

East Tennessee State University

Digital Commons @ East Tennessee State University

Appalachian Student Research Forum

2019 ASRF Schedule

Apr 12th, 2:00 PM - 2:15 PM

Synthesis and Evaluation of 1,2,4-oxadiazolidinones: The Search for Potential non- β -lactam β -lactamase Inhibitors.

Chimdi E. Kalu

East Tennessee State University

Noah Lyons

East Tennessee State University

Abbas G. Shilabin

East Tennessee State University

Chimdi Kalu

East Tennessee State University

Follow this and additional works at: <https://dc.etsu.edu/asrf>

Kalu, Chimdi E.; Lyons, Noah; Shilabin, Abbas G.; and Kalu, Chimdi, "Synthesis and Evaluation of 1,2,4-oxadiazolidinones: The Search for Potential non- β -lactam β -lactamase Inhibitors." (2019). *Appalachian Student Research Forum*. 159.
<https://dc.etsu.edu/asrf/2019/schedule/159>

This Oral Presentation is brought to you for free and open access by the Events at Digital Commons @ East Tennessee State University. It has been accepted for inclusion in Appalachian Student Research Forum by an authorized administrator of Digital Commons @ East Tennessee State University. For more information, please contact digilib@etsu.edu.

Synthesis of 1,2,4-oxadiazolidinone derivatives:

