Medicinal Chemistry & Drug Discovery

Silica Supported Synthesis and Quorum Quenching Ability of Isoxazolones Against Both Gram Positive and Gram Negative Bacterial Pathogens

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Isoxazolones are synthesised using easily available, economical and reusable silica (TLC grade) catalyst. High yields are obtained in aqueous reaction system with substrate tolerance without affecting the yield. This multigram scale, purification free method exhibits prospects for a large scale use in future. These compounds were screened for their potential application as quorum quenchers in pathogenic bacteria. The prepared compounds were analysed for quorum quenching (QQ) activity on Gram negative bioreporter strain *Chromobacterium violaceum* by inhibiting its pigment production i.e. violacein production in a concentration dependent manner. Some Isoxazolone derivatives showed very good quorum quenching activity. Moreover these derivatives also showed very good antibiofilm activity against both Gram negative (*Pseudomonas aeruginosa* ATCC 27853) and Gram positive *(Staphylococcus aureus* ATCC 6538) bacterial human pathogens through Quorum Quenching mechanism. Isoxazolones thus have enormous potential to be exploited in the medical field against bacterial infections caused by both Gram negative and Gram positive bacterial human pathogens.

Introduction

Isoxazolones are a very important class of heterocyclic compounds which are known for effectiveness in medicinally challenging areas. The position of N & O in the five membered ring also supports its interaction in various biological pathways.[1–3] The presence of supporting substituents on this framework have exhibited its usefulness for pesticides, antifungal, anticancer, antibacterial, and for various other challenging medicinal applications (Figure 1).[4,5]

Quorum sensing is a cell-to-cell communication between the bacterial cells. This enables the bacteria to adjust gene expression based on the cell density. The processes which are energetically more expensive and metabolically costly to be performed by single bacterial cells are expressed in a group with the help of quorum sensing.[6,7] It is well known that the pigment production in *Chromobacterium violaceum* is controlled by quorum sensing mechanism and their pigments contribute to their pathogenicity. Quorum sensing involves production, detection and response to extracellular, low molecular weight signalling molecules called autoinducers.[6] The autoinducers are synthesized and secreted by bacterial cells which are sensed by other bacteria in the surrounding and respond to it in a cell density dependent manner. As the bacterial cell density increases, the autoinducers accumulated in the surrounding environment are monitored with the help of membrane associated or cytoplasmic receptors. The change in the cell number and the type of autoinducer is thus tracked and gene expression is altered. Autoinducers employed by Gram negative bacteria belong to N-Acylated Homoserine Lactone (AHL) whereas the autoinducers of Gram positive bacteria are small peptides or cyclic peptides.[8–10] Quorum sensing regulated phenotypes include biofilm formation, virulence factor production, bioluminescence, pigment production, conjugation, sporulation, antibiotic production, swimming, twitching and swarming motility.[9] These phenotypes are associated with most of the pathogenic bacteria thus causing diseases in humans, animals and plants, and are responsible for huge economical and health impacts.[11]

Antibiotics became a major weapon to tackle the deadly infectious diseases in past few decades.[12] However, the indiscriminate use of antibiotics has led to development of resistance and further emergence of Multiple Drug Resistant (MDR) bacteria. Horizontal gene transfer (conjugation, trans-

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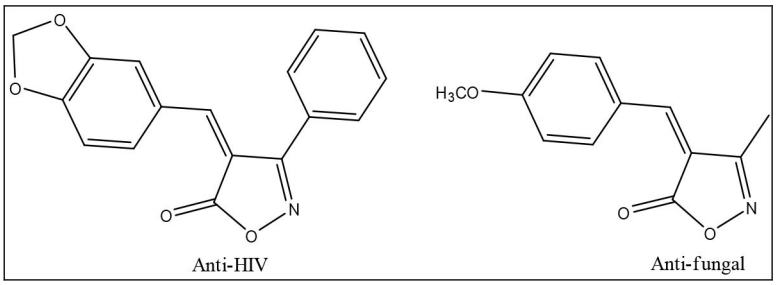


Figure 1. Medicinally important Isoxazolones.

formation) between bacteria which is controlled by quorum sensing mechanism is responsible for spread of antibiotic resistance between bacteria.[12] Human pathogenic bacteria are resilient and evolve to develop antibiotic resistance as survival strategy under the pressure of antibiotics. There is an urgent need for an alternative strategy to combat disease development and growth of pathogenic bacteria.[13] Targeting quorum sensing by interfering in communication between bacteria, rather than inhibition of growth, provides an efficient alternative. Since in quorum quenching, selective agents like antibiotics are not generally used, the development of resistance is less likely to occur. [13] Also, the usage of various natural as well as synthetic quorum sensing inhibitors leads to a decreased use of antibiotics, consequently preventing resistance development.[14,15] Inhibiting intercellular communication between the bacterial cells involved in expression of phenotypes for disease development can serve as an efficient alternative to combat infectious diseases.[16–19]

Several methods are available in literature for one pot preparation of isoxazolones using different reagents, catalysts and supports, such as H_2SO_4, H_3BO_3, Citric acid, Starch, DABCO, AIBN, Montmorillonite, Fe, ZrO_2, etc.[20–24] Challenges such as availability of supporting reagents, catalyst reusability, substrate tolerance, harmful solvents, and energy expensive conditions, restricts their usability for preparations directed towards long sighted applications. The need for simple, easy handling, efficient and a versatile method prompted us to undertake this study.

In this paper, we report a silica supported synthesis of Isoxazolones using aldehyde, ethylacetoacetate and hydroxylamine hydrochloride, and quorum quenching ability of these compounds for their potential application against pathogenic bacteria.

