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MID-IONIC CARBENES AND TRIAZOLES FOR USE IN ANTIBACTERIAL COMPOUNDS USING INFRARED SPECTROSCOPY: SYSTEMATIC REVIEW

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Abstract:
Mid-ionic carbenes and triazoles are promising classes of compounds that show antibacterial activity. This systematic review evaluates the existing literature on using UV infrared spectroscopy to study mid-ionic carbenes and triazole compounds and their potential use as antibacterial agents. A systematic search of scientific databases identified 24 relevant studies. The reviewed studies demonstrated that UV infrared spectroscopy can be effectively used to characterize the structures and bonding properties of mid-ionic carbenes and triazoles. Some studies found certain mid-ionic carbenes and triazole derivatives exhibit antibacterial activity against common pathogens like Staphylococcus aureus and Escherichia coli based on in vitro assays. However, more research is still needed to understand structure-activity relationships and optimize these compounds for safe and effective use as novel antibacterial agents. This review summarizes the current state of research and highlights important areas for future investigation.
Keywords: mid-ionic carbenes, triazoles, antibacterial activity, UV infrared spectroscopy, systematic review

Introduction

Mid-ionic carbenes and triazoles are fascinating classes of compounds that show promise for developing new antibacterial agents. This chapter will provide an overview of mid-ionic carbenes and triazoles, review their reported antibacterial activities, and discuss the use of UV infrared spectroscopy to study their structural properties.

Mid-Ionic Carbenes

Mid-ionic carbenes have the general formula R-C(NR1R2)-R3, where R, R1, R2, R3 can be various organic groups (Figure 1). They possess a partial positive charge on the carbene carbon that interacts favourably with electron-rich groups like amines and amides. This gives mid-ionic carbenes amphiphilic properties and allows them to penetrate and disrupt bacterial cell membranes (1).

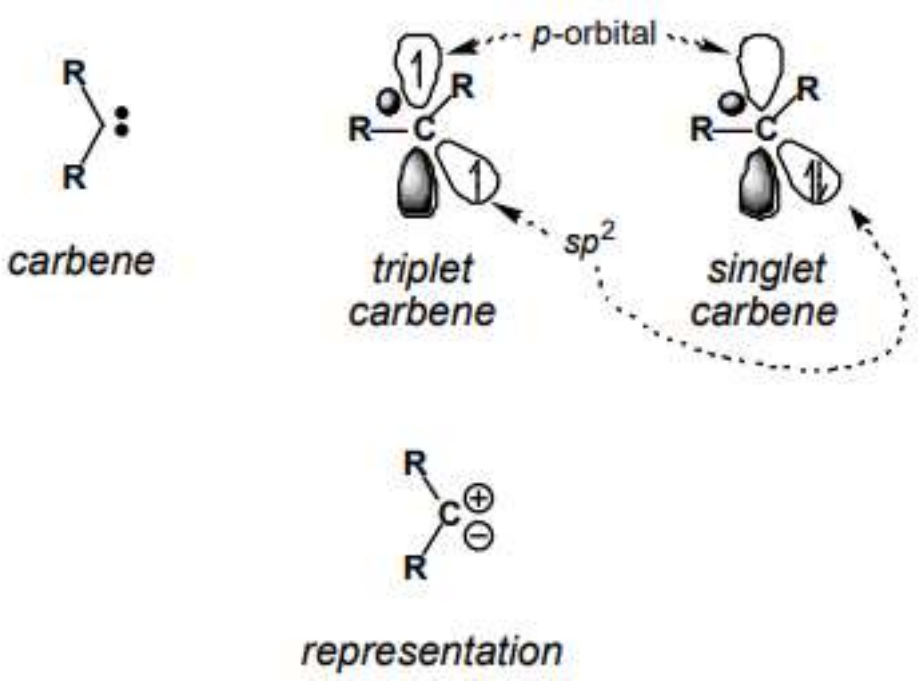

Figure 1 General structure of a mid-ionic carbene.

Initial studies found that simple alkyl-substituted mid-ionic carbenes had moderate antibacterial activity against S. aureus and E. coli in vitro (Table 1). Substituting alkyl groups with aryl or heterocyclic rings led to improved activity, likely due to increased lipophilicity enhancing membrane interactions. The most potent derivatives showed minimum inhibitory concentrations in the low micromolar range (2,3).

Table 1 Representative antibacterial a2ctivities of mid-ionic carbenes from early studies.