The Search for Potential Non- β -lactam β -Lactamases Inhibitors

presented by

Chimdi Kalu

Supervisor: Dr. Abbas G. Shilabin

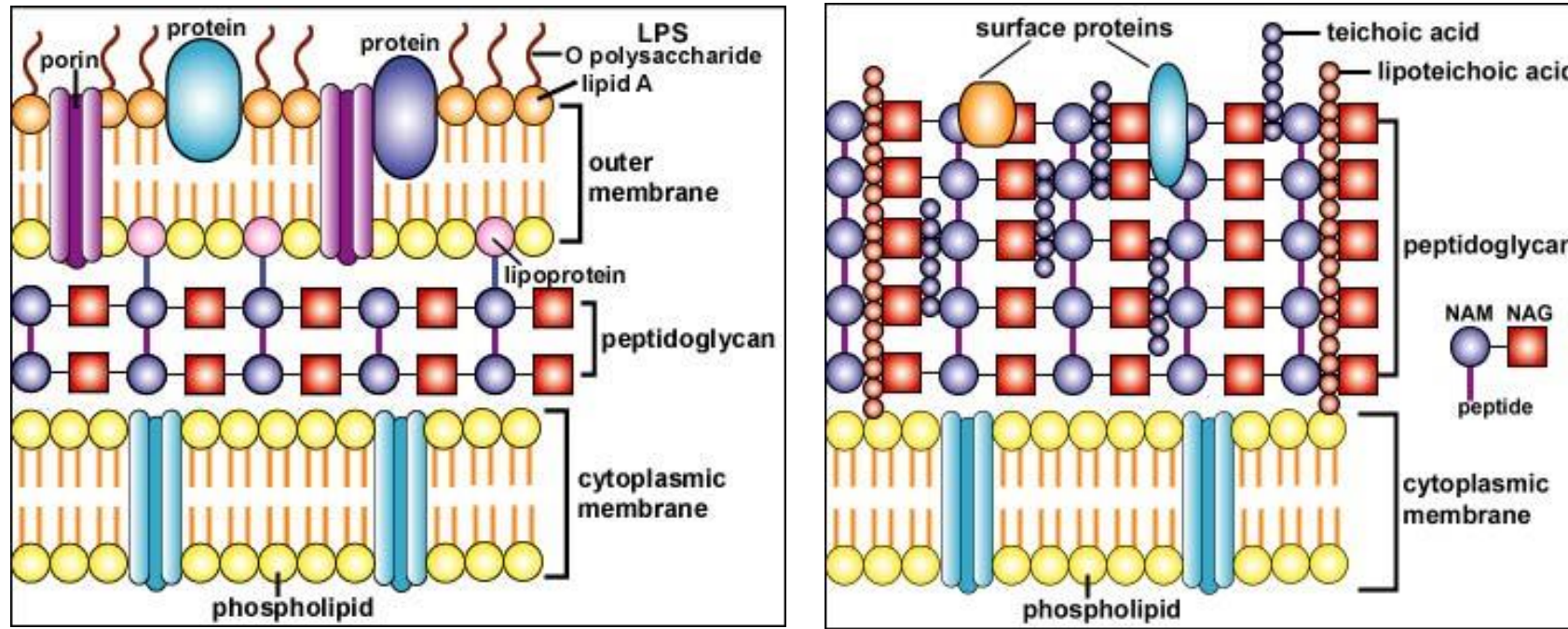
Outline

- Introduction
- Research objectives
- Bacteria cell wall structure
- β -lactam antibiotic drugs
- Non β -lactam β -lactamase inhibitor
- Synthesis, characterization, and biological activities of 1,2,4-oxadiazolidinone analogs
- Conclusion

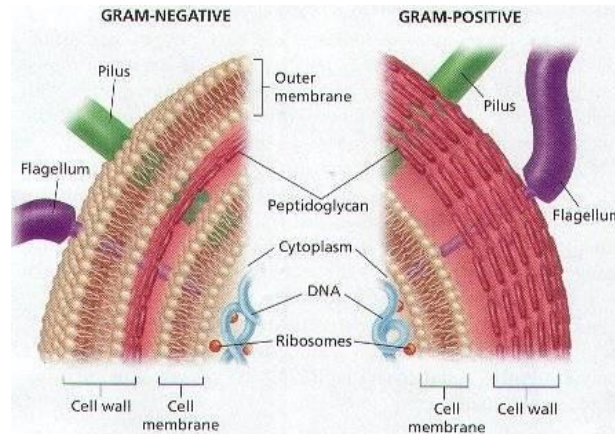
Research Objectives

- To synthesize a 1,2,4-oxadiazolidinone derivatives via 1,3-dipolar cycloaddition of nitrones with substituted isocyanates.
- To evaluate the biological significance of the synthesized inhibitors.
- To improve or restore the potency of antibiotic agents that lost their effectiveness due to continuous evolution of bacteria's β -lactamases.