Table 1. Optimation studies for Isoxazolones using silica (TLC grade).

Entry	Silica [g/0.01 mol]	Temp. [°C]	Time [h]	Isolated Yield [%][a]
1	2	rt	24	92
2	1	rt	24	91
3	0.5	rt	24	42
4	1	60	24	92
5	1	100	24	91
6	1	rt	12	24
7	1[b]	rt	24	56

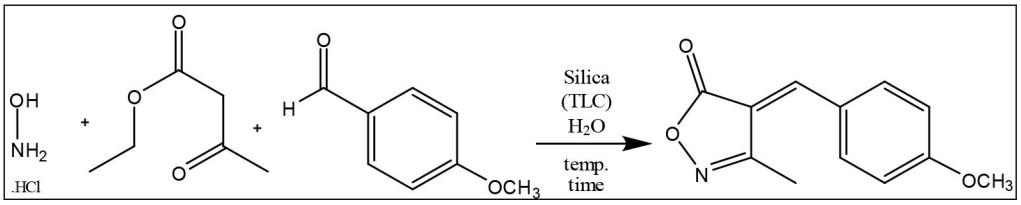
[a] Reaction condition: Anisaldehyde (5 mmol), Ethylacetoacetate (5 mmol), Hydroxylamine hydrochloride (5 mmol), Silica-TLC grade, H_2O (5 mL) Temp., Time. [b] 60–120 mesh.

Results and Discussion

In our preliminary studies (Scheme 1), we stirred anisaldehyde, ethylacetoacetate and hydroxylamine hydrochloride at room temperature and were encouraged by the quantitative conversion (>92% yield) to the corresponding Isoxazolone using silica as listed in Table 1. These results on further optimisation by fine-tuning the mole ratio of silica and reaction conditions revealed an efficient protocol.

This protocol (Scheme 2) was further exploited to study its versatility, by subjecting various substituted aromatic aldehydes as well as heteroaromatic aldehyde to give corresponding Isoxazolones in very good yields (Table 2). Characterization studies of prepared compounds revealed parallel similarities with the reported literature data and undoubtedly supported the assigned structures.[25–44]

A probable mechanism for this silica supported transformation is given in Scheme 3. The role of silica is herein depicted for activating the dicarbonyl reactant as well as aldehyde and further facilitating the dehydration.



Scheme 1. Optimation studies for Isoxazolones using silica.

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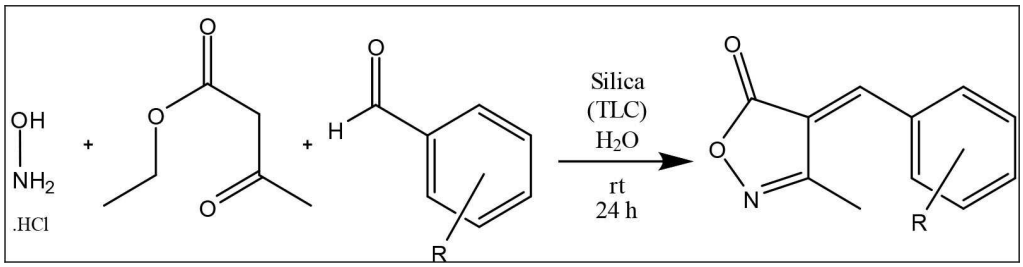
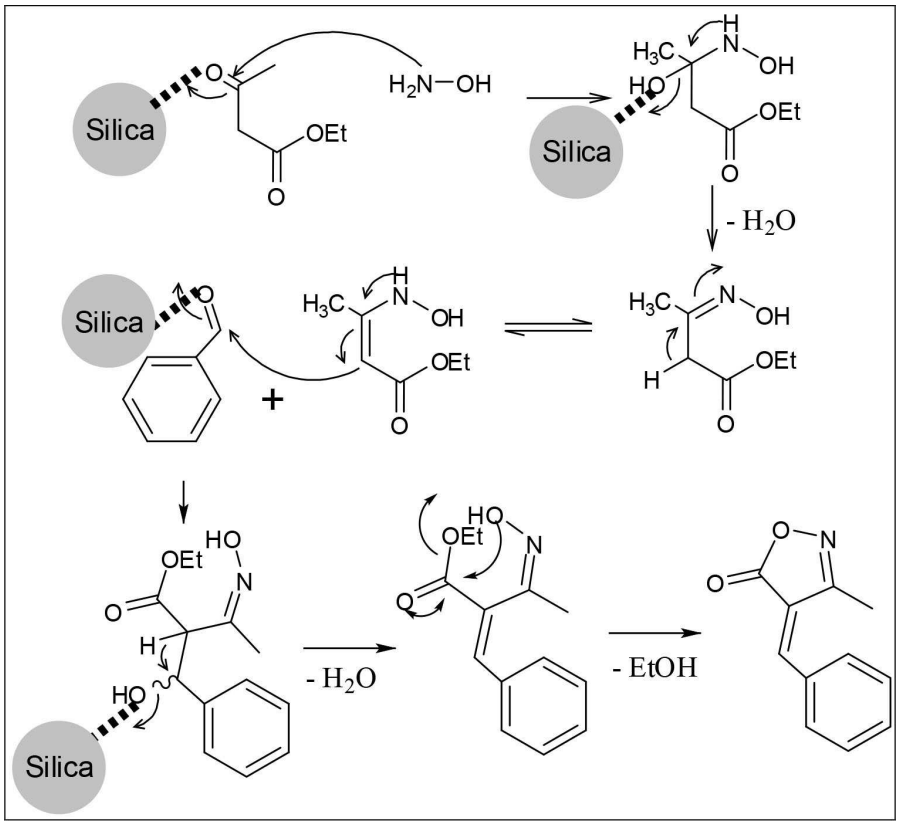


Scheme 2. Derivatives of Isoxazolones.



