, integrating the nitrobenzamide fragment from a non-native LasR agonist known as **TP1** [57-59]. Retaining a 4-bromophenyl motif for the side chain known to be favorable in the AHL analog and LasR antagonist **26**, the target compound with the reverse amide **27** exhibited high potency as a novel LasR antagonist with IC₅₀ values of 4.8 μM (Figure 11). On this basis, a library of compounds with different substituents on the phenyl ring was prepared with many of them showing significant activity as LasR antagonists. Both **28** and **29** retained considerable inhibitory activity (IC₅₀ = 6.6 μM and 6.5 μM, respectively). The conversion of amide to reverse amide largely maintained their

LasR inhibitory activities. The reported X-ray crystal structures of the LasR *N*-terminal ligand-binding domain with **TP1** [60] and with OdDHL [61] confirmed that both led to the same hydrogen bonding network. The nitro group of **TP1** is involved in H-bond with Trp60 and the reverse amide interacts through H-bonds with Tyr56 (C=O) and Asp73 (NH) (Figure 11).

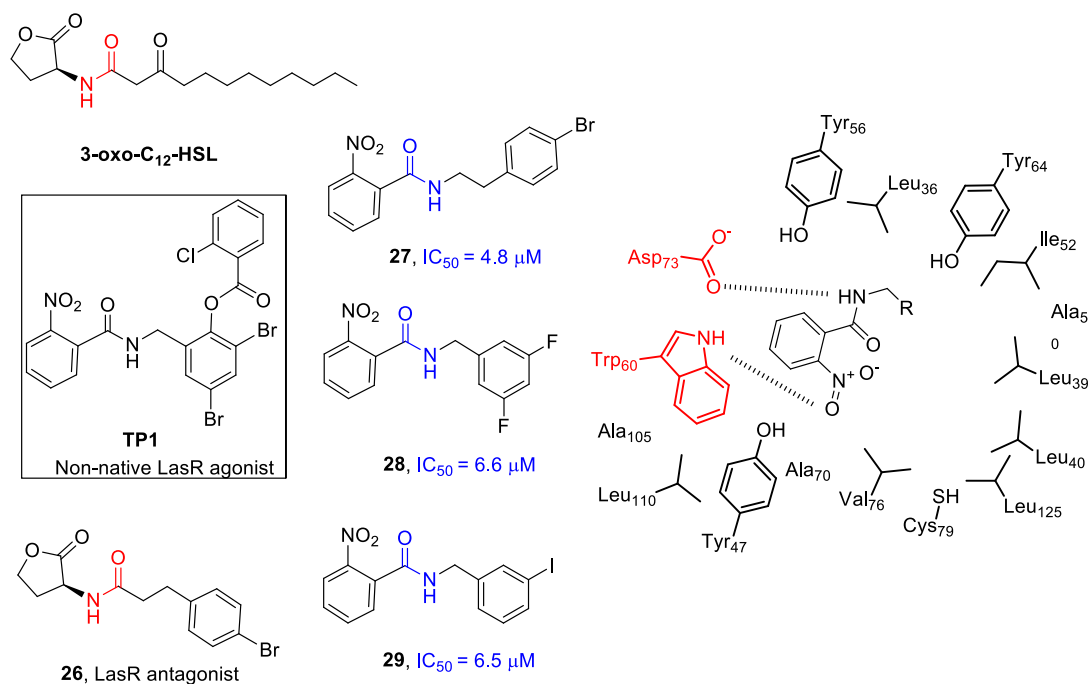


Figure 11. TP1/reverse amide hybrids and their interactions in LasR-regulated QS inhibition.

Building on the same idea to integrate the **TP1** motif, another series of reverse amide triaryl LasR modulators (Figure 12) was reported [62]. The biological evaluation showed that the 2-nitrophenyl analog **30** possessed potent agonistic activity with an EC₅₀ of 371 nM. The corresponding reverse amide **TP1** (EC₅₀ = 58 nM) displayed more potent activity in terms of its activation of LasR in *P. aeruginosa*. For the 2,3-difluorophenyl compounds **31** (EC₅₀ = 46 nM) and **32** (IC₅₀ = 65 μM), further exploration indicated that reversing the amide linkage resulted in an opposite activity. Among the compounds examined, in most cases, altering the orientation of the amide linker led to a slight influence on the potency of the analog. In certain instances,

reversing the amide linkage appears to induce a switch from LasR agonism to antagonism.

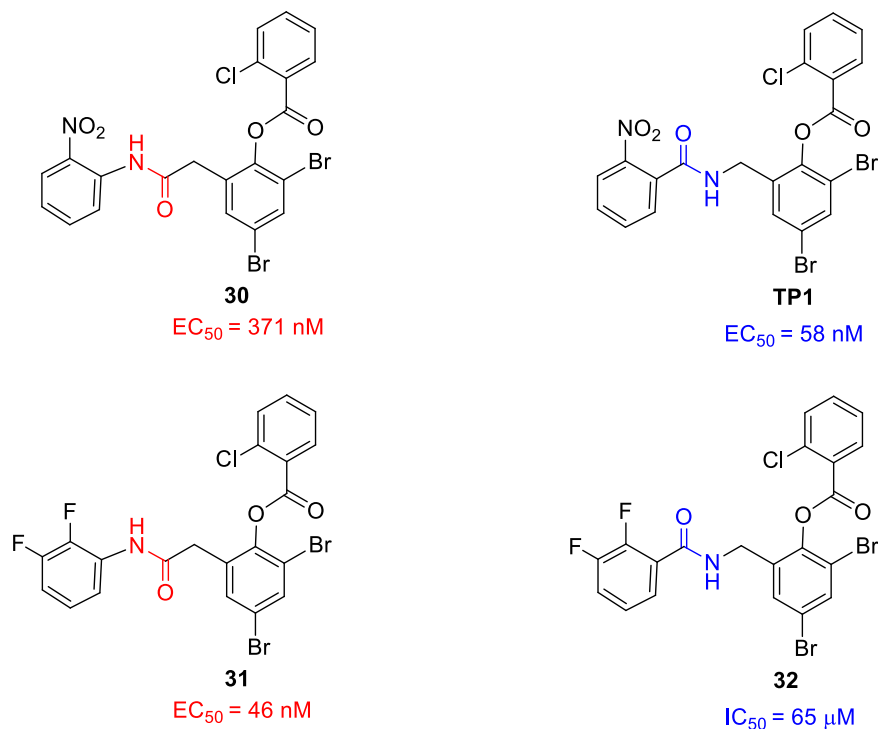


Figure 12. Reverse amide vs amides in triaryl LasR-regulated quorum sensing modulators.