Bacterial cell wall



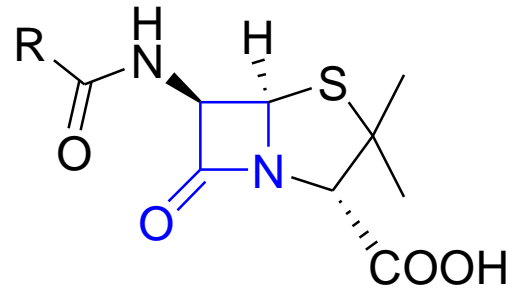
Gram Negative



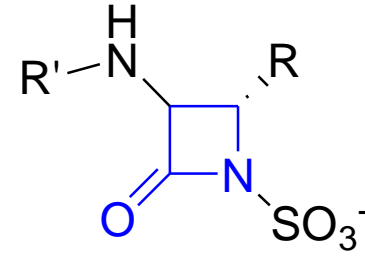
Gram Positive

Figure 1: A section of Gram-negative and Gram-positive cell wall

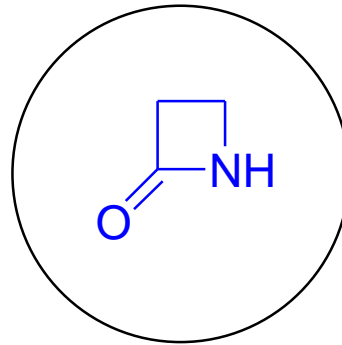
β -lactam antibiotic drugs



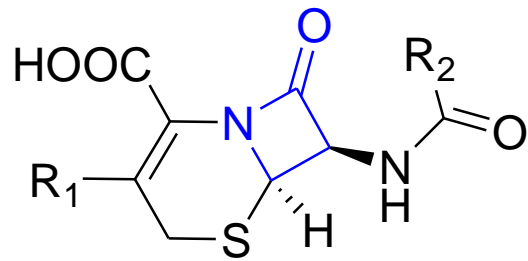
Penicillin



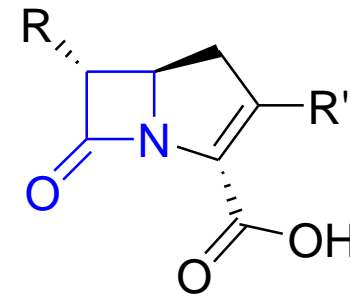
Monobactam



β -Lactam Ring



Cephalosporin



Carbapenems

Figure 2: Some β -lactam Antibiotics

Bacteria' β -lactamases

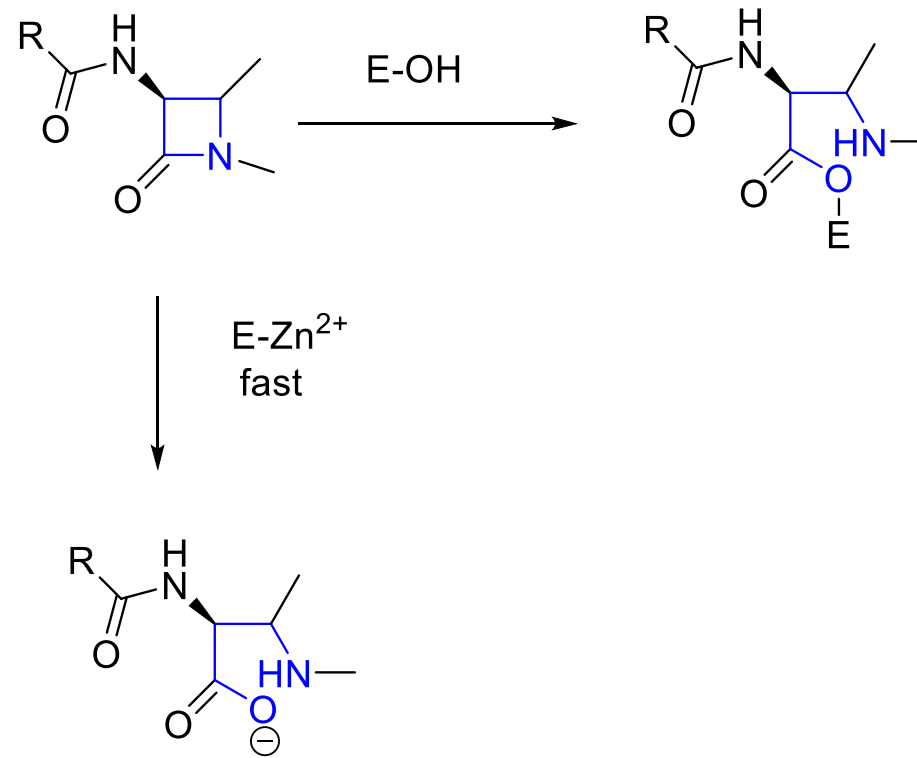


Figure 3: Mechanism of resistance to antibiotics.