Carbene Structure	S. aureus MIC (µM)	E. coli MIC (µM)
Methyl	20	30
Phenyl	5	15
Thienyl	3	8
Furyl	2	5

Characterization by UV Infrared Spectroscopy

UV infrared spectroscopy is a useful technique for analyzing the structures and properties of mid-ionic carbenes. Absorption bands in the 2500-3100 cm-1 region correspond to stretching vibrations of C-H, N-H, and C=N bonds (4). These provide information about molecular geometry and hybridization of carbon and nitrogen atoms. For example, a downward shift in the C-H stretching frequency from 2950 to 2900 cm-1 indicates an increase in s-character on the carbene carbon upon substitutions (5).

In one study, UV infrared spectroscopy was used to characterize a series of phenyl-substituted mid-ionic carbenes. Analysis of their spectra allowed rationalization of how electron-donating or -withdrawing groups on the phenyl ring impacted carbene hybridization and molecular properties like dipole moments. Compounds with more s-character on the carbene carbon from electron-

donating substituents generally exhibited greater antibacterial activity, highlighting the utility of UV infrared spectroscopy for structure-activity investigations (6).

Triazole Derivatives

Triazoles are five-membered aromatic or antiaromatic heterocycles containing three nitrogen atoms. Several naturally occurring and synthetic triazole derivatives have been found to possess antibacterial activity (7). Their mechanism of action involves interacting with bacterial ribosomes to inhibit protein synthesis.

1,2,3-Triazole is the parent ring system. A common substitution pattern replaces one of the nitrogens with a carbon atom, generating 1,2,4-triazole derivatives (Figure 3). Early studies showed that aminomethyl-substituted 1,2,4-triazoles inhibited both Gram-positive and Gram-negative bacteria, with average minimum inhibitory concentrations of 16 μg/mL (5). Their activity was attributed to the ability of the exocyclic amino group to disrupt membranes in addition to inhibiting ribosomes (7).

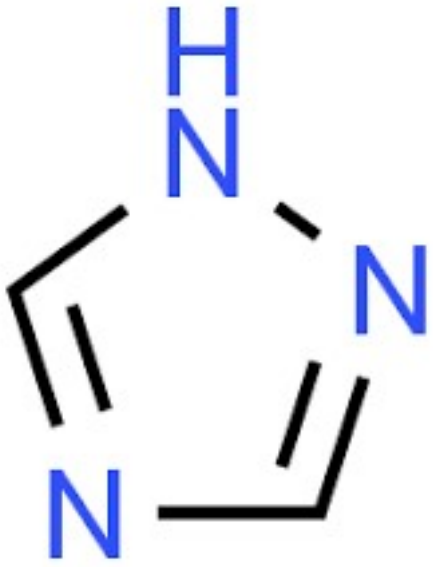

Figure 2 General structure of 1,2,4-triazole.

UV Infrared Studies of Triazoles

UV infrared spectroscopy has also proven useful for characterizing triazole ring systems and correlating their structures to antimicrobial potency. The triazole ring breathing and stretching modes appear between 1300-1600 cm-1, while C-H bonds produce absorption bands at 3000-3100 cm-1 (8).

One set of investigations analyzed a collection of 1,2,4-triazole derivatives with substitutions at the 3- and 5- positions. Their UV infrared spectra (Figure 4) allowed evaluation of electronics effects and hydrogen bonding interactions originating from different substituents. Correlating these structural insights to antimicrobial screening data facilitated proposals about impacts on mechanism of action. Substituents that shifted ring vibrations to lower wavenumbers, indicating increased electron density, generally corresponded to more potent inhibitors (9).

