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ARTICLE

(S)-4-(4-aminobenzyl)-2-oxazolidinone based 2-azetidinones for antimicrobial application and luminescent sensing of divalent metal cations

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Abstract

The impact of linezolid as an antibiotic against gram-positive bacteria has inspired synthetic chemists to use oxazolidinones as substrate molecule in the synthesis of newer scaffolds with important pharmacological implication. The oxazolidin-2-ones are key intermediates in the synthesis of many interesting biologically active compounds. Design and synthesis of a new series of (S)-4-(4-aminobenzyl)-2-oxazolidinone based multifunctional azetidinones were accomplished. Synthesis of the scaffolds was performed through a multi-step reaction process involving protection of amine functional group, conversion of protected (S)-4-(4-aminobenzyl)-2-oxazolidinone to its acetic acid derivative and then to acid chloride, and finally coupled with different substituted aromatic imines under mild reaction conditions in presence of an appropriate base. Structural characterization was carried out using conventional spectroscopic techniques. The compounds were screened for their antimicrobial activity against gram-positive and gram-negative bacteria and were found to possess better and promising antimicrobial property than some of the reported antimicrobial drugs like disulfonamide and tetracycline. Additionally, the scaffolds also exhibit prominent sensing property for divalent metal cations like Cu^{2+}, Zn^{2+}, and Ni^{2+}, through fluorescence quenching effect.

1 | INTRODUCTION

Multi-drug resistant bacteria strains are attracting significant scientific interest because most of the conventional antibiotics are becoming dysfunctional.[1,2] Therefore, development of new series of antibiotics has become an important research objective. Initially, antimicrobial peptides were considered for development of such drugs.[3–5] But certain limitations such as proteolytic degradation by microbial enzymes together with toxicity factor and higher production cost have restricted the use of such products.[6] The chemistry of β-lactams has taken an important place in organic chemistry after the discovery of penicillin by Sir Alexander Fleming in 1928. Even now, research in this area is stimulated because of the increasing development of drug resistant strains in bacteria to widely used antibiotics of this type. Therefore, there is a need for functionalized β-lactams or for new active principles in β-lactam series. Number of broad-spectrum chemotherapeutic agents used to treat bacterial infection and microbial diseases, including penicillin,[7] cephalosporin,[8] carbapenem,[9] and monobactams[10] contain 2-azetidinone (β-lactams) ring as a common structural feature. Nitrogen and oxygen containing heterocycles such as 2-oxazolidinones,[11] 1, 3-oxazinan-2-ones,[12] 2 oxazolines,[13] and oxazines[14] are important building blocks for synthesis of biologically active compounds. Synthetic chemists usually employ molecular building blocks for design and synthesis of new scaffolds for

important biological applications. Oxazolidin-2-ones are appearing as a key intermediate in many organic syntheses leading to novel biologically active compounds that possess potential antimicrobial activity. For example, (S)-5-aminomethyl 2-oxazolidinone is the core structure in the antibacterial agent linezolid,[15,16] the first member of synthetic oxazolidinone antibiotic effective against resistant gram-positive bacteria.[17,18] Several of these products have been commercialized while few others were discontinued due to inadequate pharmacokinetics, safety risks, and other factors. Oxazolidinone based compounds like torezolid phosphate is being tested clinically for acute bacterial skin infections.[19] Therefore, although oxazolidinone-based azetidinones sometimes might have some limitations for therapeutic use, there is still enough scope of invention of new scaffolds based on oxazolidin-2-ones for important therapeutic applications. Gram-positive resistance has gradually become a serious therapeutic problem, which have generated more interest in antibiotic research and development. These organism exhibit resistances to most of the available agents.[20] The gram-positive bacteria, such as staphylococci and enterococci are posing as a serious threat with existing antimicrobial agents due to the development of resistance. These bacteria sometimes show multidrug resistance, even to the well-known vancomycin drug.[21] Usually vancomycin always works against multidrug resistant staphylococci. This happens because of improper and indiscriminate use of antibiotics. For example, streptococcus pneumonia, which was earlier easily treated with inexpensive antibiotics, nowadays its treatment is becoming a major problem for the physicians.[22] Failure to combat such multi-drug resistant organism may lead to patient mortality. Oxazolidinones has been gaining consideration as a potent molecule for development of antimicrobial agents[23] because several characteristics possessed by this class of molecule are suitable for treatment of gram-positive bacteria and can be specifically employed for treatment of multi-drug resistant gram-positive bacteria.[24] Oxazolidines are also suitable for development of cost economic antimicrobial agents.[25] Therefore, there is a need to look for newer scaffolds based on oxazolidinones and study their antibacterial activity and pharmacological significance (Data S1).

On the other hand, such type of molecules also shows potential applicability for detection and removal of heavy metals from biological and aquatic systems, even at low concentration.[26] Because of deleterious effects of heavy metals, they are generally considered as potential environmental pollutants even at low concentrations.[27] Although several modern technologies have been introduced for this purpose including atomic absorption spectroscopy,[28] X-ray fluorescence spectroscopy,[29] electrochemical methods,[30] yet the growing popularity of many of these technologies have shortcomings such as poor solubility, low cross sensitivity, and low matrix interference.[31] Work presented here is embodiment of such efforts to find out efficient molecular framework for using as potent antimicrobial agent. Additionally, the scope of using such molecular entities for detection of heavy metals such as copper (Cu), Nickel (Ni), and zinc (Zn) has also been investigated, keeping in mind that development of efficient organic molecular scaffolds for rapid and easy detection of heavy metals often attracts significant scientific interests.

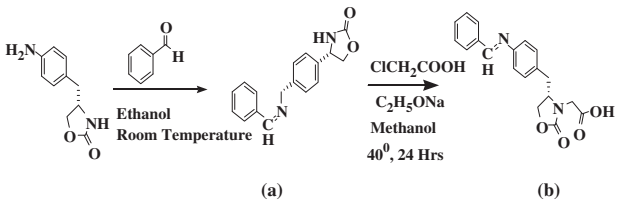
2 | RESULTS AND DISCUSSION

Oxazolidinone analogues have been established as a potential inhibitor for the growth of pathogenic bacteria. They are effective against a wide spectrum of gram-positive, gram-negative, and anaerobic bacteria. Biological activity of such molecules has been tested and documented in literature. In evaluating their biological activity, apart from structure-activity relations, other factors have also been taken into account. For example, consideration of structure space evolves and chirality is very much important. Because binding affinity can be different for different enantiomers. Choosing the right chiral structure creates the opportunity for the design of appropriate drug molecule for diverse application. Thus, key chiral structures are an important building block for generation of new libraries of chiral molecules with biological significance. In contrary, use of a mixture of enantiomers may lead to inimical effects.

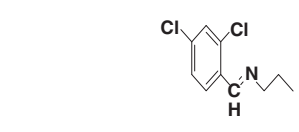
A good inhibitor is expected to have better inhibitory power than the standard ones. Most studies have shown that the incorporation of chiral auxiliary into oxazolidinone moiety dramatically improves inhibitory power.[32] Usually at a molecular level, biological systems, particularly for mammals, composed of macromolecular units like proteins, glycolipids, and polynucleotides, which in turn formed from chiral building blocks of L-amino acids and D-carbohydrates. The process of drug action or disposition involves interaction between the optical isomer of a drug molecule and chiral biological macromolecule.[33] Therefore, these interactions in biological system might even involve stereo selectivity. Normally bonding interaction results between the functional site of a drug molecule and complementary site in the receptor surface or enzyme active site. Steric factors and hence the conformation, might play significant role in case of such interactions and for stereoisomers three-dimensional spacing of the groups need to be taken into account. Based on these facts, we have designed a series of azetidinones based on (S)-4-(4-aminobenzyl)-oxazolidin-2-one. Structure of the synthesized compound is depicted in Figure 1.