Justification of 1,2,4-oxadiazolidin-5-one

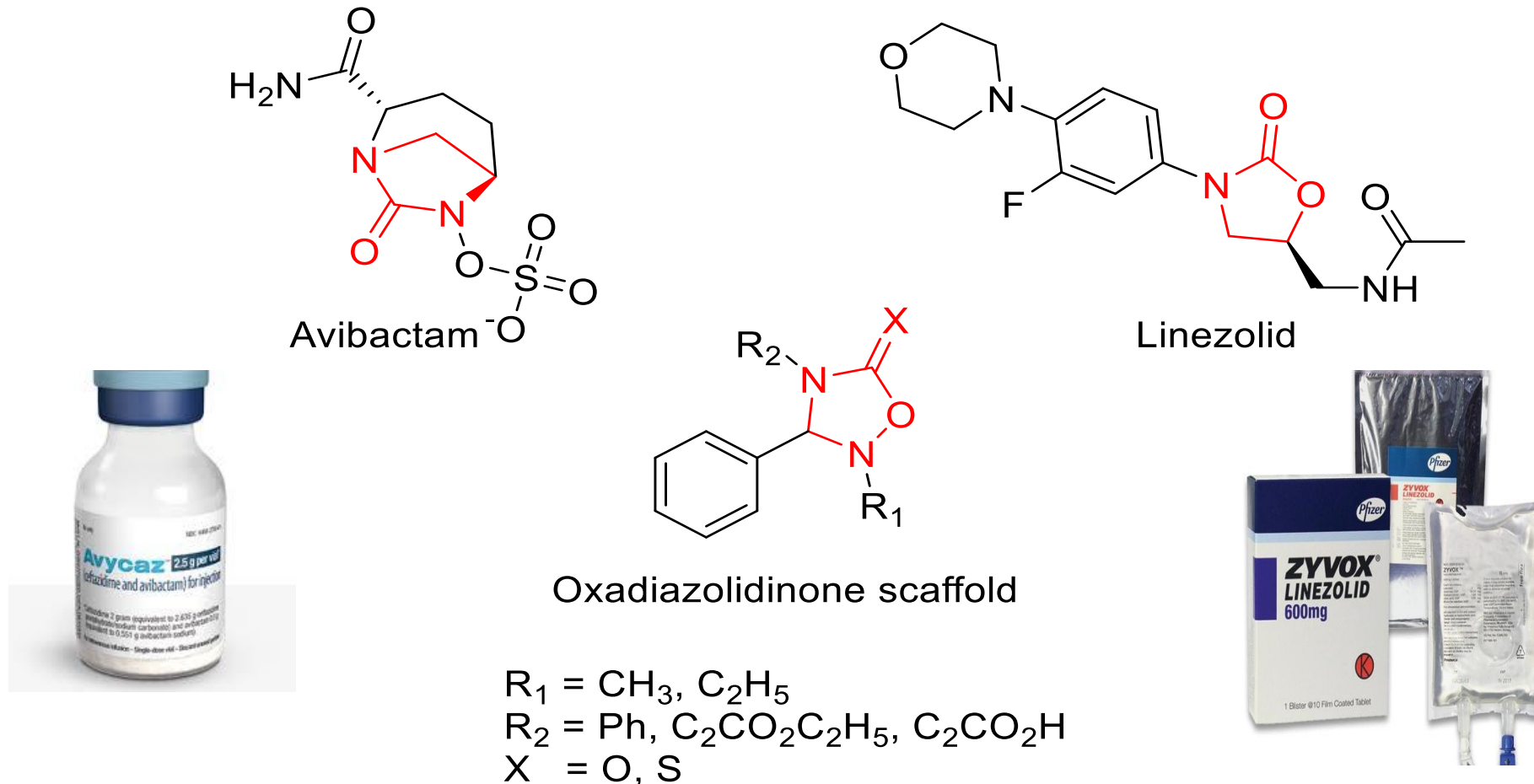
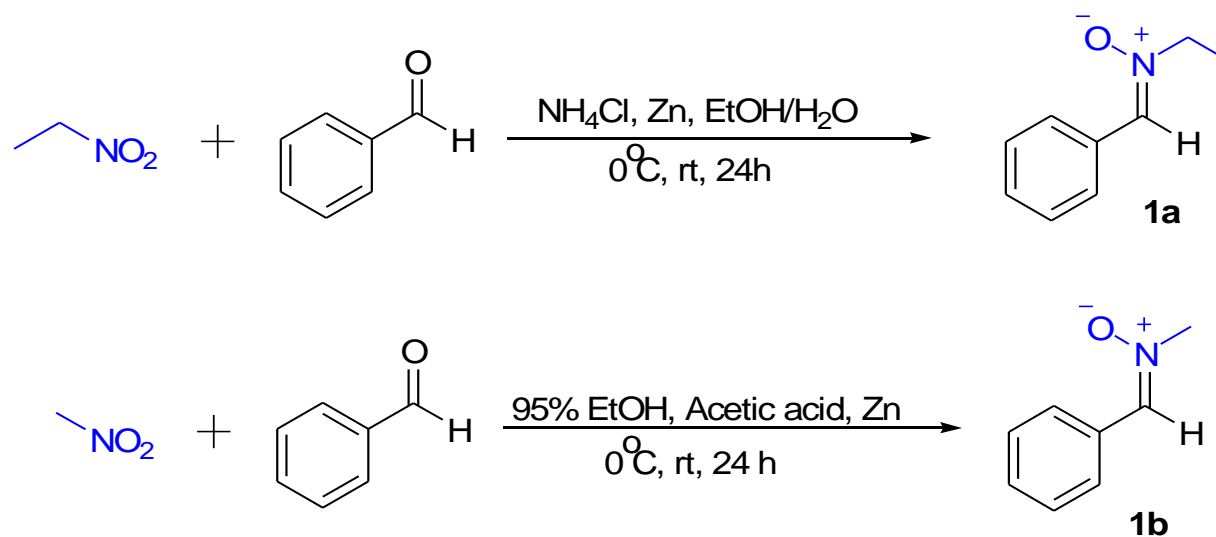