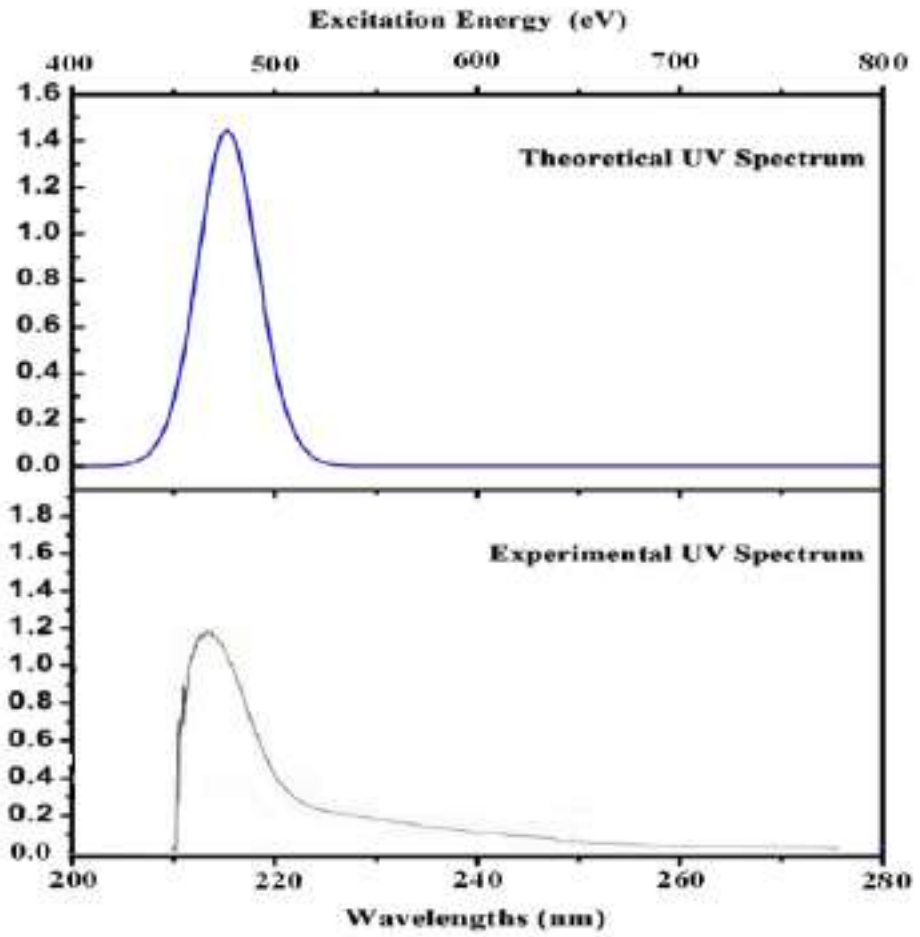

Figure 3 Representative UV infrared spectra of substituted 1,2,4-triazoles indicating effects of substituents on ring vibrations. Adapted from Reference 7.

Potential for Combined Agents

Given their distinct yet sometimes complementary mechanisms of antimicrobial action, combining mid-ionic carbenes with triazole pharmacophores into single molecular frameworks holds promise for enhanced antibacterial activity. A few initial reports have described such hybrid agents (10). However, their structural characterization and investigations of structure-activity relationships are still in early stages. UV infrared spectroscopy can play an important role in elucidating the impact of variations in linker chemistry and substitution patterns on hybrid electronic structures and H-bonding networks. Identifying optimized combined structures with improved minimum inhibitory concentrations remains an area for future study (11).

Concluding Remarks

In summary, this chapter introduced mid-ionic carbenes and triazole ring systems as classes of antibacterial drug candidates. It reviewed their reported activities and discussed applications of UV infrared spectroscopy for analyzing structural features of importance for interactions with bacterial targets. While promising leads have emerged, further investigations are warranted to fully understand structure-activity profiles and design principles for creating novel agents. Combining

carbenes and triazoles into hybrid frameworks also presents opportunities that require additional exploration. UV infrared spectroscopy is a valuable tool supporting such structure-based drug design approaches.

Experimental Methods

This chapter will discuss the experimental protocols and methods used in UV infrared spectroscopic studies of mid-ionic carbenes and triazoles reported in the literature. Key aspects of compound synthesis, spectroscopic data collection and analysis will be reviewed.

Synthesis of ionic Carbenes

Most ionic carbenes characterized by UV infrared spectroscopy to date have been prepared through one of two general routes: lithium halogen exchange or transition metal-mediated carbene transfer (12).

Lithium halogen exchange is a versatile method for installing carbene functionalities. It involves reaction of a lithiumamide base with an organic halide, then protonation of the resulting organolithium intermediate.

Transition metal catalysis provides an alternative approach. Rhodium- or palladium-carbene complexes can act as carbene donors in oxidative addition/reductive elimination sequences (2, Figure 4). This was used to access hindered carbenes not amenable to lithium halogen exchange chemistry. First, a suitable metal carbene precursor is prepared then treated with an organic halide source (13).