The sequence of synthetic steps adopted for the synthesis of 2-((S)-4-((E)-4-(benzylideneamino)phenyl)-2-oxazolidin-3-yl) acetic acid from the (S)-4-(4-aminobenzyl) oxazolidin-2-one is depicted in Scheme 1.

A series of molecules were synthesized by in situ conversion of 2-oxazolidinone acetic acid derivatives into corresponding acid chloride and then coupling with a set of aromatic imines. As a representative case, we have used propyl amine and butyl amine as aliphatic amine, and aniline as aromatic amine for imine synthesis. The purpose of using propyl and butyl amine for the synthesis

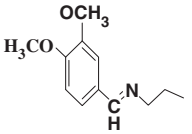


SCHEME 1 Synthesis of (A) Imines and (B) 2-((S)-4-((E)-4-(benzylideneamino) phenyl)-2-oxazolidin-3-yl) acetic acid



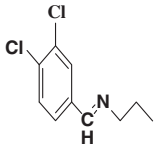
(*E*)-*N*-(2,4'-dichlorobenzylidene)propan-1-amine

1



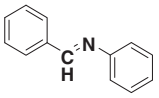
(*E*)-*N*-(3,4'-dimethoxybenzylidene)propan-1-amine

2



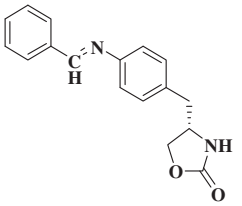
(*E*)-*N*-(3,4'-dichlorobenzylidene)propan-1-amine

3



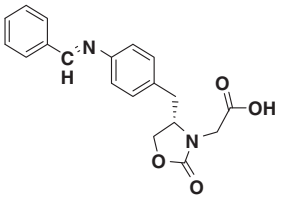
(*E*)-*N*-benzylidenebenzenamine

4



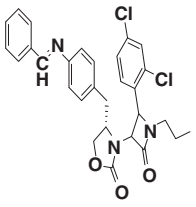
(*S*)-4-((*E*)-4-(benzylideneamino)benzyl)oxazolidin-2-one

5



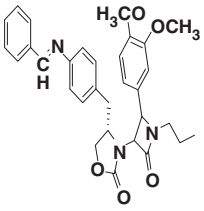
2-((*S*)-4-((*E*)-4-(benzylideneamino)benzyl) -2-oxooxazolidin-3-yl)acetic acid

6



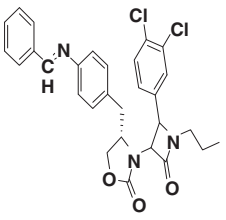
(*S*)-4-((*E*)-4-(benzylideneamino)benzyl)-3-(2-(2,4'-dichlorophenyl)-4-oxo-1-propylazetidin-3-yl) oxazolidin-2-one

7



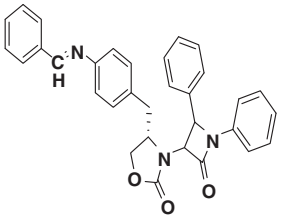
(*S*)-4-((*E*)-4-(benzylideneamino)benzyl)-3-(2-(3,4'-dimethoxyphenyl)-4-oxo-1-propylazetidin-3-yl) oxazolidin-2-one

8



(*S*)-4-((*E*)-4-(benzylideneamino)benzyl)-3-(2-(3,4'-dichlorophenyl)-4-oxo-1-propylazetidin-3-yl) oxazolidin-2-one

9



(*S*)-4-((*E*)-4-(benzylideneamino)benzyl)-3 -(2-oxo-1,4'-diphenylazetidin-3-yl)oxazolidin-2-one

10

FIGURE 1 Chemical structures of the imines (**1**-**5**) and acetic acid product (**6**) and azetidinones (**7**-**10**)

is to investigate the effect of increasing length of side chain on the inhibitory activity of the products. The following synthetic scheme (Scheme 2) was applied for synthesis of the azetidinones.

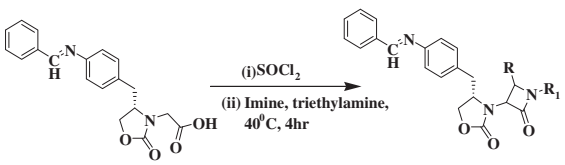
Mechanistic route for the formation of the azetidinones of (S)-4-Aminobenzyl-oxazolidinone-2-one can be depicted as shown in Scheme 3.

Research interests of many scientists are focusing on the search for new antimicrobial molecules because of the fact that many organisms are developing resistant to the available antimicrobials. This happens due to frequent use of antibiotics. A series of small molecules were synthesized and tested for their potential utility as antimicrobial agent. For that purpose, the zone of inhibition test, which is also known as, Kirby-Bauer Test, was carried out over an agar plate using a sterile swab and then incubating in the presence of the antimicrobial agent.[34] The bacterial samples used for the purpose were *Escherichia coli* and *B. subtilis*. Usually, if the bacteria are susceptible to the antimicrobial agent then a zone of inhibition appears on the agar plate but if they are resistant to the antimicrobial agent then no inhibition zone appears on the plate. Therefore, greater the inhibition zone, the more antimicrobial potential the compound has. Zone of inhibition calculated for the series of products against *Bacillus subtilis* (MTCC 441) and *E. coli* (MTCC 739) is represented in Table 1, along with the values calculated for the standard drug Chloramphenicol.

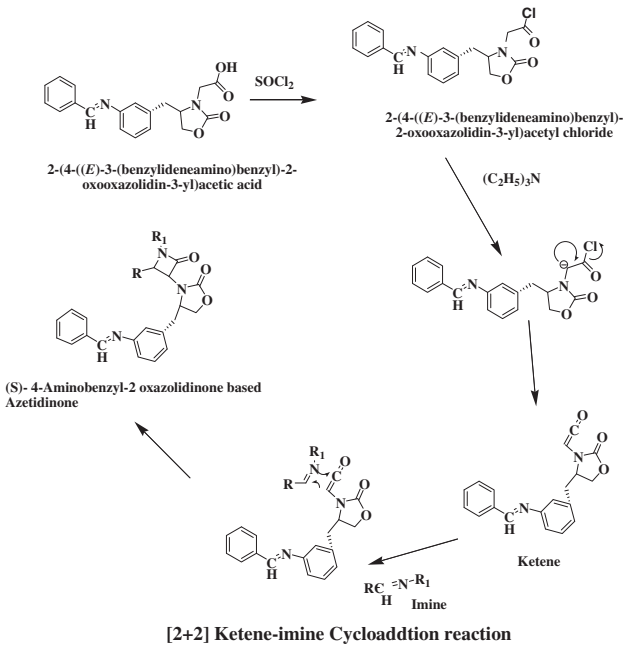
The values presented in the table strongly indicates that the compounds exhibit good to excellent antimicrobial activity and even in few cases the values are closer to the values of chloramphenicol. It has been observed that in case of compound **7**, **8**, and **10**, even with 30 μg/mL concentration, the compounds exhibit some sort of antimicrobial activity. Further, as indicated in the table, antimicrobial activity of the azetidinones are far better compared to the antimicrobial activity of the parent acetic acid derivative of (S)-4-aminobenzyl-2 oxazolidinone(**6**). For *Bacillus subtilis*, compound **7** showed excellent activity at 30 μg/mL while **7**, **8**, **9**, and **10** did not. However, the overall comparison shows that **8** had the highest activity for *Bacillus subtilis* as it was showing the highest inhibition zone (23 mm) at 100 μg/mL. General observation is that all the products have good to excellent antimicrobial activity against *Bacillus subtilis*.