Scheme 3. Proposed mechanism.

Industrial applicability of this method was tested by carrying out this reaction (Scheme 4) at multigram scale (0.05 mol) giving the expected high yield.

The reusability of silica was studied by washing with chloroform giving consistent yield up to 5 cycles.

These Isoxazolone derivatives (Table 2) were screened for their quorum quenching potential. The screening of the compounds was done based on their ability to inhibit pigment production, i.e. Violacein production in *Chromobacterium violaceum*. This approach is widely used as the pigment production in *Chromobacterium violaceum* is regulated by AHL based quorum sensing circuits CviI/CviR.[6] Also, it is known that pigment violacein is required for pathogenicity of opportunistic pathogen *Chromobacterium violaceum*.[45] The qualitative screening carried out by agar well diffusion method revealed that Isoxazolone derivatives **1a**, **1b**, **1e**, **1f** and **1j** inhibited pigment production without growth inhibition, thus producing an opaque zone of pigment inhibition around the well where Isoxazolone derivatives had diffused in a concentration dependent manner (Figure 2).

Quantitative estimation of inhibition of pigment production by Isoxazolone derivatives **1a**, **1b**, **1e**, **1f** and **1j** was carried out. Based on the zone size of pigment inhibition and quantitative studies, the substituted Isoxazolone derivatives **1b** and **1j**, revealed to have an impressive AHL based quorum quenching potential in *Chromobacterium violaceum*. Isoxazolone derivatives **1b** and **1j** were capable of inhibiting violacein production in *Chromobacterium violaceum* in a concentration dependent manner (0 μg/mL as solvent control, 10 μg/mL–500 μg/mL). Substantial reduction in Violacein production by

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Table 2. Derivatives of Isoxazolones.

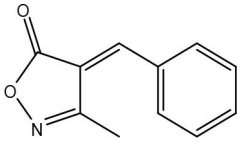
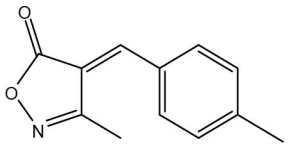
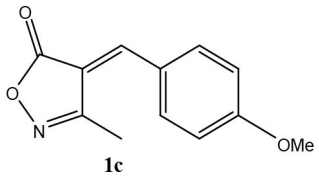
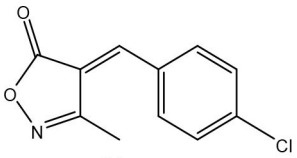
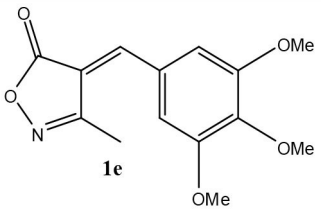
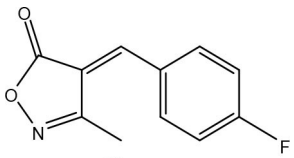
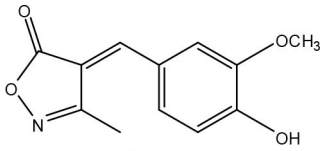
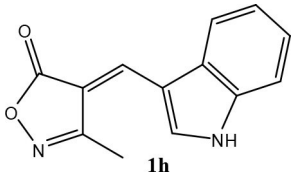
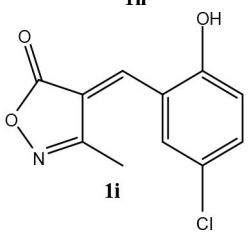
Entry	Product	Isolated Yield [%] [a]	Observed M.P. [°C]	Literature M.P. [°C]	Ref.
1	 **1a**	92	141–142	137–138	Kalhor et al. [40]
2	 **1b**	90	130–131	131–132	Kalhor et al. [40]
3	 **1c**	91	174–175	176–177	Kalhor et al. [40]
4	 **1d**	87	116–117	116–118	Hamid et al. [39]
5	 **1e**	93	176–177 (decomp.)	171–173	Ghorbani et al. [26]
6	 **1f**	92	136–137 (decomp.)	–	Wang et al. [44]
7	 **1g**	90	216–217 (decomp.)	210–212	Ghorbani et al. [26]
8	 **1h**	87	240–241 (decomp.)	244–245	Kulkarni [41]
9	 **1i**	85	180–182 (decomp.)	–	–

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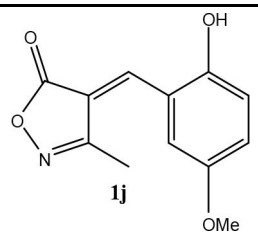
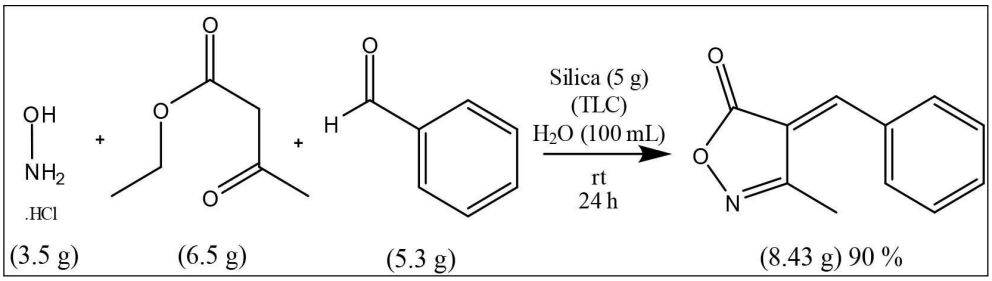
Table 2. continued

Entry	Product	Isolated Yield [%] [a]	Observed M.P. [°C]	Literature M.P. [°C]	Ref.
10	 **1j**	89	200–202 (decomp.)	–	–

[a] Reaction condition: Aldehyde (10 mmol), Ethylacetoacetate (10 mmol), Hydroxylamine hydrochloride (10 mmol), H_2O (10 mL) Silica-TLC grade (1 g), rt, 24 h.