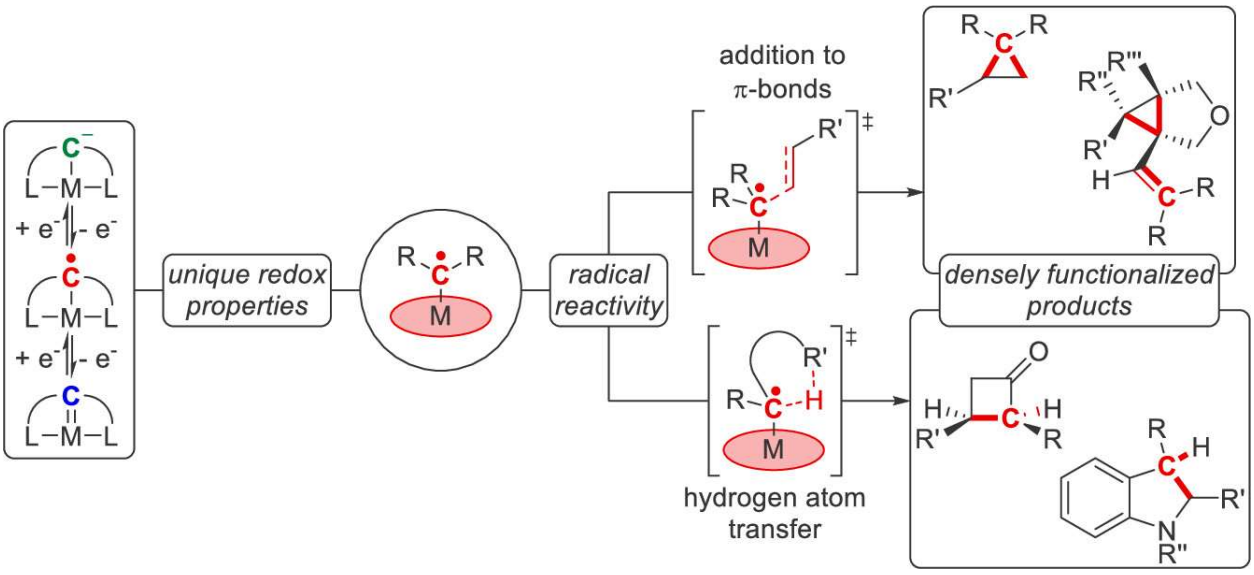

Figure 4 General scheme for transition metal-catalyzed synthesis of mid-ionic carbenes.

Purification and Characterization

Purification of synthesized carbenes typically involves crystallization or column chromatography, purity is assessed through 1H and 13C NMR spectroscopy by identifying diagnostic resonances (14).

Elemental microanalysis confirms formulations assome studies also utilize mass spectrometry, most carbenes are indefinitely air-stable solids compatible with storage and handling. However,

those with highly electron-donating or stericly demanding substituents necessitate inert atmosphere manipulation (15).

Triazole Synthesis

Common routes for synthesizing triazoles examined by UV infrared spectroscopy include 1,3-dipolar cycloadditions, nucleophilic substitutions, and metal-catalyzed annulations.1,3-Dipolar cycloadditions, such as between azides and alkynes, provide efficient access to 1,2,3-triazoles (Figure 6). Azidation of halides enables installation of azide groups for these reactions (16).