Similarly, for *E. coli*, compound **7** showed the highest antimicrobial activity as it was showing the highest inhibition zone of 24 mm at 100 μg/mL. Compound **7** showed antimicrobial response even at 30 μg/mL (11 mm). Compound **8** and **10** also showed antimicrobial activity at the lowest concentration, that is, 30 μg/mL. Therefore, overall conclusion arrived from the results is that the molecules are equally responsive against *E. coli*. We have also observed that with increase in the length of the alkyl chain of the imine unit, the antimicrobial activity of the compound decreases. Among all the azetidinones reported here, compound **7** has higher potential as antimicrobial agent. However, all the other molecules exhibit good antimicrobial activity.

For more clear understanding of the efficacy of the reported azetidinones as antimicrobial agent, we have also calculated the zone of inhibition of standard antimicrobial drug chloramphenicol (one of the well-known broad spectrum antibiotics) against *B. subtilis* and *E. coli*, under identical condition. Results of the analysis are shown in Table 1 along with the respective values for the reported compounds. Values indicate maximum inhibition of 37 mm against *B. subtilis* and inhibition zone of 38 mm against *E. coli* at 100 μL. These data revealed the fact that although the azetidinones reported in this work have lesser activity than the standard chloramphenicol, still respective values for the molecules are significant enough for using as antimicrobial agent and even few of them can be advocated as a substitute for the standard drug chloramphenicol.

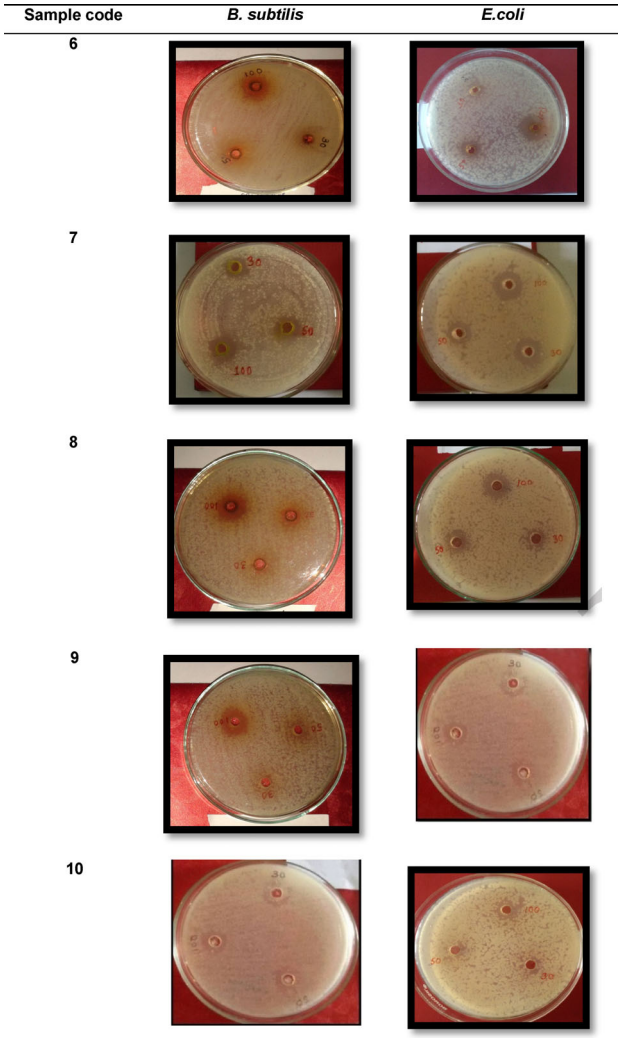


SCHEME 2 Synthetic scheme of the azetidinones of (S)-4-Aminobenzyl-oxazolidinone-2-one



SCHEME 3 Mechanistic route for formation of (S)-4-aminobenzyl-2 oxazolidinone based azetidiones

The zone of inhibition of azetidinone and standard chloram-phenicol are depicted in Figure 2.



3 | STRUCTURE ACTIVITY RELATIONSHIP

Bioisosterism is an important aspect related to drug discovery, where modifications to parts of a molecule are performed to improve some properties while maintaining others.

In this work, four types of bioisoteric replacements (modifications of substituents in the aromatic unit) were performed in the parent compound (S)-4-((E)-4-(benzylidene-amino)benzyl)oxazolidin-2-one, with the objective of manipulating the biological properties of the compounds. For the two different cases, that is, with *B. subtilis* and *E. coli*, the zone of inhibition for different concentration of the azetidinones have been plotted in the form of a histogram, as shown in Figure 3. The histogram clearly displays several interesting facts about the biological activities of the compounds. For *B. Subtilis*, substantial increase in antimicrobial activity was noted for the methoxy (—OCH_3) substituted azetidinone (8) and hence it can be concluded that the methoxy group positively influences the inhibitory effect of the azetidinones. Compared to gram-negative bacteria, *E. coli*, the inhibitory effect of 8 is more prominent in case of gram-positive bacteria *B. Subtilis*.

Similarly, the histogram also clearly indicates that compared to other substituted products, chlorosubstituted products **7** and **10** possess remarkably high antimicrobial activity for gram-positive bacteria as well as for gram-negative bacteria. In this case, the 2, 4-dichloro substituted compound **7** possess relatively higher zone of inhibition than 3, 4-substituted ones. As expected with substituted aromatic compounds, we have noted that substitution at ortho and para position exerts more electronic influence than in meta position. The same is reflected in case of these two compounds and the

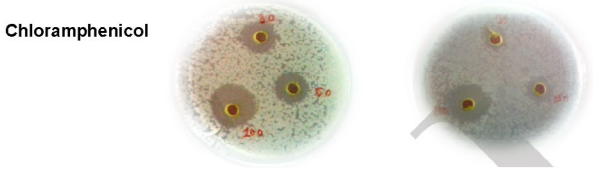


FIGURE 2 Zone of inhibition of the 2-azetidinones and standard chloramphenicol against *B. subtilis* and *E.coli* (disk diffusion method)

TABLE 1 Zone of inhibition of samples

Compound	Zone of inhibition in diameter (mm)					
	Bacillus subtilis (MTCC 441)			*Escherichia coli* (MTCC 739)		
	30 µL	50 µL	100 µL	30 µL	50 µL	100 µL
6	—	07	11	—	14	16
7	12	18	22	11	17	24
8	—	16	23	09	13	18
9	—	12	13	—	09	12
10	—	14	21	16	20	18
Chloramphenicol	30	34	37	31	36	38

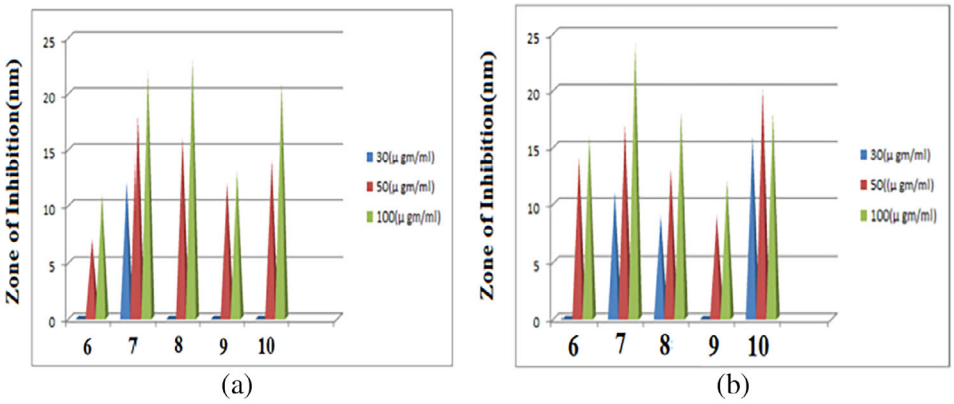


FIGURE 3 Histogram plotted for zone of inhibition of compound **6**, **7**, **8**, **9**, and **10** against *B. Subtilis* (a) and *E. coli* (b), for three different concentrations of the azetidinones

TABLE 2 Log *P* values of synthesized compounds

Compound	Log *P* value
6	2.98
7	6.37
8	5
9	6.37
10	6.09

respective inductive effect generated by the chlorine substituents creates the differences in their antimicrobial activities for the two azetidinones, compounds **7** and **10**. Another important observation from the histogram is that azetidinones with no substituents in the aromatic ring also possess significant antimicrobial activity. However, compared to substituted azetidinones (compounds **7**, **8**, and **10**), their zone of inhibition was less. Therefore, substituents in the azetidinones markedly influence the biological activities of the compounds.