Very recently, Garah and co-workers [63] described several analogs of the PQS native ligand, including chromone-based compounds, wherein the amide functionality was replaced with a reverse amide moiety (Figure 13). The biological evaluation for the ability to inhibit biofilm formation in *P. aeruginosa* showed that several chromone-based derivatives **33-36** were potent inhibitors with more than 50% inhibition at 50 μM , especially 2,4-dinitro benzamide **36** up to 90% inhibition. The docking study suggested that the orientation of the amide linkage weighed very slightly in their binding mode within the PqsR receptor.

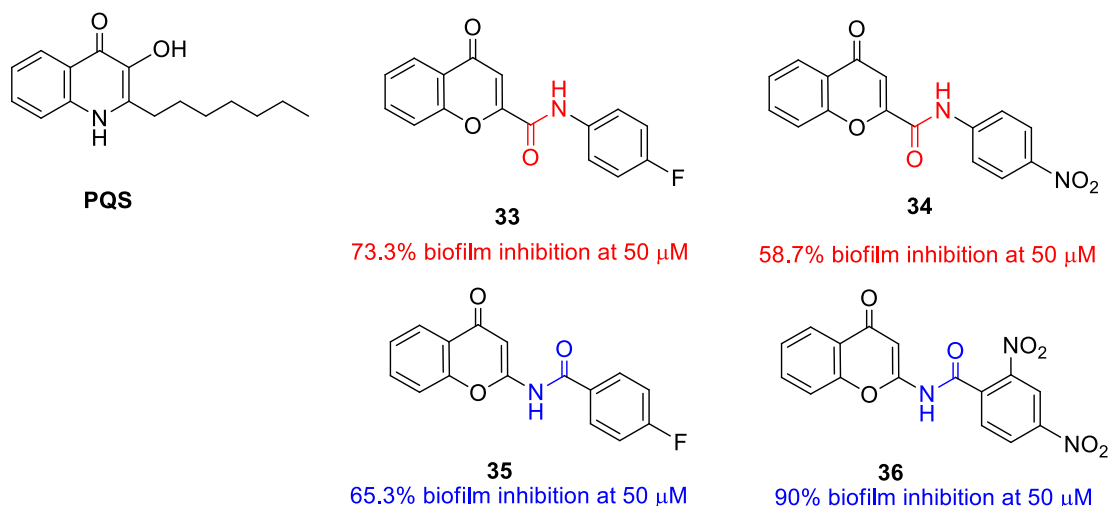


Figure 13. Reverse amides in Pqs quorum sensing modulators.

Overall, the results of these efforts confirmed that the reverse amide or reverse sulfonamide replacement of an amide bond was an acceptable pathway for keeping the bioactive conformation essential for ligand-receptor interaction.

2.3 Urea, thiourea, sulfonylurea as amide bioisosteres

Urea, thiourea and sulfonylurea are well-established moieties in medical chemistry, occurring in various biologically active agents and drugs with a wide range of pharmacological properties [64-67]. The characteristics of the urea functional group are the planarity of this system due to the mesomeric effect and the additional NH as an H-bond donor. This group can be thus considered as “double amide”. Many approved drugs contain urea or thiourea moiety and considerable investigations have been focused on the design of bioactive molecules based on (thio)urea scaffold [68]. From the viewpoint of hydrogen binding affinity, (thio)urea is capable of interacting with various receptor targets by hydrogen bonds, which is of significance for biological activity and molecular recognition. Additionally, urea is a natural product produced by the metabolism of living organisms. Recently, urea in urine was identified as a natural QS inhibitor in mammals against chronic bacterial infection caused by *P. aeruginosa* [69].

Among urea-containing AHL analogs, compounds **37** and **38** bearing a phenyl group displayed potent antagonistic activity with IC_{50} in the 3 μM range (Figure 14) [70]. Interestingly, several alkyl-substituted urea analogs **39** and **40** with short chains (C5 to C6) displayed a remarkable antagonist activity with IC_{50} in the 1 μM range. It was also noted that the C4 thiourea equivalent AHL analog was inactive. Docking modeling indicated that an additional hydrogen bond with Asp79 was formed for the urea compared to the natural ligand (Figure 14). This is a relevant example of the additional NH group of urea derivatives interacting with this residue Asp79. Both D and L enantiomerically pure urea-containing AHL analogs were later reported [36] for examining possible differences of activity between the two isomers, showing that only the L one displayed significant inhibitory activity. The D isomer was unable to promote the additional H-bond in the receptor binding site as the L isomer did.