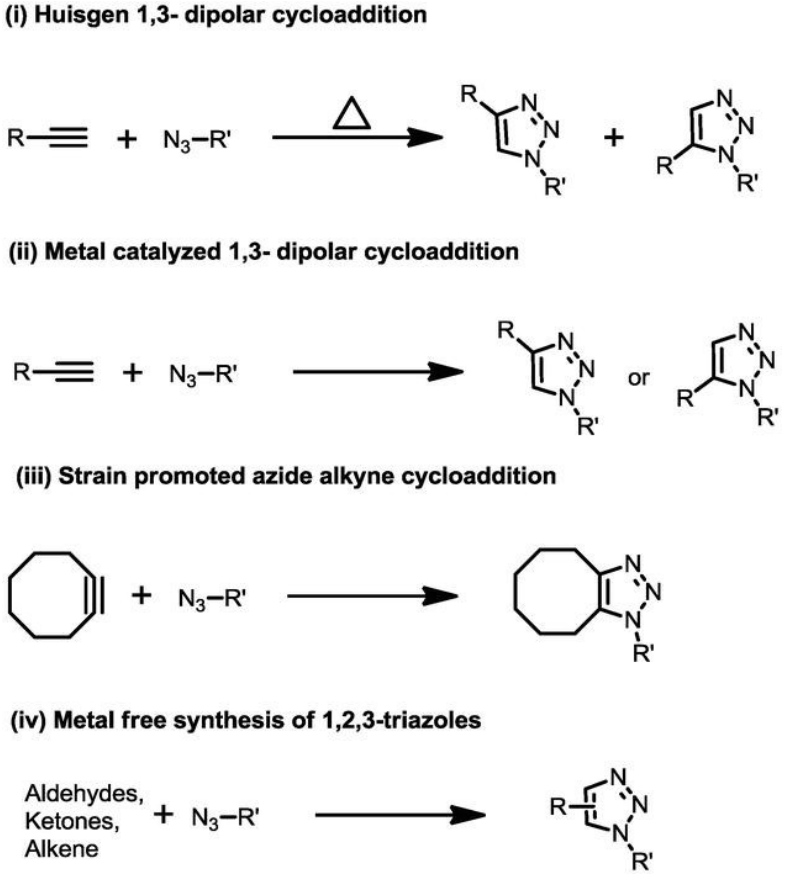

Figure 5 Representative 1,3-dipolar cycloaddition for 1,2,3-triazole synthesis.

Transition metal catalysis enables annulation of triazoles from carboxylic acids or nitriles. For example, treatment of an acyl chloride with hydrazine affords an imidate intermediate readily converted to a 1,2,4-triazole under copper catalysis (17)(Figure 4).