For the gram-positive bacteria, *B. Subtilis*, compared to chloro substituents (—Cl), the methoxy (—OCH_3) substituent has a more positive influence on the biological activity of azetidinones while reverse observation was noted for the case of gram-negative bacteria, *E. coli*. For *E. coli*, the maximum inhibition zone was recorded for 2, 4-dichloro azetidinone. This fact indicates that the inductive effect of the chlorine group is more prominent than that of methoxy (—OCH_3) group. On the mechanistic front, the azetidinone derivatives interfere with the enzymes that are actively involved in the synthesis process of the bacteria cell walls. They interfere with the enzymes, which are required for the synthesis of the peptidoglycan layer that binds to the terminal D-alanine residues of the nascent peptidoglycan chain,[35] thereby preventing the cross-linking steps required for stable cell wall synthesis. Azetidinones are also taking advantage of the bacterial ribosomes that differ in structure from their counterparts in eukaryotic cells. Therefore, they can selectively bind to the 30S subunit of the ribosome, whereas chloramphenicol binds to the 50S subunit.[36]

4 | LOG P VALUES AND ANTIBACTERIAL ACTIVITY

Lipophilicity is one of the most interesting physicochemical properties for biological activity of drugs. Positive value of log *P* denotes the lipophilic behaviour of the drugs. Table 2 shows the predicted log *P* values from chemaxon for the synthesized compounds. From the table, we have observed that compared to substituted acetic acid product **6**, log *P* values are higher for other four compounds (**7**-**10**). This fact reveals better penetrating ability of the newly synthesised compounds through a polar cell membranes and hence enhanced antibacterial activity than the parent compound. As compound **7** possess the highest log *P* value, therefore apparently it can be claimed to have highest zone of inhibition, which we practically observed. However, compounds with same log *P* values may have different levels of antibacterial activity depending on the nature and position of substituents on the molecule. In our case, although compounds **7** and 9 possess the same log *P* values, but compound **7** exhibit more antimicrobial activity compared to compound **9**. Both the molecules are identical and possess same type of substituents in the aromatic ring of the imine unit, but the positions of substituents are different in both which eventually causes the differences in their antimicrobial activities.

5 | MINIMUM INHIBITORY CONCENTRATION (MIC)

MICs of the extracts were determined for the bacterial strains which were sensitive to the extracts in the well diffusion assay. A broth macro-dilution method was used

TABLE 3 MIC and MBC values of different compounds against bacterial strain *B. subtilis (*MTCC *441)* and *E. Coli*

Tested organism		7 (μg/ml)	8 (μg/ml)	9 (μg/ml)	10 (μg/ml)
Bacillus subtilis (441)	MIC	15.62	31.25	31.25l	31.25
	MBC	15.62	62.50	62.50	62.50
	MBC/MIC	1	2	2	2
Escherichia coli (MTCC 739)	MIC	15.62	15.62	31.25	15.62
	MBC	15.62	15.62	62.50	15.62
	MBC/MIC	1	**1**	2	1

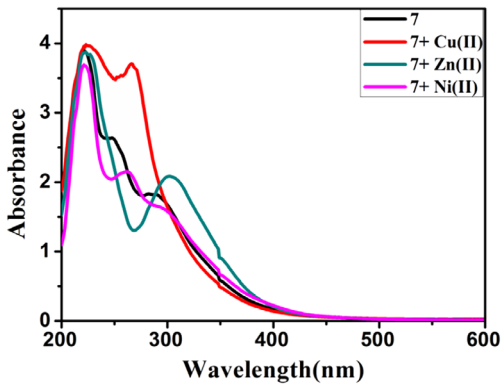


FIGURE 4 UV-visible spectra of compound **7** (0.01 M) in the absence and presence of Cu^{2+}, Ni^{2+}, and Zn^{2+} ions in MeOH-H_2O (1/1, vol/vol) solutions

with a slight modification.[37] The broth dilution method is a simple procedure for testing a small number of isolates, even for a single isolate. Stock solution of 2 mg/mL of the plant extract was prepared by mixing with DMSO. A row of sterile screw capped tubes containing 2 mL of nutrient broth each was arranged. Plant extract (2 mL) from appropriate stock solution was mixed with the nutrient broth. The content was mixed using a pipette and 2 mL was transferred to the second tube. The content of the second tube was mixed well and 2 mL of it was transferred to the next tube. The dilution was continuously prepared by following the same procedure as mentioned above.

Thus, concentrations of 1000, 500, 250, 125, 62.5, 31.25, 15.62, 7.8, and 3.9 μg/mL were prepared. The last tube without plant extract was used as control. The tubes were then inoculated with 50 μL of broth culture of the test organism. After incubation of the cultures at 37°C for 18 hours, the MIC value was determined. MIC is expressed as the lowest dilution that can inhibit the growth of an organism and is determined by the absence of turbidity in the tube. MIC values determined for the reported compounds against bacterial strain *B. subtilis* (MTCC *441)* and *E. coli* (MTCC 739) are tabulated in Table 3.

Values represented in the table confirm the fact that the reported compounds exhibit significant antimicrobial activity against the bacterial strains of *B. subtilis* and *E. coli*. For *B. subtilis*, MIC value for compound **7** is quite good (15.62 μg/mL) compared to the other three products **8**, **9**, and **10**. MIC value for these three products is 31.25 μg/mL. This fact reflects the superiority of compound **7** over the other three molecules with respect to *B. subtilis*. Similarly, considering the case of *E. coli*, from the MIC value it can be stated that Compounds **7**, **8**, and **10** showed highest activities compared to **9**. Available literature data indicates that disulfonamide, which is a very important antimicrobial agent, shows minimum activity at 100 μg/mL against *E. coli*.[38] From Table 2, we can also observe that the minimum bactericidal concentration (MBC) ranges from 15.62 to 62.50 μg/mL.

According to Fauchère and Avril (2002), an antibiotic is described as bactericidal when the MBC value of an antibiotic on a given strain is close to the MIC ($1 \leq$ MBC/MIC ≤ 2. As the MBC/MIC of our products are well within this range, we can strongly argue that they possess significant bactericidal property.

Similarly another important drug tetracycline shows minimum activity at 25 μg/mL against *B. Subtilis*.[39] Therefore, if we compare the values for the reported compounds with that of the standard ones referred above, we can certainly conclude that products reported in this work has promising antimicrobial activity which in other words reflects the novelty of the work. The compounds can be a better alternative as antimicrobial drug against broad spectrum of gram-negative and gram-positive bacteria. Work presented in this article increases the hope of discovering new bioactive molecules based on (S)-4-Aminobenzyl-2-oxazolidinone, which are potent antimicrobial agents.