Figure 4: Comparison of compound of interest with Avibactam and linezolid

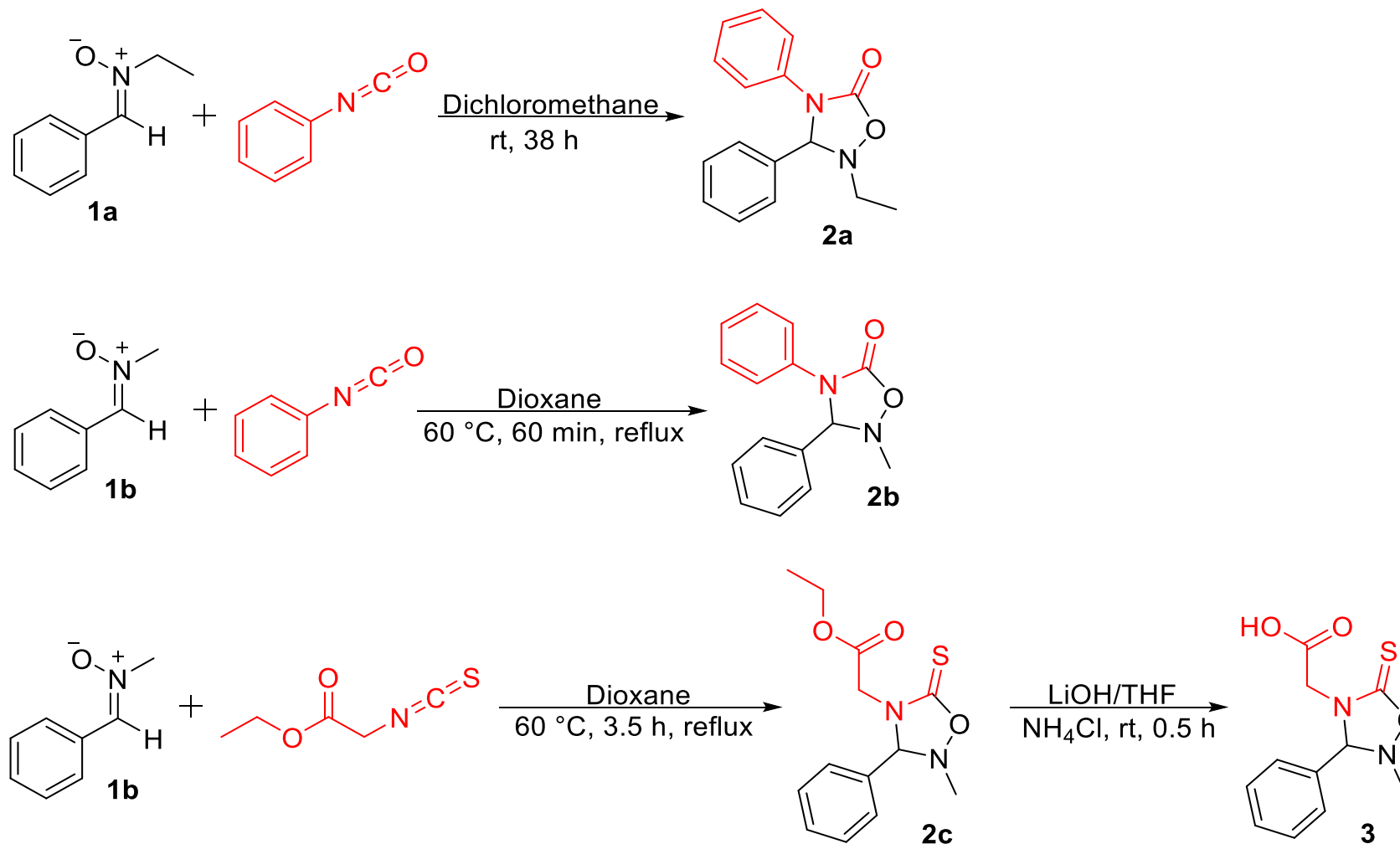
<https://pubchem.ncbi.nlm.nih.gov/compound/9835049>
www.idstewardship.com/drugs/ceftazidime-avibactam
<http://www.avalonpharmacy.com/product/zyvox-linezolid/>

Synthesis of nitrones



Scheme 1: Reaction of nitro compounds with benzaldehyde.