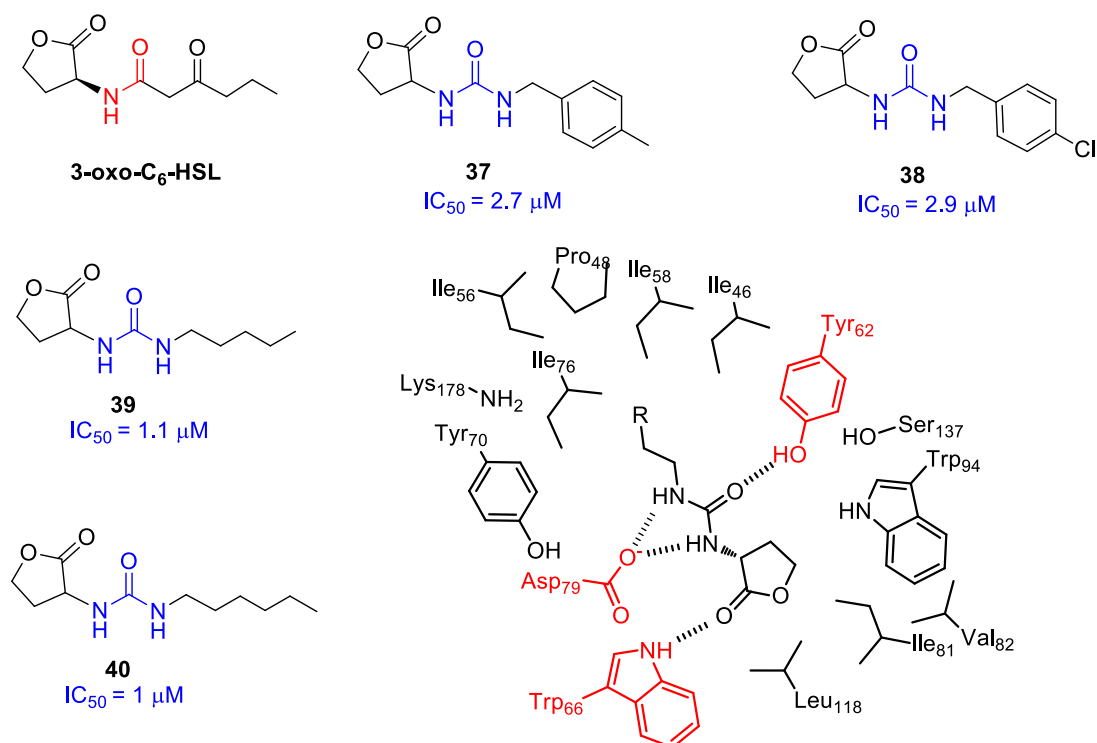


Figure 14. Urea AHL analogs as LuxR antagonists, schematic diagram showing interactions of urea derivatives within the LuxR binding site.

The synthetic routes for the preparation of urea-containing AHL analogs involve the use of isocyanates. The reaction of the isocyanates with amines or their salts (including homoserine lactone hydrobromide) led to the target urea.

The urea strategy was also applied in the above mentioned work targeting LecB inhibitors, possibly acting against biofilm formation in *P. aeruginosa*. A series of amide **41** and thiourea **42** were synthesized and evaluated for their ability to bind LecB [50] (Figure 15). Both series exhibited similar inhibiting activity with IC_{50} ranging from 5 to 9 μ M. Further docking study indicated that the thiourea moiety acted in its tautomeric thiol form. Here, an example where the replacement of amide with thiourea produced a beneficial impact is described. In this case, the H-bond with the residue Ser23 appears to be crucial to explain the activity of those compounds.



Figure 15. Thiourea moiety as an amide bond bioisostere in LecB inhibitors.

Another kind of transformation of the amide group is the incorporation of a sulfonylurea moiety. For example, Doutheau's group described the synthesis and biological evaluation as LuxR inhibitors of a series of racemic sulfonylureas, using 3-oxo-C₆-HSL as a parent structure [71]. The result showed that compounds containing a phenyl group at the extremity exhibited weaker activity than those possessing a simple alkyl chain. The pentyl-sulfonylurea **44** proved the most potent activity with the IC_{50} value of 2 μ M (Figure 16). Compound **43** possessing a phenyl group resulted in less potent inhibitory activity ($IC_{50} = 6.4 \mu\text{M}$). Docking modeling within the TraR receptor binding site indicated similar binding modes for both the amide and the sulfonylurea, consistently with similar geometry of both groups. For

the benzyl-sulfonylurea **43**, the sulfonyl group was suggested to be involved in an additional H-bond with a Tyrosine residue, Tyr61 (Figure 16).

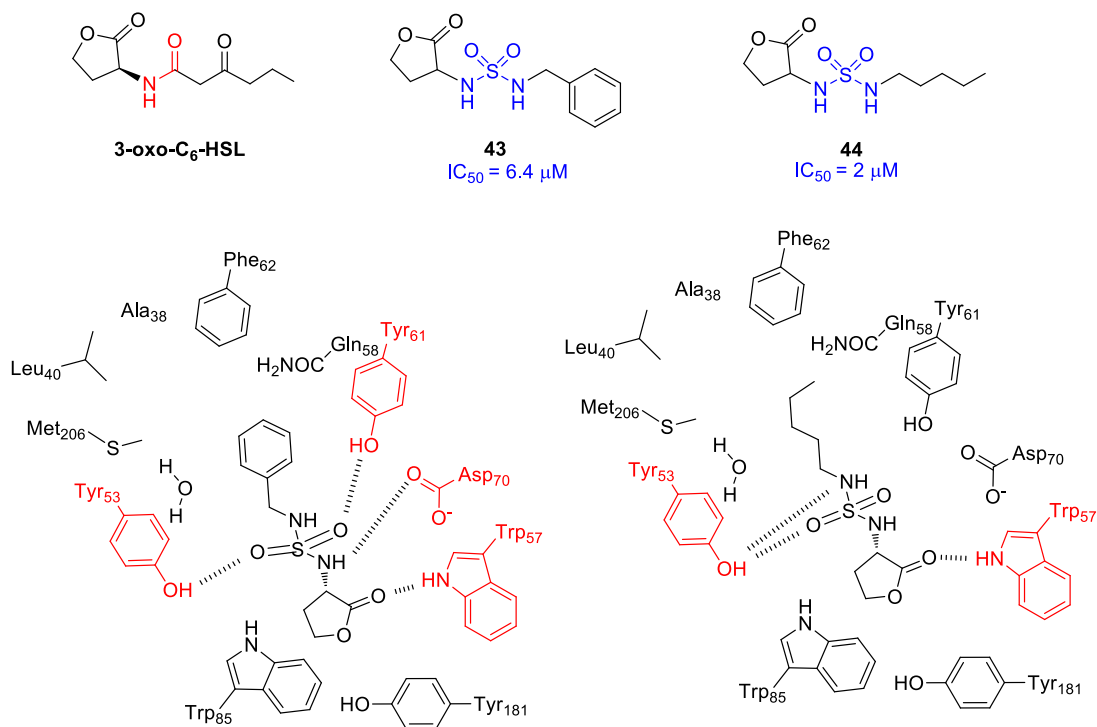


Figure 16. AHL sulfonylureas analogs as LuxR antagonists, schematic diagrams showing interactions of compound **43** and **44** within the TraR binding site.

Overall, this section exemplifies the validity of using a urea linkage in place of the amide one when designing novel possible quorum sensing inhibitors.

2.4 Carbamate and thiocarbamate as amide bioisosteres

The carbamate linkage is regarded as chemically structurally correlated with amide-ester hybrid characters [72]. Generally, carbamates exhibit good chemical and proteolytic stabilities. Thanks to these features, the carbamate motif and its derivatives appear to serve as a key bioisosteric replacement of amides in the context of designing novel bioactive molecules. Several efforts in this direction have been made in the field of QS modulators [73-75]. This functional group, as the urea group may lead to a H-bond formed by the additional oxygen atom.