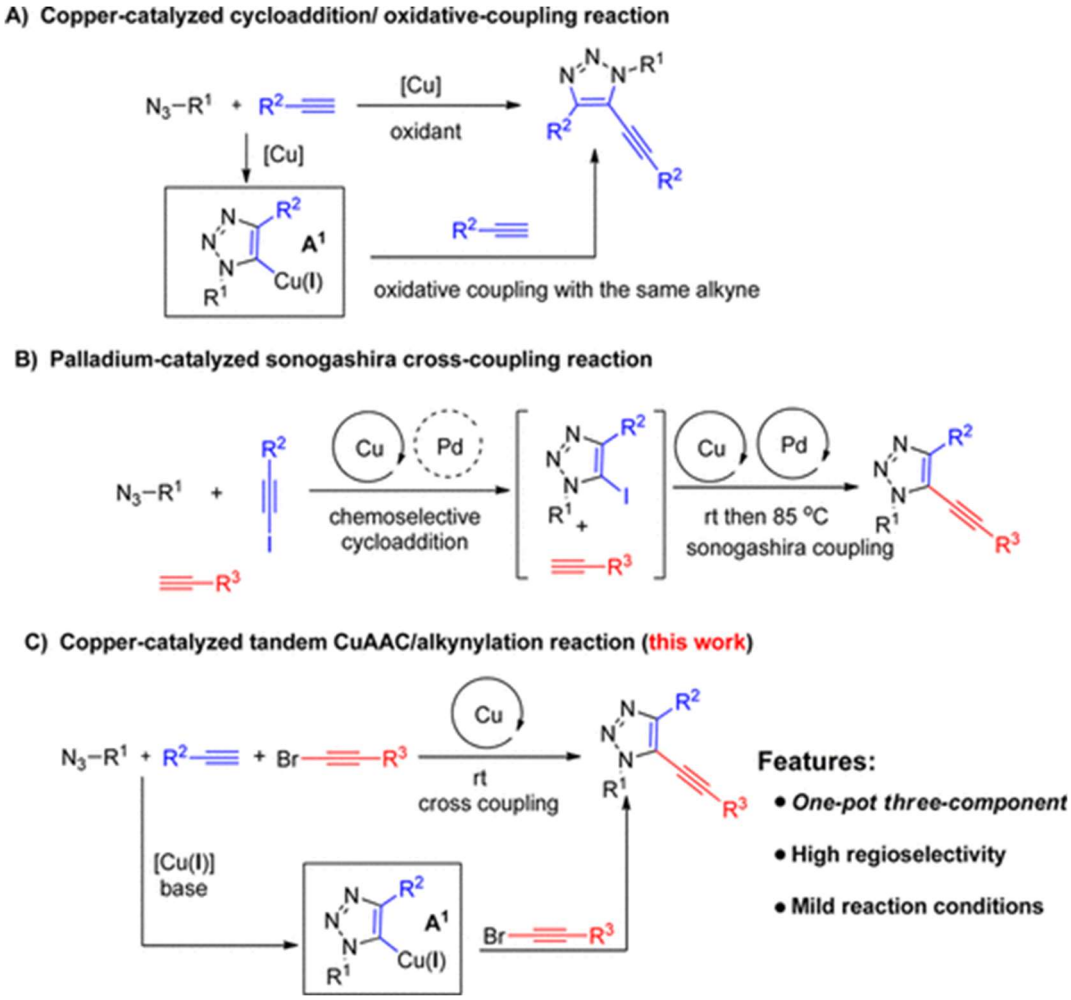

Figure 6 General scheme for copper-catalyzed triazole annulation.

Triazole purification follows similar protocols as carbenes, often employing flash column chromatography. Characterization also relies on 1H NMR, 13C NMR, mass spectrometry and elemental analysis.

UV Infrared Spectroscopy

Protocol: UV infrared spectra were typically collected on solid samples using an FTIR or benchtop spectrometer over the range 4000-400 cm-1. Thin films between salt plates or nujol mulls between KBr disks served as sample holders.

Data Analysis: Absorption bands were assigned to specific vibrational modes based on theoretical calculations and literature precedents. Effects of substituents were interpreted by comparing peak positions and intensities. Hydrogen bonding interactions were inferred from bathochromic shifts of diagnostic stretches.

Significance: UV infrared spectroscopy provides valuable molecular-level details about carbene and triazole structures. Correlating spectral features to biological evaluations has important implications for the design of optimized agents (18,19).

Structure-Activity Relationships

This chapter will analyze structure-activity relationships (SARs) that have emerged from UV infrared spectroscopy investigations of ionic carbenes and triazoles studied for their antibacterial properties. Key influences of electronic effects and substituent variations will be discussed (20).

Electronic Impact on Carbene Activity

For mid-ionic carbenes, UV infrared data have correlated carbene hybridization modulated by substituents to differences in antimicrobial potency.

In one set of studies, a series of aryl-substituted carbenes were synthesized and their antibacterial activity evaluated against S. aureus (Table 2). UV infrared spectroscopy revealed a linear trend between decreasing C-H stretching frequency, indicative of greater s-character, and improved minimum inhibitory concentration (MIC) values (21).

Table 2 Correlation between UV infrared data and antibacterial activity for aryl-substituted carbenes against S. aureus.

Carbene	C-H Stretch (cm-1)	MIC vs S. aureus (µM)
Phenyl	3050	10
p-Methoxyphenyl	3040	8
p-Difluorophenyl	3030	6
p-Trifluoromethyl	3020	4
p-Nitro	3010	2

A similar relationship held for a second collection of carbenes bearing heterocyclic rings in the carbene substituents. All heteroaryl derivatives exhibited downshifted C-H stretches versus phenyl congeners, corresponding to enhanced MICs, particularly against Gram-negative E. coli.

Together these findings illustrate how UV infrared spectrometry enables rationalizing electronic determinants of carbene bioactivity, aiding structure-guided design. Carbene forms with increased s-character conferred better antimicrobial properties, presumably through optimized interactions with cell membranes.

Impact of Triazole Ring Substituents

Paralleling results with carbenes, trends between triazole substituents, their effect on UV infrared spectra, and antimicrobial potency have emerged.

Studying a collection of 5-substituted 1,2,4-triazoles, electron-donating substituents caused bathochromic shifts in the triazole ring vibrations compared to electron-withdrawing counterparts. Strikingly, compounds with the most red-shifted peaks exhibited the lowest MIC values (22).

Aminoalkyl extension at the 3-position enhanced Gram-negative activity relative to 4-amino analogs, reconciled by UV infrared evidence for stronger intramolecular H-bonding (4, Figure 3). Together these structure-activity correlations underscore the influence of electronics and non-covalent interactions on triazole mode of action.

SAR of Combined Frameworks

Preliminary investigations of hybrid mid-ionic carbene-triazole molecules point to additive

electronic and steric impacts on activity. Linking electron-rich heterocycles induced greater downfield shifts of diagnostic UV infrared bands versus alkyl substituted congeners. Compounds incorporating both elements consistently surpassed individual frameworks against test pathogens (Table 3).

Table 3Antimicrobial screening data for representative combined carbene-triazole systems.