Scheme 4. Multigram scale study.

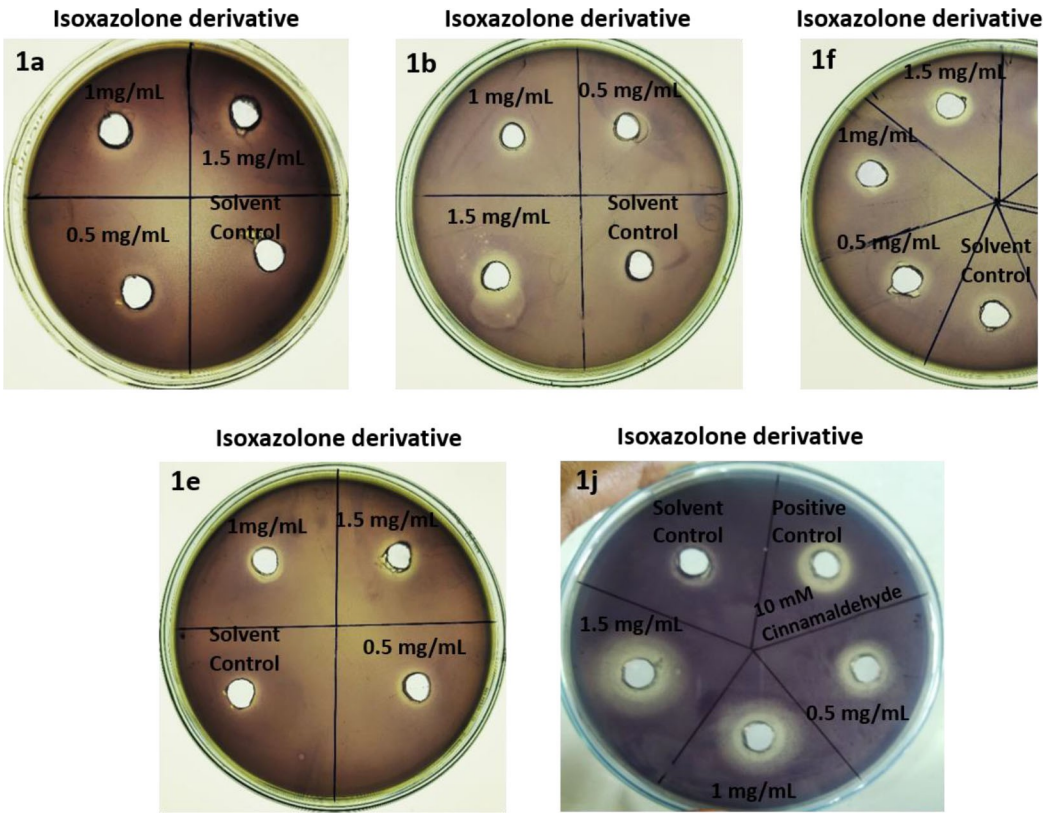


Figure 2. Agar well diffusion Method showing qualitative inhibition of violacein production in *Chromobacterium violaceum* with increasing concentration of Isoxazolone derivatives - **1a; 1b; 1e**; **1f; 1j**. Solvent control: DMSO; Positive control: 10 mM Cinnamaldehyde.

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Isoxazolone derivative **1b** was observed at the concentration range of 50–500 μg/mL which is 19.8% at 50 μg/mL, 21.4% at 75 μg/mL, 34.8% at 100 μg/mL, 81.6% at 250 μg/mL and 100% at 500 μg/mL. Likewise, significant percentage reduction in violacein production by Isoxazolone derivative **1j** was observed at the concentration range of 25–500 μg/mL. Observed percentage reduction was 16.94% at 25 μg/mL, 22.59% at 50 μg/mL, 30.32% at 75 μg/mL, 33.71% at 100 μg/mL, 99.71% at 250 μg/mL and 100% at 500 μg/mL for Isoxazolone derivative **1j** (Figure 3).

Cinnamaldehyde is a known standard for quorum quenching.[17] Based on the results obtained it was revealed that the quorum quenching activity of Isoxazolone derivative **1b** is almost comparable to that of Cinnamaldehyde, while Isoxazolone derivative **1j** was found to have much better quorum quenching activity than Cinnamaldehyde. Therefore, Isoxazolone derivative **1j** proved to have better potential as a quorum quenching compound owing to its superior quorum quenching property than the standard compound used in this study (Figure 2, 3 and 4).

The bacterial growth was also checked in the presence of **1b** and **1j** to ensure that the reduction in pigment production is because of quorum quenching and not due to the growth inhibition. On examining the absorbance at 600 nm, it was noticed that there was no considerable growth inhibition with increasing concentration, and only a significant decrease seen at the concentration of 500 μg/mL (Figure 4).

The substituted Isoxazolone derivatives **1b** and **1j**, were also checked for its antibiofilm activity against Gram negative and Gram positive bacterial human pathogens. Isoxazolone derivatives **1b** and **1j** showed a considerable decrease in biofilm formation in Gram negative *Pseudomonas aeruginosa* ATCC 27853 and Gram positive *Staphylococcus aureus* ATCC 6538. It is well known that biofilm formation in bacteria is a quorum sensing mediated phenomenon and is regulated by AHL based LasI/LasR system in *P. aeruginosa* and peptide autoinducer based Agr system in *Staphylococcus aureus*.[6] It was reported by Amara et al.[46] that downregulation of even a single QS regulator can decline biofilm formation even though it has been regulated by several QS systems and some additional factors.