1,3-dipolar cycloaddition reaction



Scheme 2: Reaction of nitrones with various isocyanates

CHARACTERIZATION AND BIOLOGICAL ACTIVITIES

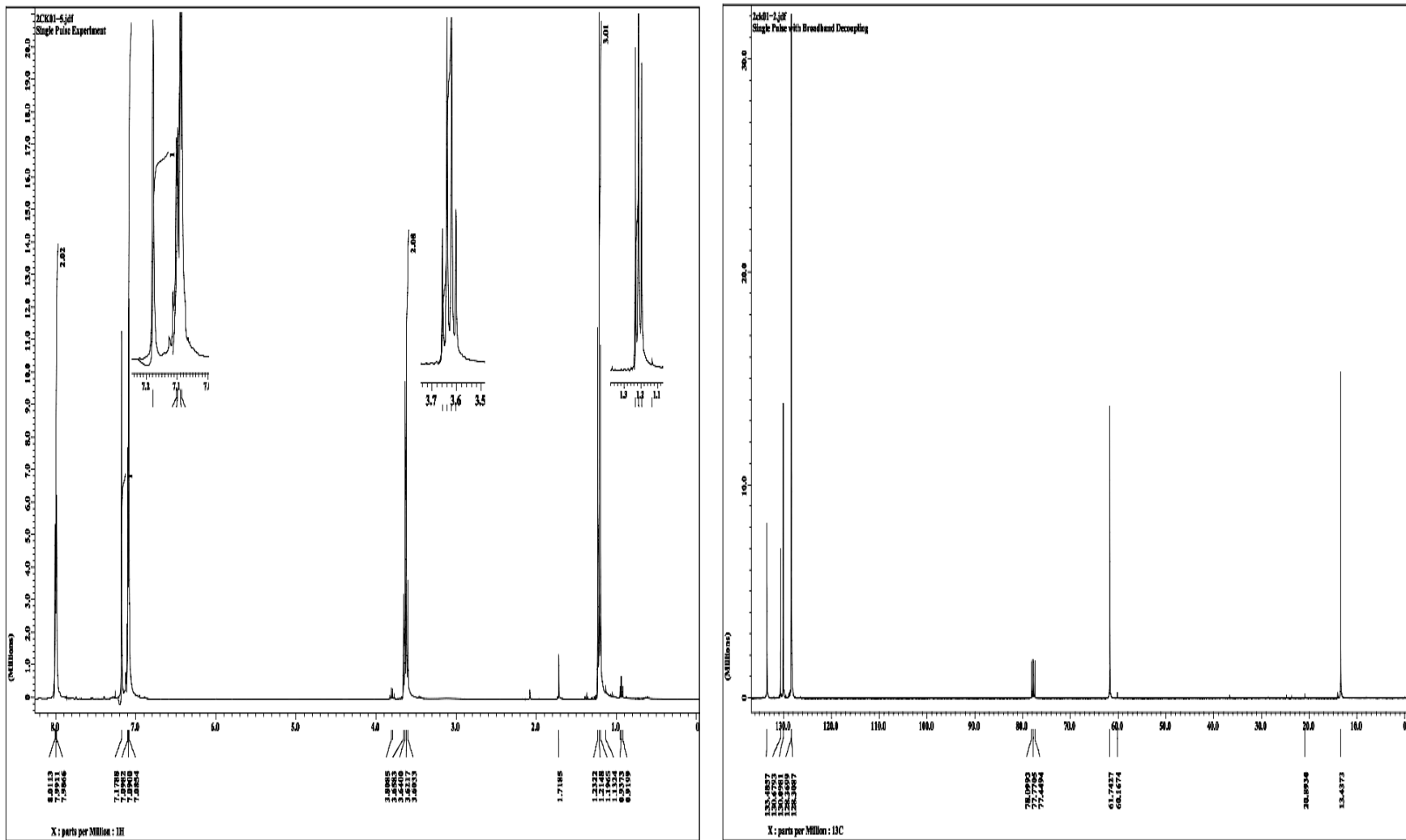
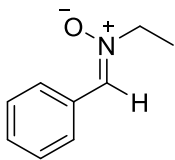