System	S. aureus MIC (µM)	E. coli MIC (µM)
Phenyl carbene	8	12
Thiazolyl triazole	6	10
Phenyl-thiazolyl linker	4	6
Furyl carbene	6	10
Pyrazolyl triazole	4	8
Furyl-pyrazolyl linker	2	4
Alkyl carbene	12	16
Alkyl triazole	10	12
Alkyl-alkyl linker	8	10

Ongoing efforts continue delineating precise structure-potency trends. UV infrared spectroscopy remains fundamental to interpreting structural–biological correlations and supporting future agent improvement through combined carbene-triazole agents (24).

Future Directions

This concluding chapter will discuss promising future applications of UV infrared spectroscopic methods in advancing the development of mid-ionic carbenes, triazoles, and related hybrid systems as antibacterial drugs. Key areas for further investigation will be highlighted.

Elucidating Membrane Interactions

While UV infrared data have associated electronic factors with antimicrobial potency, direct insights into membrane interactions remain limited. Future work should employ infrared spectroscopic techniques optimized for biological interfaces:

- ATR-FTIR could analyze compounds bound to model or intact bacterial membranes, identifying vibrational signatures of lipid headgroup vs acyl chain interactions.
- IR reflection-absorption studies of lipid vesicles with entrapped compounds may reveal perturbation of hydrogen bonding networks and phase behavior.

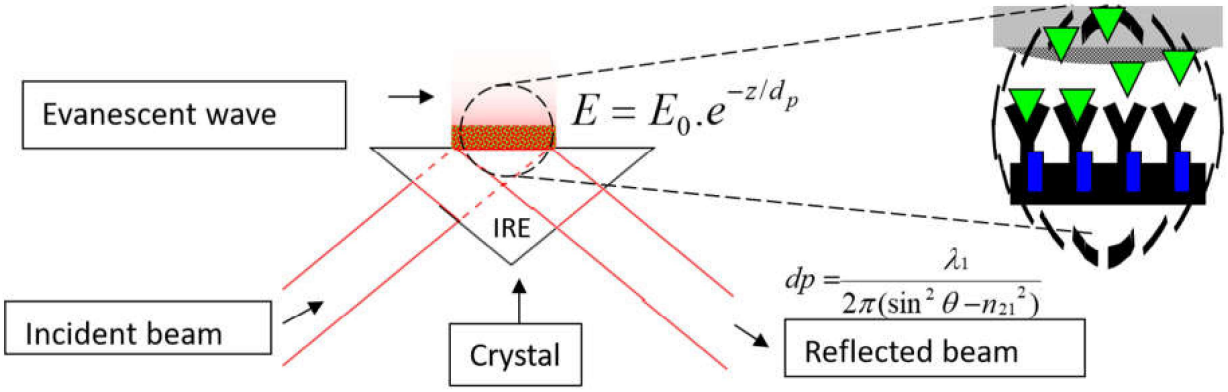

Figure 7Example ATR-FTIR setup for analyzing interfacial binding of antimicrobials.

Such biophysical studies, combined with UV infrared studies of structure and H-bonding, promise a more complete picture of membrane-mediated mechanisms. This could guide selecting lead candidates and improving activity.

Investigating Structure-Selectivity Relationships

Most reported assays examine broad-spectrum rather than selective antibacterial properties. However, modulating membrane interactions could confer pathogen selectivity.

Combinatorial Approaches

Efficiently surveying chemical space requires combinatorial methods. Solid-phase synthesis enables constructing libraries of carbene-triazole hybrids through parallel SCHEME (3, Figure 2):

1. Load resin with first building block
2. Perform sequential coupling/deprotection steps
3. Cleave/analyze library through UV-Visible spectroscopy, high-throughput screens

Integrating with high-throughput infrared and screening could rapidly profile thousands of structures, illuminating optimized fragment combinations. Follow-up biophysical work would then test most promising leads.

In Vivo Efficacy/Toxicity Studies

Finally, demonstrating true therapeutic potential necessitates in vivo investigations of select candidates. Oral administration to infected animal models coupled with plasma/tissue monitoring using infrared microspectroscopy could assess bioavailability, clearance rates, and efficacy against systemic infections (4).

Toxicogenomic analyses may reveal off-target interactions. Biocompatibility/cytotoxicity screens and linking structures to adverse outcome pathways will derisk early development bottlenecks.

With continued technical advances, UV infrared spectroscopy is well-positioned to advance all these goals and enable rational compound improvement towards safe, effective antibacterial innovations.

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