In presence of Isoxazolone derivative **1b**, percent reduction observed in *Pseudomonas aeruginosa* biofilm formation was 28.8% at 100 μg/mL, 29.6% at 250 μg/mL and 55.6% at 500 μg/mL, while in *Staphylococcus aureus*, percent decline in biofilm formation due to derivative **1b** was 20.6% at 50 μg/mL, 31.6% at 100 μg/mL, 42.7% at 250 μg/mL and 68.6% at 500 μg/mL (Figure 5 and 6).

Similarly, in the presence of Isoxazolone derivative **1j**, percent reduction seen in biofilm formation of *Pseudomonas aeruginosa* was 29.64% at 25 μg/mL, 36.72% at 50 μg/mL, 40.26% at 100 μg/mL, 52.21% at 250 μg/mL and 100% at 500 μg/mL, while, percent decline in *Staphylococcus aureus* biofilm formation by derivative **1j** was 41.9% at 25 μg/mL, 56.98% at 50 μg/mL, 61.64% at 100 μg/mL, 68.51% at 250 μg/mL and 71.39% at 500 μg/mL.

Based on the results of biofilm estimation carried out by crystal violet assay it was revealed that Isoxazolone derivative **1j** exhibited better biofilm inhibitory potential as compared to Isoxazolone derivative **1b**. Derivative **1j** at the concentration of 500 μg/mL showed complete inhibition of biofilm formation in *Pseudomonas aeruginosa* as well as 71.39% reduction in *Staphylococcus aureus*. Biofilm formation is a quorum sensing mediated process. Thus, it can be inferred that Isoxazolone derivatives **1b** and **1j** have quorum quenching potential against both Gram negative and Gram positive human pathogenic bacteria.

Reduction of biofilm formation was not associated with growth inhibition, as there was no significant decrease in the viable planktonic cells with the increase in concentration of

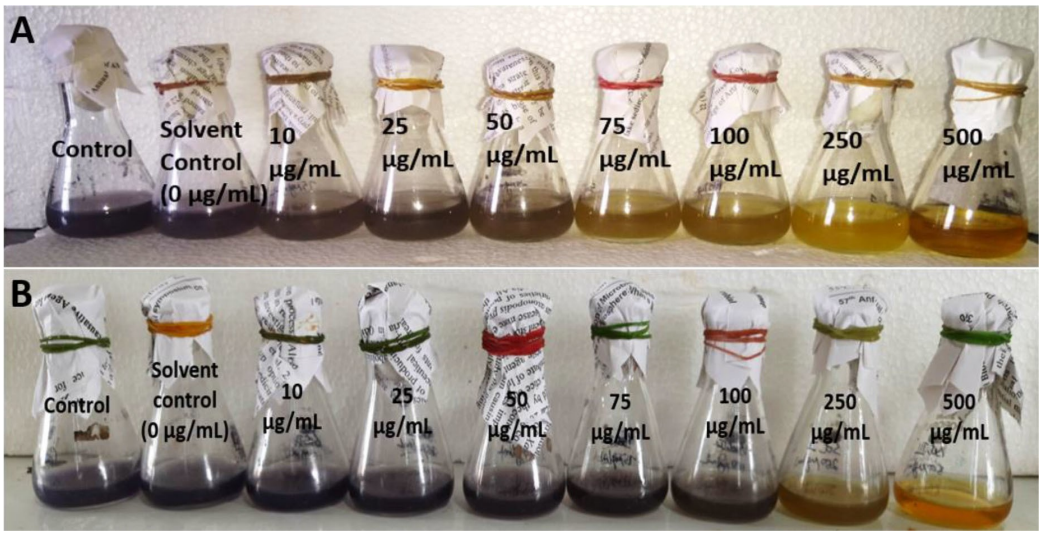

Figure 3. A) Culture broths of *Chromobacterium violaceum* showing decreasing violacein production with increasing concentration (10–500 μg/mL) of Isoxazolone derivative **1b**. B) Culture broths of *Chromobacterium violaceum* showing decreasing violacein production with increasing concentration (10–500 μg/mL) of Isoxazolone derivative **1j.**