Such a replacement was first seen in Wu and coworkers' study [73] to develop novel

AHL analogs containing a dithiocarbamate moiety. The compounds **45** and **46** were designed and synthesized by introducing a phenylurea group at the terminal position of the side chain (Figure 17). The biological assay suggested that these compounds displayed remarkable QS inhibition against *C. violaceum* CV026 and *P. aeruginosa* PAO1, the most active compound being **45** with a naphthyl terminal group compared to **46** bearing a 3-methyl phenyl group. Furthermore, an examination of the influence of the substituent electronic character upon its QS inhibitory activity revealed that compounds with electron-donating groups on the terminal phenyl group provided potent inhibitory activity.

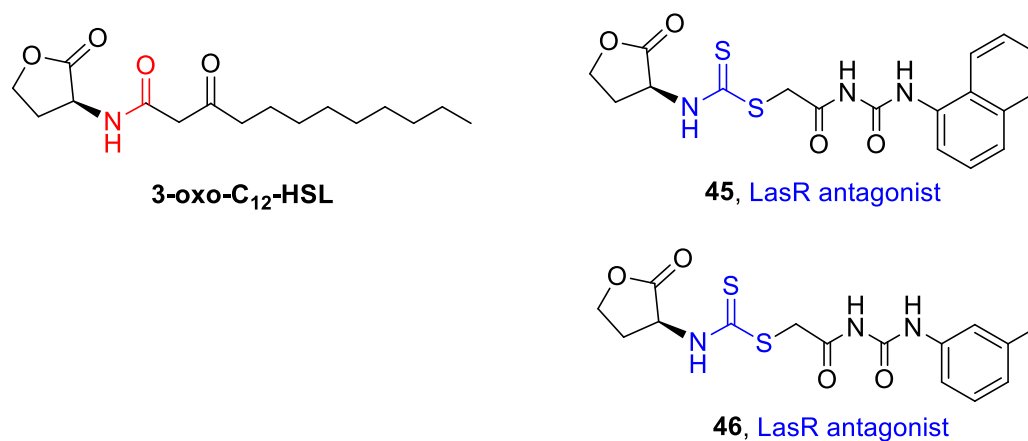


Figure 17. Dithiocarbamate containing AHL analogs as LasR antagonists

Queneau and Soulère group investigated the ability of AHL analogs to modulate LuxR-regulated quorum sensing [74], with carbamate and thiocarbamate derivatives exhibiting moderate antagonistic activity (Figure 18). In this collection, the 4-nitrobenzyl carbamate **48** and thiocarbamate **50** are proved to be the most active compounds with IC_{50} values of about 20 μ M. In the same series, carbamate **47** (IC_{50} = 73 μ M) and thiocarbamate **49** (IC_{50} = 45 μ M) without an aromatic functionality exhibited a slight decrease in activity. The docking study conducted on the LuxR model revealed that an additional hydrogen bond with the residue Tyr70 was induced by the heteroatom (O/S), leading to a different hydrogen-bond network (Figure 18).

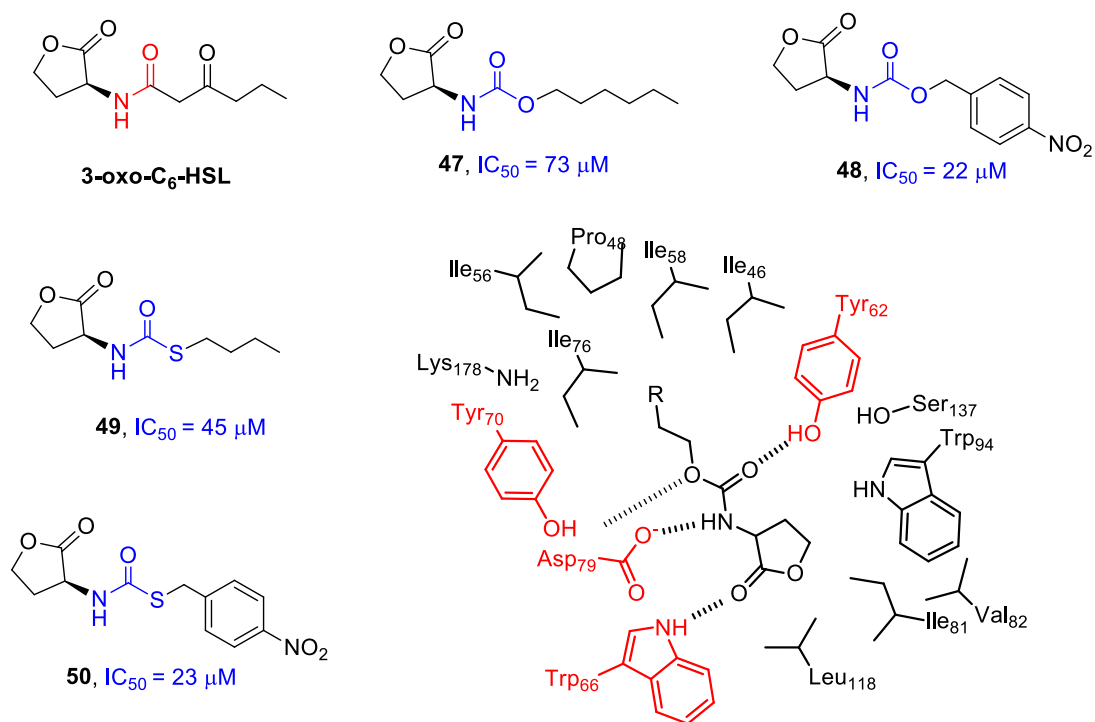


Figure 18. Carbamate or thiocarbamate AHL analogs as LuxR antagonists, schematic diagram showing interactions of thiocarbamate derivatives within the LuxR binding site.

Very simple methods were employed for the synthesis of the carbamates or thiocarbamates, involving either the alkoxycarbonylation of homoserine lactone with chloroformate or *p*-nitrophenyl (thio)carbonate (a frequently utilized alkoxycarbonylating reagent obtained from *p*-nitrophenyl chloroformate and the corresponding alcohol in basic medium [76-78]).

A set of azamacrolides containing the carbamate motif were synthesized and evaluated for QS inhibition in *A.tumefaciens* [75]. The carbamate **51/52** exhibited moderate antagonistic activity against *A.tumefaciens*. In terms of macrolide size, the 16-membered azamacrolide **52** was more active than the 12-membered one **51** (Figure 19). 3D-QSAR models were established and showed the potentialities of the azamacrolides to exert new H-bonds.