6 | ION SENSING PROPERTIES

β-Lactum compounds also possess the scope for using as a receptor molecule for important guest molecules or ions,[40] which unveils the possibility of their application

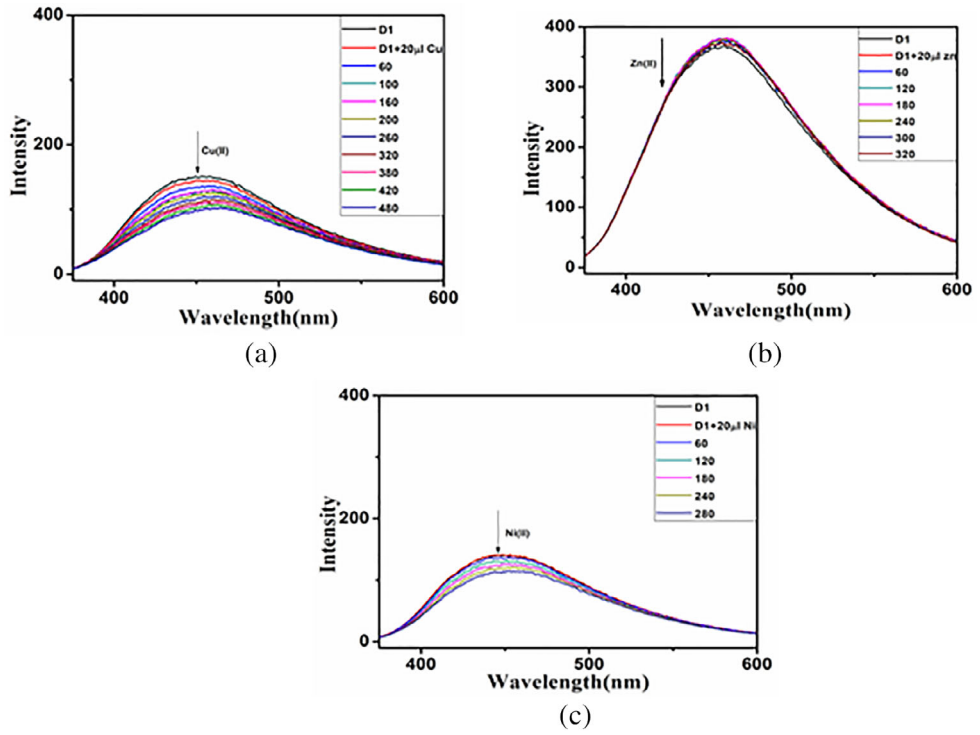


FIGURE 5 Change of emission spectra of compound **7** in the presence of varying concentrations of Cu^{2+}, Zn^{2+}, and Ni^{2+} ions (.01 M) in MeOH-H_2O (1/1,vol/vol) solutions at 360 nm excitation wavelength

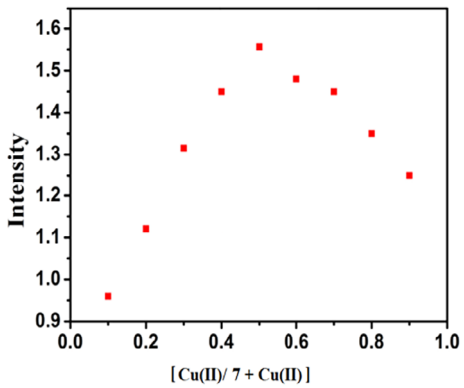


FIGURE 6 Job's plot for stoichiometry of binding between compound 7 and Cu^{2+}

in the field of molecular recognition, host-guest chemistry and for ion sensing. Therefore, with the hope of unambiguously establishing the interaction between the metal ion guest and the azetidinone host, we have examined the sensing property of compound **7** by UV-Visible spectroscopy and fluorescence titration, in which the intensity of the sample was measured by immersing different concentration of the metal ions (Cu^{2+}, Ni^{2+}, and Zn^{2+}) with fixed concentration of the host azetidinone (**7**).

Compound **7** displayed specific interaction pattern with divalent metal cations such as Cu^{2+}, Zn^{2+}, and Ni^{2+} ion, as manifested in Figure 4. It has been observed that UV-visible spectra of compound **7** exhibits an intense absorption band at 220 nm due to $\pi \rightarrow \pi^*$ transition and two mild absorption bands at 250 and 290 nm due to an $n \rightarrow \pi^*$ transition. On addition of Zn^{2+} ion to compound **7** solution, the band at 250 nm disappeared and a new significant band appeared with a red shift at 300 nm. Correspondingly, by addition of Cu^{2+} ion and Ni^{2+} ion, a red shift was noticed for the band at 250 nm. It can be obvious to find that the interaction with the metal ion stabilize the electronic excited state relative to the ground state of the compound **7** (and hence decreased the energy gap between the excited and ground state) resulting in red-shift. Again the observed red shift of the $n \rightarrow \pi^*$ band can be attributed to the interaction between carbonyl oxygen of Oxazolidinone unit and metal ions. Thus, UV-visible experiment revealed effective interaction of compound **7** with the metal cations.

Fluorescence active compounds often used as a sensor to identify metal ions in biological, environmental, and sewage testing[41] and usually response in fluorescence spectroscopy is generally considered more sensitive than UV-visible spectroscopy.[42] Due to fluorescence quenching effects of biologically active ions, development of new molecules as fluorescence turn-on sensors has become an important research area.[43] Being encouraged by the responses in UV-Visible spectroscopy, we also studied the sensing properties of compound **7** as a representative case for the new series of compounds. The sensing property of the compound **7** was monitored by florescence titrations with varying concentrations of Cu^{2+}, Zn^{2+}, and Ni^{2+} ions (.01 M). All the titrations were attained in MeOH-H_2O (1/1, vol/vol) solutions. The fluorescence spectra of compound **7** (.01 M) exhibit an

TABLE 4 The LOD and LOQ calculation of compound **7** for the three metal cations

Metal	SD (S_a)	Slope (b)	Limit of detection (mg/L)	Limit of quantitation (mg/L)
Copper (Cu)	9.44	0.149	0.756	0.402
Nickel (Ni)	7.92	0.143	0.748	0.317
Zinc (Zn)	4.07	0.0789	1.725	0.337

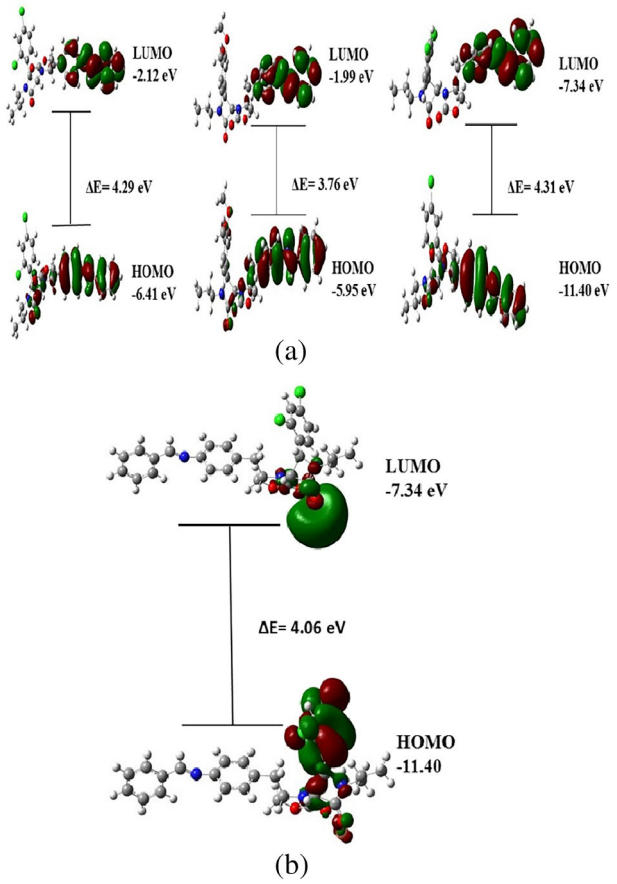


FIGURE 7 Frontier HOMO-LUMO energy gap of (A) compounds **7**, **8**, **9**, and (B) and Compound **7**-Complex with Cu^{2+}

emission band at 458 nm. As illustrated in Figure 5, fluorescence intensity of emission band of the compound **7** gradually declined upon progressive addition of metal ions in all the cases. This dramatic fluorescence quenching of emission band is attributed to the formation of a charge-transfer complex between compound **7** and M^{2+}. Thus, compound **7** may be used as a turn-off fluorescent probe towards divalent metal ions.[44]

For the binding mode study the Job's method was utilised to find out the stoichiometry of binding between the receptor and the metals. For that we have taken a constant total concentration of the ligand and the metal with a continuous variable mole fraction of guest. This study confirms 1:1 stoichiometry for Cu, Ni, and Zn. Figure 6 shows the Job's plot for 1:1 stoichiometry of compound **7** with Cu^{2+}.