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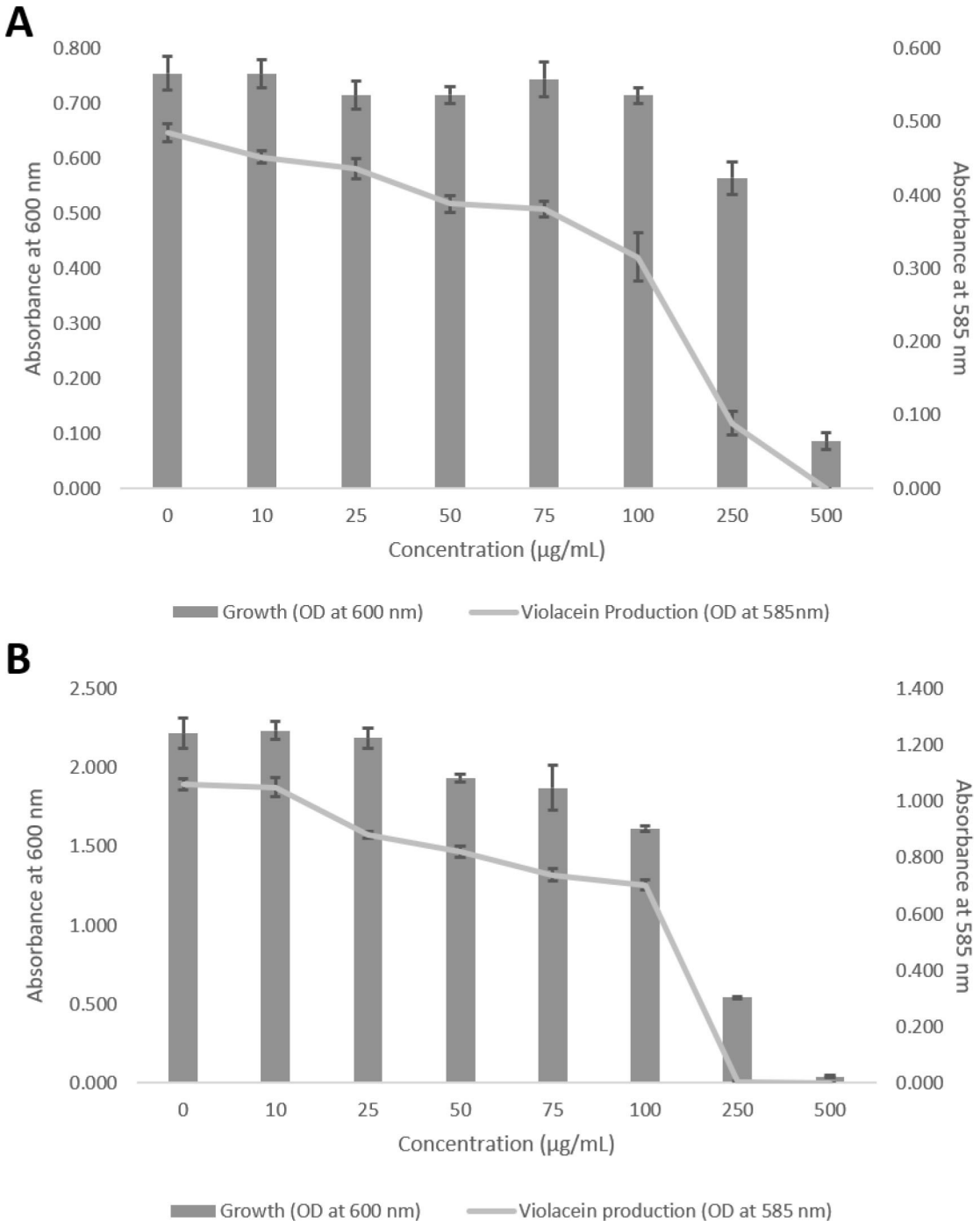

Figure 4. A) Graph showing inhibition of Violacein production in *Chromobacterium violaceum* with the increasing concentration (10–500 µg/mL; 0µg/mL as solvent control) of Isoxazolone derivative **1 b**. B) Graph showing inhibition of Violacein production in *Chromobacterium violaceum* with the increasing concentration (10–500 µg/mL; 0 µg/mL as Solvent control) of Isoxazolone derivative **1 j.**

Isoxazolone derivatives **1 b** and **1 j**. Substantial inhibition was seen only at very high concentrations of Isoxazolones.

Quorum quenching based pigment inhibition as well as antibiofilm studies have been performed and reported in literature with several natural and synthetic compounds (Table 3). Concentration dependent inhibition of pigment production and biofilm formation by natural biomolecules (Plant extracts, Essential oils, spices, microbial extracts),[16,17,47,48] synthetic compounds (p-coumaric acid, N-acyl cyclopentilamides),[49,50] as well as nanomaterials (Ag, ZnO, AgCl-TiO_2),[18,51,52] is known.

The substituted Isoxazolone derivatives **1 b** and **1 j**, proved to have a remarkable quorum quenching potential causing considerable reduction in violacein production, and biofilm