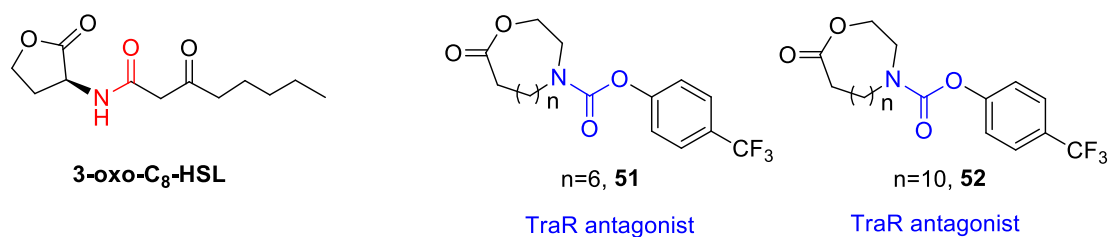


Figure 19. Azamacrolide carbamates as TraR antagonists.

These studies indicate that the carbamate motif (and its thio equivalent) having the feature of good chemical and proteolytic stabilities can replace the amide bond in the search for novel QS inhibitors. The additional oxygen atom of this group may also participate in the binding of protein targets and thus modulate their activity as demonstrated in the case of the *V. fischeri* LuxR modulation *via* an additional H-bond with Tyr70 [74].

2.5 Ester as amide bioisosteres

Esters are labile to hydrolysis and could act as weak hydrogen bond acceptors while not as hydrogen bond donors. The ester function is considered more structurally flexible since it is less involved in geometric variations [26].

In the screening conducted by Greenberg identifying many different possible QS active molecules [79], one compound, amide **V-06-018**, was shown to be a highly active antagonist against the LasR receptor with an IC₅₀ value of 10 μM. Moving to an ester in place of the amide has been the object of a recent study in which β-keto esters such as ethoxycarbonyl acetophenones **53** structurally similar to **V-06-018** were synthesized and evaluated as QS inhibitors (IC₅₀ = 76 μM) [80] (Figure 20). A structural variation in the phenyl group led to the identification of several active compounds, with the 4-fluoro **54** being the most potent with an IC₅₀ value of 23 μM against the wild-type reporter strain *V. harveyi* BB120.

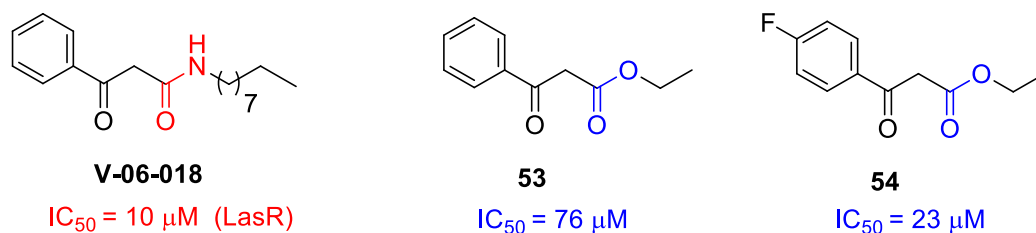


Figure 20. Replacement of an amide bond with ester in LasR-regulated quorum sensing inhibitors.

Another example of the application of the amide bond replacement with an ester group was illustrated by Chen et al [81] in their study dedicated to LasR antagonists and the synthesis of 3-nitrophenol ester derivatives. Among these candidates, the 3-nitrophenol ester **56** produced the most significant LasR inhibiting activity with an IC_{50} value of 22 μM without effect on bacterial growth, which displayed an order of magnitude more potent than the parent **55** (Figure 21). Further biological evaluation revealed that compound **56** displayed significant inhibition against *P. aeruginosa* virulence factor. In this case, the replacement of an amide bond with an ester bond results in better activity. Therefore, the ester moiety was an acceptable isosteric replacement for the amide group. However, the ester group was vulnerable to chemical or biochemical hydrolysis. Due to its instability *in vivo*, the ester bioisosteres were regularly used to address metabolism issues.

The general approach for the synthesis of 3-nitrophenol ester **56** involved the coupling of variously substituted phenols with carboxylic acid in the presence of a condensing agent.



Figure 21. Replacement of an amide bond with ester in LasR-regulated quorum sensing inhibitor **56**.

2.6 Tetrazole, triazole and imidazole as amide bioisosteres

Tetrazoles, triazoles, and imidazoles are nitrogen-containing heterocycles widely and frequently used in medical chemistry to optimize lead compounds [82-84]. Such heterocycle amide mimics are considered to be excellent bioisosteres [85,86], therefore they have been selected for the rational design of quorum sensing modulators in several studies.

Greenberg and coworker [79] identified a series of quorum sensing inhibitors against *P. aeruginosa* by an ultra-high-throughput screen, among which a 2,5-disubstituted tetrazole termed **PD12** was the most active agent, with an IC_{50} value of 30 nM (Figure 22) making it one of the most powerful QS inhibitors ever reported. When discussing the structure-activity relationship of **PD12** and its derivatives, the first factor weighing heavily on the biological activity was the alkyl chain length, with at least a 12-carbon atom chain as optimal inhibition activity. The second factor was the regioisomeric substitution at either the N-1 or the N-2 position of the tetrazole, with 2,5-disubstituted tetrazole derivative **PD12** displaying higher potency to inhibit LasR reporter systems than 1,5-disubstituted one **57**.

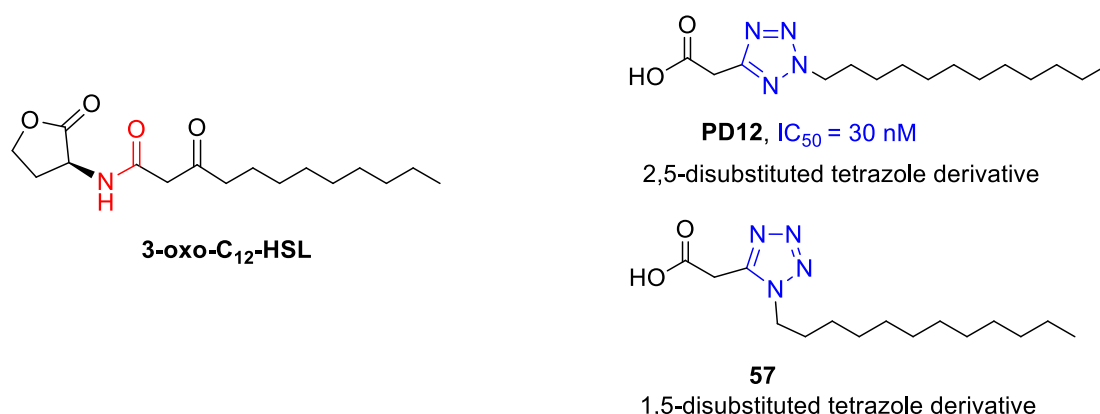


Figure 22. Tetrazoles in LasR antagonists design.