The limit of detection (LOD) and limit of quantitation (LOQ) of Cu^{2+}, Zn^{2+}, and Ni^{2+} ions with compound **7** was calculated from the plot of emission intensities vs metal ion concentrations and using the formula $3S_a/$ b & $10S_a/b$, where "S_a" is the SD and "b" is the slope of the straight line.[45] The concentration was found to be at ppm level (Table 4). According to World Health Organisation (WHO) report 2003, the permissible limit of copper, nickel, and zinc in drinking water is 1, .05, and 3.0 mg/L, respectively.[46] The result obtained from the LOD and LOQ are found to be very close to permissible limit and therefore, compound **7** can be used as a chemosensor for the detection of heavy metals in drinking water. Same justification can be believed to hold true for the other three reported compounds.

7 | HOMO-LUMO ENERGY GAP AND CHEMICAL HARDNESS: A DFT STUDY

All the calculations were performed by DFT method with 6-311G(d,p) basis set using Gaussian 09 W software package. HOMO-LUMO energies were studied at time-dependent TD-SCF based on the optimized structure. The molecular HOMO/LUMO picture of the ligands compounds **7**, **8**, and **9** as well as the complex of **7** with Cu^{2+} is depicted in Figure 7.

From the figure there is a clear observation of conjugation and delocalisation of charge over the entire framework. For all the azetidinones, zero charge delocalization was observed on the ring. After formation of the complex, the charge density moved towards the azetidinone ring. This fact confirms the coordination of the azetidinone ring with Cu^{2+}.

The chemical hardness generally rationalizes the relative stability and reactivity of chemical compounds. And large HOMO-LUMO gap is associated with hard and more stable compounds.[47] The definitions of universal concepts of molecular structure stability and reactivity can be provided using DFT method. For definition of hardness ç, following equation is developed[48]:

$\eta = 1/\ 2\ (I - A)$,where I and A are the vertical ionization energy and the vertical electron affinity, respectively.

According to Koopman theorem, the ionization energy and electron affinity can be equalized through HOMO and LUMO orbital energies (EA = −E HOMO and IP = −E LUMO). So, the hardness depends on the

Compound	HOMO/eV	LUMO/eV	Gap/eV	Hardness
7	−6.41	−2.12	4.29	2.14
8	−5.95	−1.99	3.76	1.88
9	−6.35	−2.04	4.31	2.15
7 + Cu^{2+} complex	−11.40	−7.34	4.06	2.03

TABLE 5 HOMO-LUMO energy gap and chemical hardness data

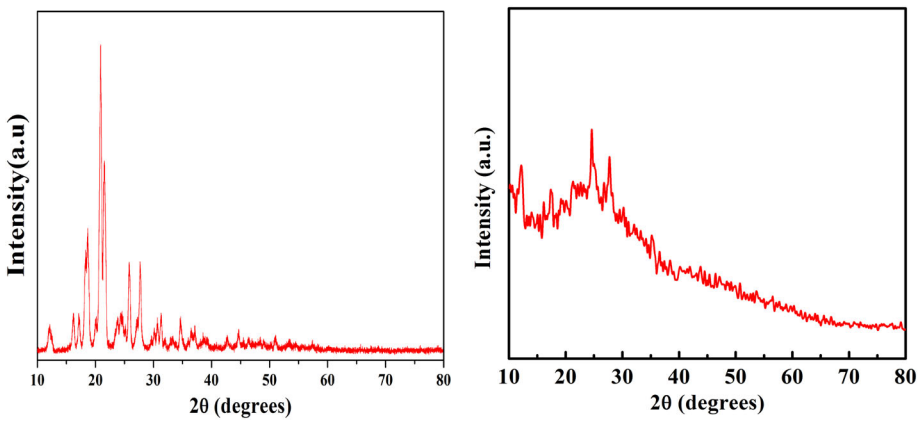


FIGURE 8 X-ray diffraction pattern for compound **5** and **7**

energy gap between HOMO and LUMO orbital. Larger the HOMO-LUMO energy gap, the harder molecule is.

As observed from Table 5 HOMO-LUMO energy gap of compounds **7**, **8**, and **9** were found as 4.29, 3.76, and 4.31 eV, respectively. On the other hand, the energy gap for **7**-Complex with Cu^{2+} was found 4.06 eV. Indeed chemical hardness data also confirms the fact that the hardness of the complex is lesser than the ligand azetidinone. This fact reveals that the metal chelation reduces the stability of the independent medium.

8 | CONCLUSIONS

Successfully synthesized a series of 2-azetidinones based on (S)-4-Aminobenzyl-2 oxazolidinone and evaluated their antibacterial activities against gram-positive and gram-negative bacteria like *B. Subtilis* and *E. Coli*. Results of zone of inhibition and MIC values strongly indicates that these molecules have much wider scope for using as antibacterial drugs for broad spectrum of microorganisms. Even there are scopes of using such molecules as an alternative for known antibacterial drugs like chloramphenicol. Fluorescence study reveals that molecules show excellent sensing capabilities for divalent metal cations, especially for copper (Cu), zinc (Zn) and nickel (Ni), with detection limit in ppm level. Most interestingly, we have noted that the limit of detection (LOD) and limit of quantitation (LOQ) for the respective metal cations are closer to the reported permissible limit of World Health Organization (WHO, 2011),[49] which in other words reflects the novelty of the work.

9 | XRD ANALYSIS

Linezolid or other oxazolidinone derivatives are known to exhibit polymorphism and two crystalline forms are so far known.[50] X-ray powder diffraction patterns of crystal form of compounds **5** and **7** are illustrated in Figure 8. From the figure, we have observed that compound **5** possess crystalline behaviour contrary to compound **7** (after formation of the azetidinone) which shows semi-crystalline behaviour. As polymorphism is a common characteristics of oxazolidinone, therefore, we have noted the observed changes in crystal behaviour of compound 7. For compound **5**, the diffraction peaks 2θ were observed at 12.04, 16.12, 17.18, 18.71, 20.82, 21.42, 24.43, 25.82, and 27.62. On the other hand, for azetidinone (compound **7**) peaks were observed at 12.22, 17.34, 21.27, 24.59, and 27.63. The analogy observed for few of the 2θ values of the two compounds provides clear indication about the formation of the compound.