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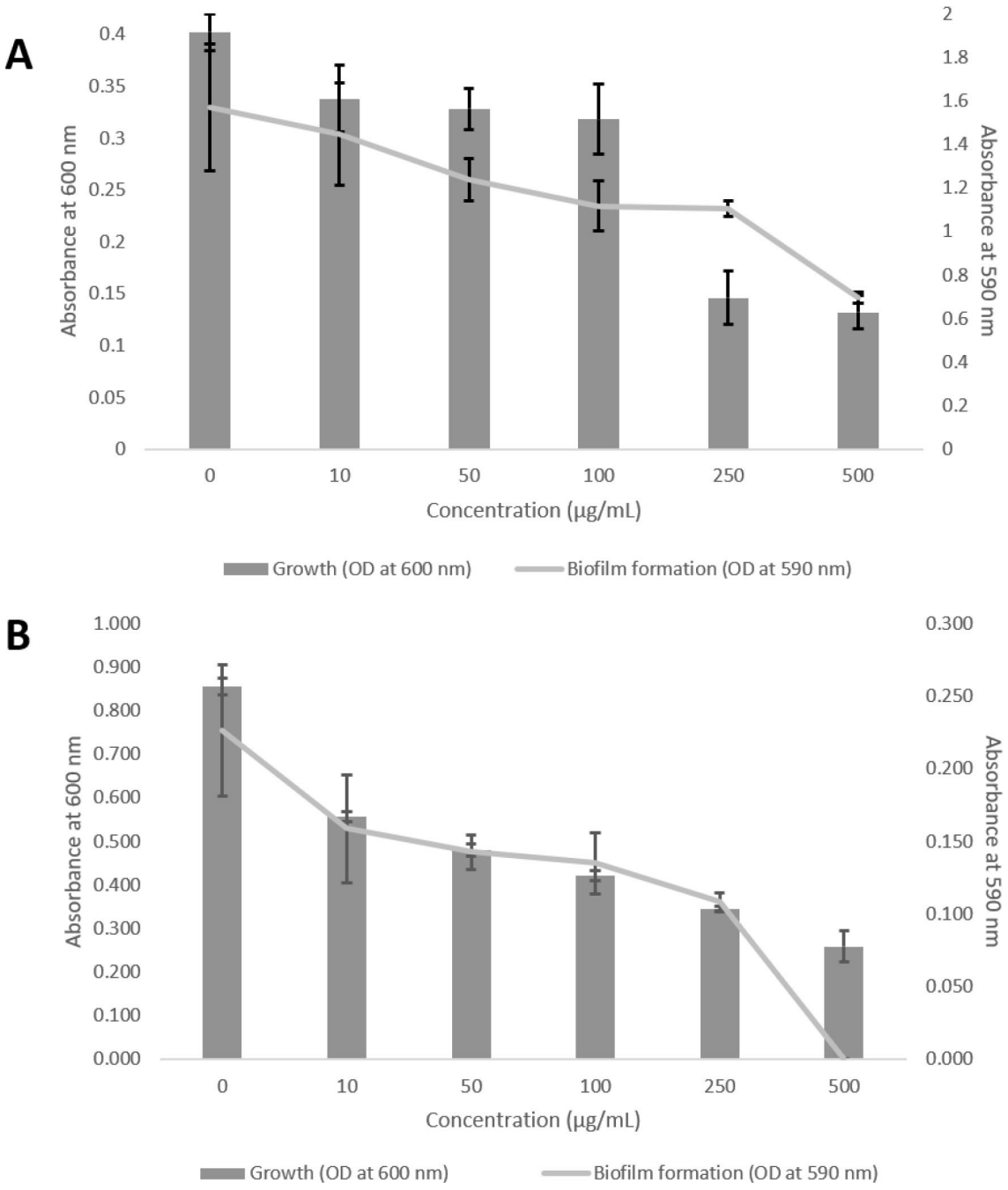

Figure 5. A) Graph showing inhibition of biofilm formation in *Pseudomonas aeruginosa* with the increasing concentration (10–500 µg/mL; 0 µg/mL as solvent control) of Isoxazolone derivative **1 b**. B) Graph showing inhibition of biofilm formation in *Pseudomonas aeruginosa* with the increasing concentration (10–500 µg/mL; 0 µg/mL as solvent control) of Isoxazolone derivative **1 j.**

formation. The ability of isoxazolone derivatives to inhibit both biofilm formation and violacein (virulence factor) projects huge applications in the medical field, since biofilm formation is a crucial factor contributing towards antibiotic resistance and pathogenesis of human pathogens, such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*,[46] while violacein production is virulence factor in opportunistic pathogen *Chromobacterium violaceum* controlled by quorum sensing mechanism.

In the present investigation, the substituted Isoxazolone derivatives **1 b** and **1 j** are capable of inhibiting biofilm formation in both Gram negative and Gram positive human pathogenic bacteria, along with pigment inhibition which is responsible for virulence in *Chromobacterium violaceum*. Earlier reports show studies on biofilm inhibition either in Gram negative or Gram positive bacteria. In addition, only few reports have described the ability of a compound to have both pigment inhibitory potential as well as antibiofilm activity. In

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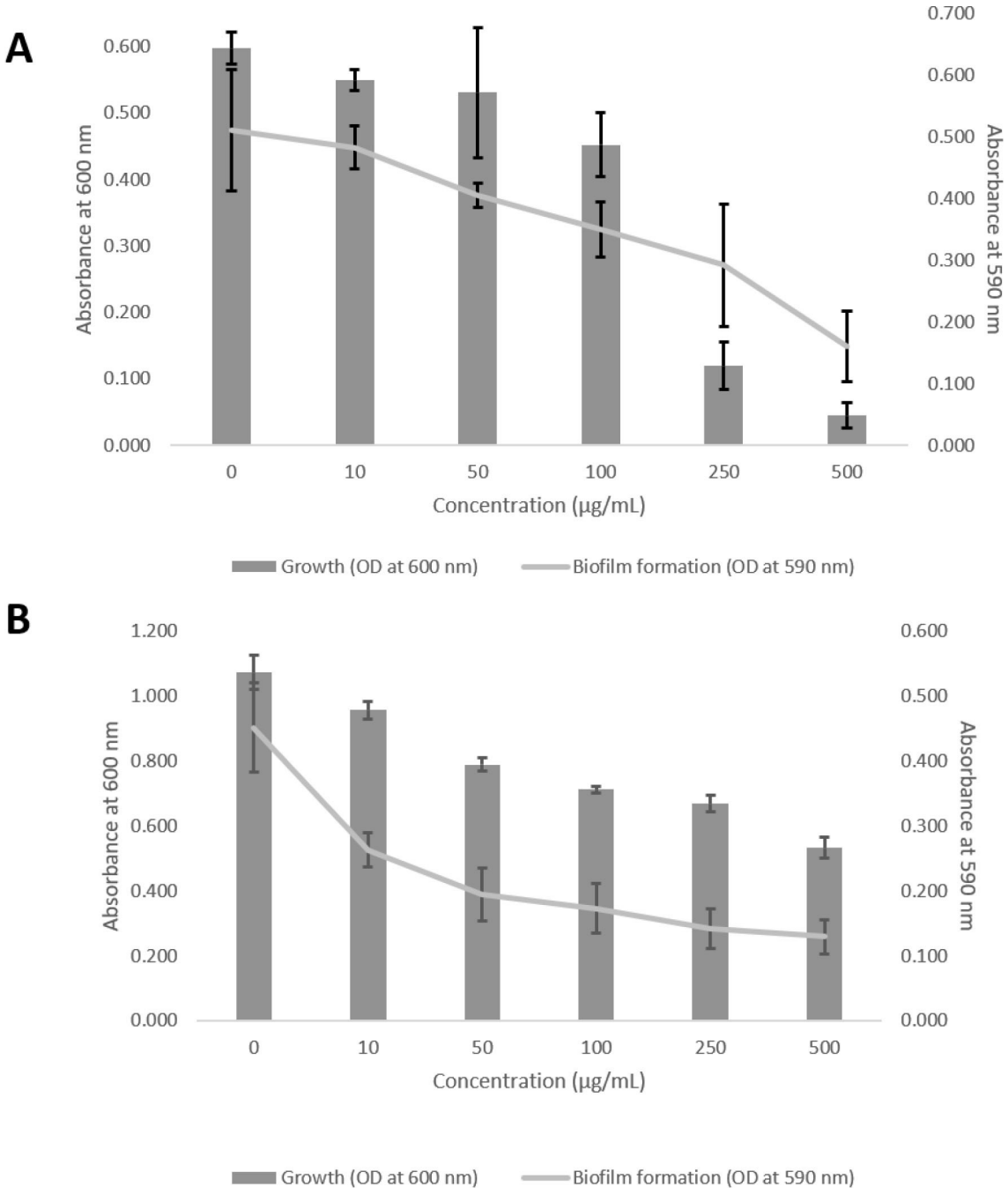