In another study inspired by the one of Greenberg and coworker, Queneau, Soulère, and colleagues [87] reported the synthesis and the biological evaluation of a series of AHL analogs based on a triazole or tetrazole scaffold (Figure 23). In this work,

several butyrolactone-tetrazole hybrids, in which the lactone motif was linked to either the nitrogen atom or the carbon atom of the tetrazole ring, were systematically investigated. Notably, the biological evaluation indicated that the two types of compound **58** and **59**, having different linkages between lactone motif and tetrazole ring, either a C-C bond or a C-N bond, exhibited opposite activity on the LuxR-regulated quorum sensing. The agonistic activity of analog **58** ($EC_{50} = 10 \mu\text{M}$) was ascribed to a closer structural similarity of the C-N linkage in analog **58** with that of the amide function in the natural ligand. In contrast, compound **59** with a “C-C” connection was not active as an agonist and exhibited antagonistic activity ($IC_{50} = 80 \mu\text{M}$). In the same series, other compounds were evaluated, notably the 2,5-disubstituted tetrazole **60** which proved to be inactive, while the triazoles **61** and **62** equipped with a short alkyl chain were moderate antagonists ($IC_{50} = 51 \mu\text{M}$ and $94 \mu\text{M}$, respectively). SAR was discussed based on docking simulations on the LuxR model for these compounds and showed their ability to exert new H-bonding via nitrogen atoms. In particular, for the tetrazole derivatives **58** and **59**, key H-bonds with Tyr62 (**58**) or Tyr70 (**59**) were suggested to explain their agonistic or antagonistic activities, respectively. For the antagonist triazole derivative **62**, interactions with Trp66, Tyr62 and Ser137 could be displayed (Figure 23).

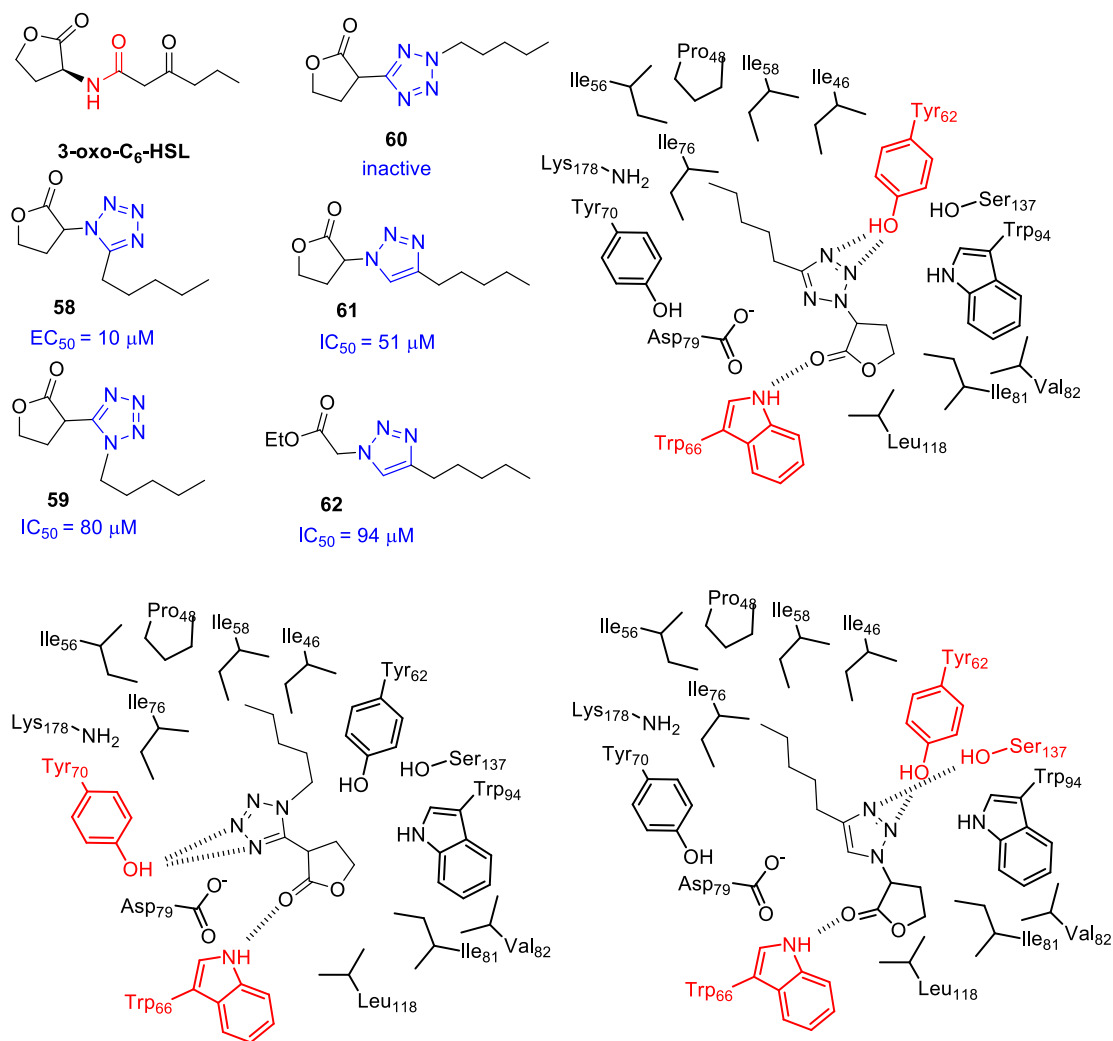


Figure 23. Tetrazole or triazole-based AHL analogs as LuxR-regulated QS inhibitors, schematic diagram showing interactions of compounds **58**, **59** and **61** within the LuxR binding site, schematic diagrams showing interactions of these compounds within the LuxR binding site.

The Brackman group focused on the triazole ring in a study looking for AHL-based QS systems active on biofilm formation in *P. aeruginosa* and *B. cenocepacia* (Figure 24) [88]. The biological results showed that all the series of compounds **63-65** bearing a triazole moiety could block C₆-HSL-based QS whereas only compounds **64** and **65** with a long alky chain or benzyl group at the terminal position inhibited 3-oxo-C₁₂-HSL-based QS. Further investigation suggested that the most active QS

inhibitor **63** ($IC_{50} = 307 \mu\text{M}$) in this series also exhibited strong inhibitory activities against biofilm formation by *B. cenocepacia* and *P. aeruginosa*. Nielsen's group reported another series of AHL mimics containing 1,4-disubstituted triazoles and 1,5-disubstituted triazoles linked with a short alkyl chain or aromatic group were deprived of activity against *P. aeruginosa* [89].