10 | EXPERIMENTAL SECTION

10.1 | Materials

2,4-dichlorobenzaldehyde, 3,4-dichlorobenzaldehyde, Benzaldehyde, (S)-4-(4-Aminobenzyl-2-oxazolidone,-chloro acetic acid, *n*-propyl amine, *n*-butyl amine, sodium ethoxide, and triethylamine were procured from Sigma-Aldrich and TCI, Japan and were used as received, without further purification. Methanol, diethylether, dichloromethane solvents were used after drying by

standard procedure. Reported literature procedure was used for the synthesis of the Imines. Carry 630 FT-IR spectrophotometer was used to record the Infrared (IR) spectra and expressed as ν_{max}/cm. Bruker AvIII HD-400 MHz FTNMR spectrometer was used for the nuclear magnetic resonance (NMR) spectra using tetramethylsilane (TMS) as internal standard. Mass spectral data were recorded on Waters UPLC- TQD (ESI-MS) and Triple Quadrupole (LC-MS/MS) mass spectrometer. Elemental analysis was performed in Thermo finnigan FLASH EA 1112 CHN/CHNS/O analyser and Perkin Elmer PR 2400 series II elemental analyser.

10.2 | Antimicrobial study

The Mueller Hinton agar plates were inoculated with 2.0 mL of inoculum by spreading the swab over the plate. With the help of sterile borer, wells of 8 mm diameter were cut on the agar plates and loaded with sample solution of different concentrations. Tetracycline of 1 mg/mL, concentration was used as a control antibacterial agent. All plates were incubated at 37°C for 24 hours. After incubation period, the inhibition diameters were measured with Hi-Media scale.[51]

10.3 | General procedure for synthesis of imines

Synthesis of imines (**1-4**) was performed using literature procedure. Aromatic aldehyde (2.0 mmol) was dissolved in 1.0 mL methanol in a test tube. An equimolar amount of amine was dissolved separately in another test tube containing 1.0 mL of 0.018 M H_2SO_4 acid solution. The solutions were then mixed properly in a 25.0 mL round bottom flask. The reaction mixture was then transferred into a microwave oven maintained at 40°C. The reaction was allowed to continue for 15 minutes under microwave irradiation. Product of the reaction was extracted with dichloromethane (2 × 10.0 mL). The solvent was removed under reduced pressure to obtain the product. Products were further purified by passing through a small column using 10% Ethyl acetate solution in hexane as the eluent.[52]

10.4 | Synthesis procedure of (S)-4-((E)-4-(benzylideneamino) benzyl) oxazolidin-2-one (5)

(S)-4-Aminobenzyl-2-oxazolidone (2.0 mmol) was dissolved in 3 mL of methanol taken in a 50.0 mL round bottom flask, followed by addition of equimolar amount of benzaldehyde at room temperature for 5 minutes. After formation of the crystal it was extracted with dichloromethane (3 × 10.0 mL) and further purified by passing through a small column using 10% Ethyl acetate solution in hexane as the eluent.

10.5 | Synthesis procedure of 2-((S)-4-((E)-4-(benzylideneamino) benzyl)-2-oxooxazolidin-3-yl) acetic acid (6)

Compound **5** was dissolved in 3 mL of methanol taken in a 50.0 mL round bottom flask followed by addition of equimolar amount of chloroacetic acid. Sodium ethoxide (20 mg, 3 mmol) was used as a base in the reaction mixture and the mixture was stirred at 40°C for 24 hours. Progress of the reaction was monitored with thin layer chromatography. Product of the reaction was extracted with diethyl ether (3 × 10 mL) and was dried using anhydrous sodium sulphite. Finally, solvent was removed under reduced pressure to obtain the product.

10.6 | Synthesis procedure for (S)-4-((E)-4-(benzylideneamino) benzyl) oxazolidin-2-one based azeditinone(7-10)

Compound **6**(2.0 mmol) was dissolved in 3 mL of methanol taken in a 250.0 mL round bottom flask followed by addition of thionyl chloride (2.5 mmol). The reaction mixture was stirred at 40° for 1 hour. Then equimolar amount of imine (compounds **1-4**) was added. Triethylamine was used as a base for the reaction. The reaction mixture was again stirred for 4 hours at 40°. Progress of the reaction was monitored with thin layer chromatography. Product of the reaction was extracted with diethyl ether (3 × 10 mL) and was dried using anhydrous sodium sulphite. Finally, solvent was removed under reduced pressure to obtain the product.[53]

10.7 | Analytical data for 2,4′-dichlorobenzylimine propane (1)

Yield: 78%. IR (ν_{max}/cm): 3089(C—H),1578(CH═N), 1461,1386, 1032,915, 831, 713, 553.^{1}H NMR ($CDCl_3$,400 MHz),δ: 8.23(s, 1H, 1CH imine), 7.23 7.34 7.45(m, 3H, 3 CH arom), 3.53(t, 2H, $1CH_2$), 1.74(m,2H,$1CH_2$),.96(t, 3H, $1CH_3$).$^{13}C\{^1H\}$ NMR ($CDCl_3$, 400 MHz),δ:158.00(CH═N),130.56127.11129.5 (aromatic),134.38133.01(C—Cl),63.43(—CH_2—N), 23.94 (—CH_2), 11.82(—CH_3). Mass-216(M), 218(M + 2).

Elemental Anal. Calcd. for $C_{10}H_{11}NCl_2$- C-55.56, H-5.09, N-6.48%. Found-C54.94, H-5.23, N-6.56%.

10.8 | Analytical data for 3,4′-dimethoxybenzylimine propane (2)

Yield: 79.5%.IR (ν_{max}/cm): 3175(C—H), 2951, 28 34, 1585 (CH═N), 1280, 1152, 1014, 738, 532.^{1}HNMR (400 MHz,CD Cl_3), δ: 8.22(s,1H, CH imine), 3.59(d, 6H, 2 OCH_3), 4.00 (t, 2 H, 1 CH_2),1.35(m, 2H, 1CH_2), .96 (t, 3H, 1CH_3).^{13}C {^{1}H} NMR ($CDCl_3$, 400 MHz), δ*: 160.02 (CH═N), 129.72, 126.37, 122. 53, 62.98, 55.74, 23.79, 23.75, 11.51, 11.4. Mass-208(M + 1), 209(M + 2). Elemental Anal. Calcd*. for $C_{12}H_{17}NO_2$ C- 69.56, H- 8.21, N-6.76%. Found-C-69.2, H-8.93, N-6.46%.

10.9 | Analytical data for 3, 4′-dichlorobenzylimine propane (3)

Yield:81%. IR(ν_{max}/cm):3089(C—H),1578 (CH═N), 1461, 1386, 1035, 918, 833, 717, 557. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.25(s,1H,1CH imine), 7.22, 7.36, 7.44(m,3H,3 CH arom), 3.5(t, 2H, 1CH_2), 1.72(m, 2H, 1CH_2), .96(t,-3H,1CH_3)^{13}C {^{1}H} NMR ($CDCl_3$,400 MHz),δ:158.19 (CH═N),130.56134.38133.01,129.58, 127.11, 63.43, 23.94, 11.88. Mass-216(M), 218(M + 2). Elemental Anal. Calcd. for $C_{10}H_{11}NCl_2$- C-55.56, H- 5.09, N-6.48%. Found-C-54.94, H-5.23, N-6.56%.

10.10 | Analytical data for benzylidene-phenyl-amine (4)

Yield: 82.5%. IR (ν_{max}/cm): 2685, 2538, 1588 (CH═N),1280, 11 75, 850. ^{1}H NMR ($CDCl_3$, 400 MHz), δ:8.5(s, 1H, 1CH), 6.7, 7.3, 8.4(m, 10H, 10 CH arom).^{13}C {^{1}H} NMR ($CDCl_3$, 400 MHz), δ: 160.65(CH═N), 131.42, 129.17, 128.77, 128.39, 127.81, 120.97, Mass-181(M + 1), 182(M + 2). Elemental Anal. Calcd. for $C_{13}H_{11}N$ - C-86.19, H-6.08, N-7.73. Found-C-86.34, H-6.19, N-7.52%.