Figure 6. A) Graph showing inhibition of biofilm formation in *Staphylococcus aureus* with the increasing concentration (10–500 µg/mL; 0 µg/mL as solvent control) of Isoxazolone derivative **1 b**. B) Graph showing inhibition of biofilm formation in *Staphylococcus aureus* with the increasing concentration (10–500 µg/mL; 0 µg/mL as solvent control) of Isoxazolone derivative **1 j.**

the available literature, various Isoxazolone derivatives are reported only for their antimicrobial, aniticancer or antioxidant activities.[53,54] The present study is the first report of quorum quenching ability of Isoxazolone derivatives against both Gram positive and Gram negative bacterial human pathogens.

Literature analysis[20–44,55–57] revealed this synthetic methodology to be one of the robust method for preparing Isoxazolone derivatives with more labile functional groups. Thus provide scope for development of functionally sensitive or even optically active Isoxazolones, keeping in mind their growing importance in medicinal field.

Conclusion

An easy, high yielding, versatile, purification free, multigram scalable, aqueous method for the synthesis of Isoxazolones using aldehyde, ethylacetoacetate, hydroxylamine hydrochloride with silica (TLC grade) was developed. Some

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Table 3. Previously reported Quorum quenching potential of various natural biomolecules and chemical compounds.

Sr. No.	Source	Metabolite/ Chemical compound	Conc.	Test bacteria	Phenotype inhibited	Ref.
1	Yeast: Candida bombicola 22214	Essential Oils Sophorolipids	20 mg/mL	*Chromobacterium violaceum* CV026	Violacein production	Mukherji and Prabhune [47]
2	Bacteria: *Exiguobacterium indicum* from the rhizosphere of a Sedge species Cyperus laevigatus	3-Benzyl-Hexahydro-Pyrollo[1,2-a]-Pyrazine-1,4-Dione	0.2 −1.2 mg/mL	Pseudomonas *aeruginosa* PAO1	Biofilm formation, virulence factor production, swimming and swarming motility	Singh et al. [17]
3	Leaves of *Mangifera indica*	Extracts	100–1000 μg/mL	*Chromobacterium violaceum: Pseudomonas aeruginosa* PAO1, *Aeromonas hydrophila*	Violacein Production; Biofilm formation and virulence factor production	Hussain et al. [16]
4	Clove	Essential oil Eugenol	Upto 400 μM	*Chromobacterium violaceum*	Violacein production	Zhou et al. [48]
5	Synthetic	p-coumaric acid	0.2 mg/mL	*Chromobacterium violaceum*	Violacein production	Chen et al. [49]
6	Synthetic	N-acyl cyclopentilamides	~250 μM	*Pseudomonas aeruginosa*	Virulence factor production and biofilm formation	Ishida et al. [50]
7	Synthetic	Silver Nanowires	4 mg/mL	*Chromobacterium violaceum* *Pseudomonas aeruginosa*	Violacein production Biofilm formation	Wagh et al. [51]
8	Synthetic	Zinc Oxide Nanoparticles	50–400 mg/L	*Pseudomonas aeruginosa*	LasB gene and AHL production	Al-Shabib et al. [52]
9	Synthetic	AgCl-TiO_2 Nanoparticles	100–500 mg/L	*Chromobacterium violaceum*	Violacein production	Naik and Kowshik, [18]

substituted isoxazolone derivatives have excellent quorum quenching potential, capable of inhibiting pigment production (violacein) and biofilm formation in *Pseudomonas aeruginosa* ATCC 27853 and *Staphylococcus aureus* ATCC 6538. These derivatives have potential application in the medical field as a promising quorum quenching weapon against multidrug resistant Gram positive and Gram negative bacterial human pathogens.

Supporting Information Summary

Detailed experimental procedure for synthesis of Isoxazolones, spectral data of all the prepared compounds, procedure for quorum quenching analysis, and NMR and Mass spectra are included in the supporting information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Heterocycles · Isoxazolone · Quorum quenching · Silica · Synthetic methods

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