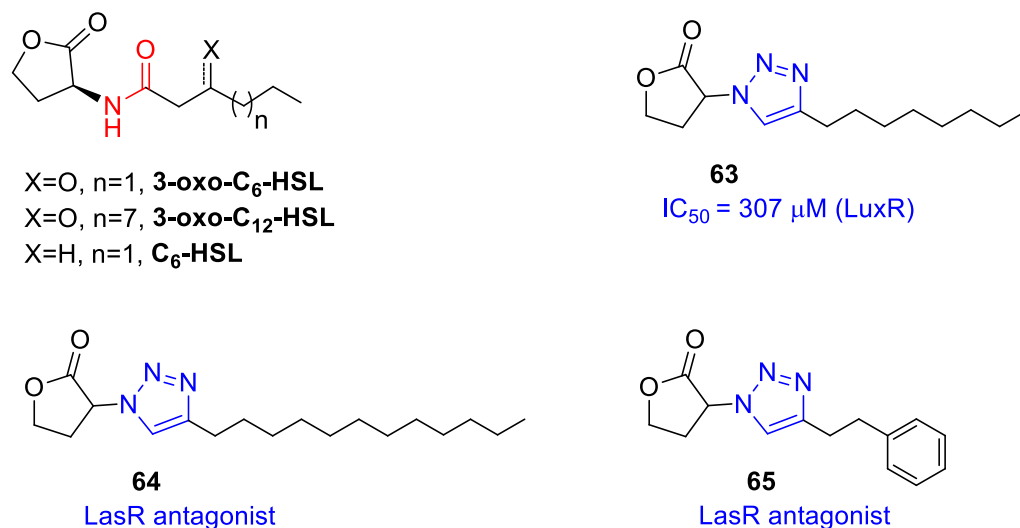


Figure 24. Triazole ring as an amide bond bioisostere in AHL-based quorum sensing inhibitors.

More recently, the effect of replacing the central amide bond in a natural autoinducer with an imidazole was investigated by the Queneau and Soulère group [90]. In their study, novel 1,4- and 1,5-disubstituted *N*-ethyl acetate and *N*- α -butyro- γ -lactone alkylimidazole derivatives were designed and synthesized (Figure 25). The biological evaluation indicated that imidazoles **66/67** displayed moderate antagonistic activity on LuxR-regulated QS with IC_{50} values ranging from 87 to 110 μM , while 1,4-disubstituted *N*- α -butyro- γ -lactone alkylimidazoles were deprived of any activity. Whereas docking simulations were not described, it can be hypothesized that H-bonds with Tyr62 and Ser137 and the unsubstituted nitrogen atom may occur as for the previous triazole derivatives explaining their antagonistic activities.

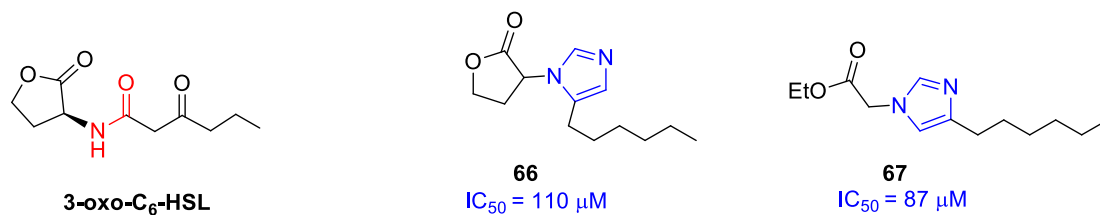


Figure 25. Imidazoles as LuxR-regulated quorum sensing inhibitors.

Some triazoles have also been investigated in the context of the Pqs system mediated by pseudomonas quinolone signal, one of the main QS circuits in *P. aeruginosa* and known to control the production of the virulence factor pyocyanin and biofilm formation [91-96].

Empting and coworkers [94] reported the replacement of an amide bond with a triazole in the parent compound **68** affording compounds **69** and **70** that retained PqsR receptor binding affinity (Figure 26). Biological evaluation showed that the initial structural modifications proved to be efficient, with triazole **69** exhibiting significant antagonistic activity (IC₅₀ = 196 nM), and better than the parent compound **68** (IC₅₀ = 490 nM). Various attempts of structural modifications on the *para*-substitution motif in the phenyl group yielded phenoxy-modified compound **70**, which exhibited a remarkably high activity with an IC₅₀ value of 11 nM. The optimization of compound **68** involving the replacement of the amide bond with triazole moiety is a rational design approach.

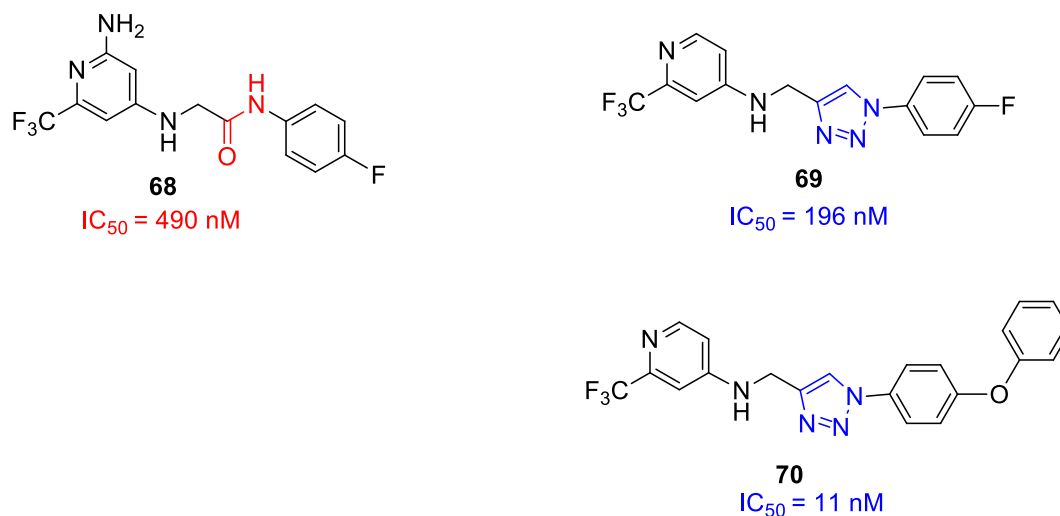


Figure 26. Pqs quorum sensing inhibitors based on a triazole ring.