10.11 | Analytical data for (S)-4-((E)-4-(benzylideneamino) benzyl) oxazolidin-2-one (5)

Yield: 77.5%.IR(ν_{max}/cm): 3240, 1740, 1680(C = 0),1578 (CH═N), 1410, 1300,1180, 1080, 924.^{1}HNMR ($CDCl_3$, 400 MHz),δ: 8.43(CH═N), 8.06(NH),7.62,7.29, 7.21,7.12 (Aromaic) 4.58, 4.45,4.17,2.89,2.70. ^{13}C NMR ($CDCl_3$, 400 MHz), δ: 160.75(C═N) 160.09(C═O), 151.15(C—N), 136.15, 131.11, 129.90, 128.98, 125.52,69.75,52.19, 45.01. Mass – 194.1 (C14 H12 N). Elemental analysis for $C_{17}H_{16}N_2O_2$ Calculated., C- 72.84, H- 5.75, N-9.99, Found C- 72.00, H-5.33, N- 9.11%.

10.12 | Analytical data for 2-((S)-4-((E)-4-(benzylideneamino)benzy- l)-2-oxooxazolidin-3-yl) acetic acid (6)

Yield: 65%.IR (ν_{max}/cm): 3350(OH), 1705, 1640, 1578 (CH═N), 1500, 1430, 1400, 1360, 1260, 1020, 905. ^{1}H NMR ($CDCl_3$, 400 MHz),δ: 11.0(-OH), 8.08(CH═N), 7.62, 7.4, 7.3, 7.2, 7.1 (Aro matic), 4. 53, 4.42, 4.19, 3.97, 2.87, 2.64. ^{13}C {^{1}H} NMR ($CDCl_3$, 400 MHz),δ:170.9 (C═O),160.7, 157.6, 143.9143.7, 134.4, 133.6, 130.23, 129.12, 128.5, 128.4, 77.5, 69.8, 54.3, 41.6, 40.5. Mass – 340.4(M + 2). Elemental analysis for C19H18N2O4 Calculated, C- 67.44, H- 5.36, N-8.28, Found C- 66.96, H- 5.22, N- 8, 32.

10.13 | Analytical data for (S)-4-((E)-4-(benzylideneamino) benzyl)-3-(2-[2,4′-dichlorophenyl]-4-oxo-1-propylazetidin-3-yl) oxazolidin-2-one (7)

Yield: 68%. IR (ν_{max}/cm): 1710(C═O), 1700, 1600, 1587 (C═N), 1450, 1400, 1250, 1200, 1100, 1050. ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 8.49(CH, imine), 7.57, 7.29, 7.23, 7.21 (Aromatic CH) 5.32, 4.83, 4.43 (s, 1H, 1CH, azetidinone), 3.62(s, 1H, 1CH, azetidinone), 3.31 (t,2H,1CH_2), 1.7(m,2H,1CH_2), .98 (t,3H,1CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$, 400 MHz), δ:168.32 (C═O, azetidinone), 159.00(C═O, oxazolidinone), 156.94(C═N, imine), 138.40, 130.76, 130.60, 129.10, 128.96, 122.61, 70.81, 64.39, 49.58, 49.37, 48.94, 22.09, 12.14. Mass. $C_{29}H_{27}Cl_2N_2O_3$, 523.0($C_{28}H_{25}$ $Cl_2N_3O_3$). Elemental analysis for $C_{29}H_{27}Cl_2$ N_3O_3 Calculated, C- 64.93, H- 5.07, N-7.83, Found C- 65.16, H- 5.02, N- 7.77.

10.14 | Analytical data for (S)-4-((E)-4-(benzylideneamino) benzyl)-3-(1-butyl-2-[3,4′-dimethoxyphenyl]-4-oxoazetidin-3-yl) oxazolidin-2-one (8)

Yield: 67%. IR (ν_{max}/cm): 2958 (—OCH_3), 2610, 2500, 1740, 17 25(C = 0), 1578(C=N), 1475, 1428, 1410, 1155, 1018. ^{1}HNMR (CD Cl_3, 400 MHz) δ: 8.26(CH═N), 7.50, 7.50, 7.29, 7.12 (Aromatic CH), 5.31, 5.12, 4.48 (s, 1H, 1CH, azetidinone), 3.98(s, 1CH, azetidinone), 3.22(t, 2H,1CH_2),1.78(m, 2H, 1CH_2), .95(t, 3H, 1CH_3).^{13}CNMR

{^{1}H}($CDCl_3$,400 MHz),δ:168.32(C═O,azetidinone),160.19 (C═O,Oxazolidinone),154.46(C═N, imine), 149.53, 130.77, 130.0, 126.82, 110.45, 108.95, 77.65, 77.23, 76.80, 56.16, 55.95, 46.07, 22.79, 8.71. Mass-526.7(M-OCH_3). Elemental analysis for $C_{31}H_{33}N_3O_5$ Calculated, C- 70.57, H- 6.30, N-7.96, Found C- 71.11, H- 6.12, N- 7.82.

10.15 | Analytical data for (S)-4-((E)-4-(benzylideneamino) benzyl)-3-(2-[3,4′-dichlorophenyl]-4-oxo-1-propylazetidin-3-yl) oxazolidin-2-one (9)

Yield: 66.5%. IR (ν_{max}/cm): 2980, 2960, 2610, 2500, 1740, 1710(C═O), 1575(C═N), 1470, 1430, 1400, 1170, 1020. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.39(C═N), 8.11, 8.05, 8.02, 7.97, 7.77, 7.74, 7.67, 7.64, 7.57, 7.55, 7.53, 7.50, 7.45, 7.43, 7.06 7.02 (Aromatic-CH),4.71,4.61, (s,1H,1CH, azetidinone),3.92(s,1H,1CH, azetidinone), 3.44, 3.38, 3.16 (t,2H,1CH_2), 1.81(m, 2H,1 C H_2), 96(t,3H,1CH_3).^{13}CNMR{^{1}H}($CDCl_3$,400 MHz),δ:167.22 (C═O, azetidinone),160.20(C═O, oxazolidinone),157.84 (C═N, imine),137.30, 131.66, 130.42, 129.32128.50, 77.66, 77.23, 76.81, 46.19, 39.76, 29.22, 19.83, 13.45. Mass 536.15 (M + 1). Elemental analysis for $C_{29}H_{27}Cl_2N_3O_3$ Calculated, C- 64.93, H- 5.07, N-7.83, Found C- 64.89, H- 5.00, N-7.72.

10.16 | Analytical data for (S)-4-((E)-4-(benzylideneamino) benzyl)-3-(2-oxo-1,4′-diphenylazetidin-3-yl) oxazolidin-2-one (10)

Yield: 68%.IR (ν_{max}/cm): 2990, 2940, 2600, 2500, 1740, 1710(C = 0), 1578(C═N), 1495, 1400, 1180, 1020, 840, 810. ^{1}H NMR($CDCl_3$,400 MHz), δ: 8.06(C═N), 7.65, 7.45, 7.44, 7.43, 7.42, 7.41,7.40 (Aromatic CH), 4.55, 4.13 (s, 1H, 1CH, azetidinone), 3.92 (s, 1H, 1CH, azetidinone).^{13}CNMR{^{1}H}($CDCl_3$,400 MHz),δ:168.79 (C═O, azetidinone),160.12 (C═O, oxazolidinone),157.32 (C═N, imine),133.05, 130.96, 130.40, 129.97, 129.66, 129.09, 128.53, 128.37, 127.00, 123.93, 77.65, 77.43, 77.23, 76.80, 46.1. Mass-500.8(M). Elemental analysis for $C_{29}H_{27}Cl_2N_3O_3$ Calculated, C- 76.63, H- 5.43, N-8.38, Found C- 77.69, H- 5.21, N- 8.44.

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