Recently, Chen's group [95] identified a series of 3-hydroxy-pyridin-4(1*H*)-one derivatives containing a triazole moiety as new *Pqs* quorum sensing inhibitors against *P. aeruginosa* (Figure 27). The triazole derivative **72** ($IC_{50} = 2.7 \mu\text{M}$) exhibited a significantly higher inhibition activity than the amide counterpart **71** ($IC_{50} = 19.4 \mu\text{M}$). The investigation of the influence of the linker on the pyocyanin inhibitory activity reveals that the triazole linker is the key moiety for the derivatives to maintain high pyocyanin inhibitory activity. Docking simulations with compounds **72** revealed a key H-bond with the residue Gln194 and the triazolyl moiety and π -interactions with Tyr258.

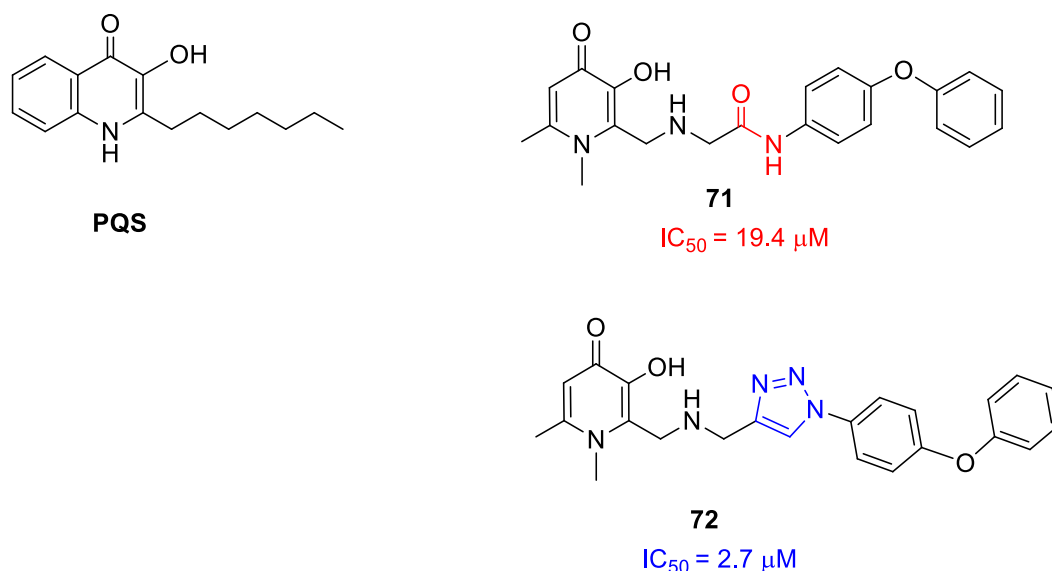


Figure 27. Amide bond bioisosteric modification in **72** with a triazole moiety.

Another application of the strategy based on amide bond replacement by a triazole moiety has been reported by Kumar et al. [96] who unveiled quinazolinone-related structural analogs **74** as *Pqs* quorum sensing inhibitors (Figure 28). The 1,2,3-triazole linkage **74** had a beneficial effect on anti-biofilm formation versus the amide derivatives **73** (73 % versus 63 % inhibition at 100 μM). The incorporation of a triazole ring is proven an effective means in the optimization of *Pqs* quorum sensing inhibitors. However, the difference in inhibitory activity between

quinazolinone-related amide and quinazolinone-related triazole is not sizable due to a comparable binding mode with H-bonding with Gln194 within the PqsR binding site as proposed in the study.

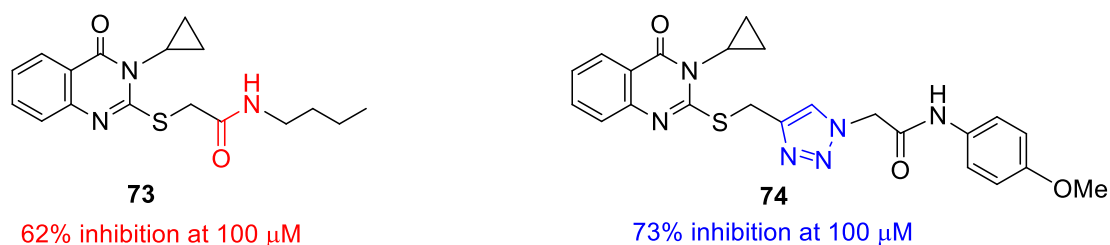


Figure 28. Replacement of an amide bond with triazole ring in *Pqs* quorum sensing inhibitors.

This section illustrated that the tetrazole, triazole, and imidazole scaffolds provided valid building blocks in the search for novel QS active compounds. Moreover, the modulation of QS with triazole-based analogs of AHL is a clear and relevant example of mimicking the amide functional group with a triazole ring which is now a classical approach through the so-called click chemistry.

Conclusion and perspectives

Tackling the quorum sensing pathway is regarded as a promising alternative to widen the strategies dedicated to the discovery of new antibacterial compounds. This review illustrates the application of the amide bond bioisosteric replacement in the design and synthesis of novel and potent quorum sensing inhibitors. Many quorum sensing inhibitors have been designed, synthesized and biologically assessed based on this strategy, replacing the amide bond found either in autoinducers, such as AHLs, or in compounds and analogs with reported QS modulation activity. The biological activities concerning various bacterial strains have been discussed, including some fighting bacterial strains of utmost importance in terms of human health.

The story is not over yet, as the effect of some other bioisosteres such as amino oxetanes or phosphonamidate remains to be fully studied in the area of quorum

sensing. It is hoped that organic chemists will find a new area of application to their synthetic methodologies while QS-focused biologists and chemical biologists will consider novel building blocks to alter the design of QS-active molecules, to the benefit of the novel anti-bacterial drugs discovery. All the studies using the bioisosteric QSI candidates will benefit the fundamental knowledge and complete the understanding of the key features of QS modulation on the molecular level.

Although many compounds have been assessed as active as quorum sensing inhibitors, the strategy is still far from clinical application, due to the lack of *in vivo* data required to confirm their clinical performance. Future work should therefore encompass the inclusion of candidates in systematic biological assays as pure compounds or in drug cocktails, such as the combination with traditional antibiotics.

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