Figure 5: ¹H & ¹³C NMR spectra of Nitronium 1a

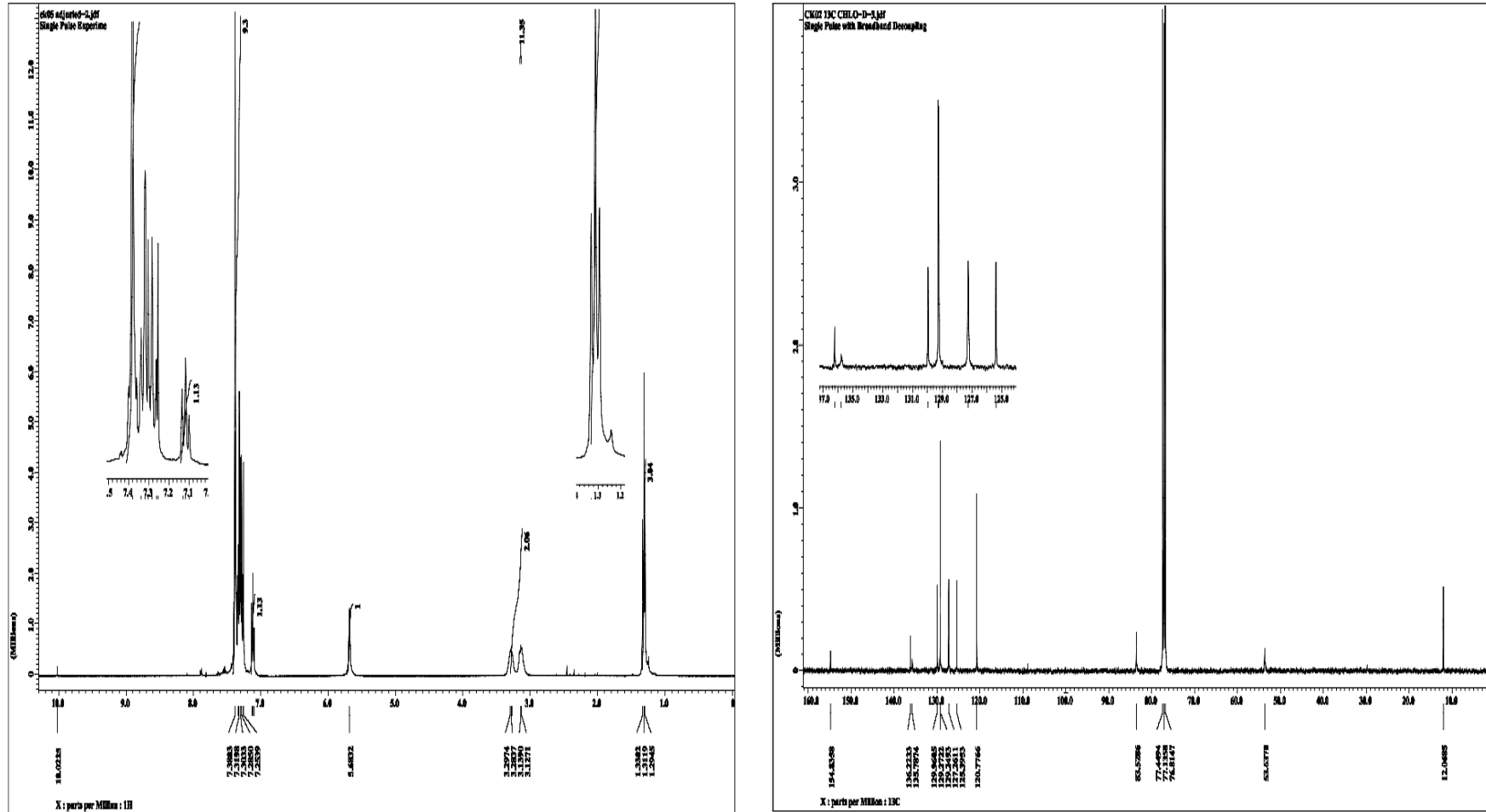
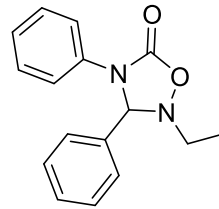


Figure 6: ¹H & ¹³C NMR spectra of oxadiazolidinone 2a

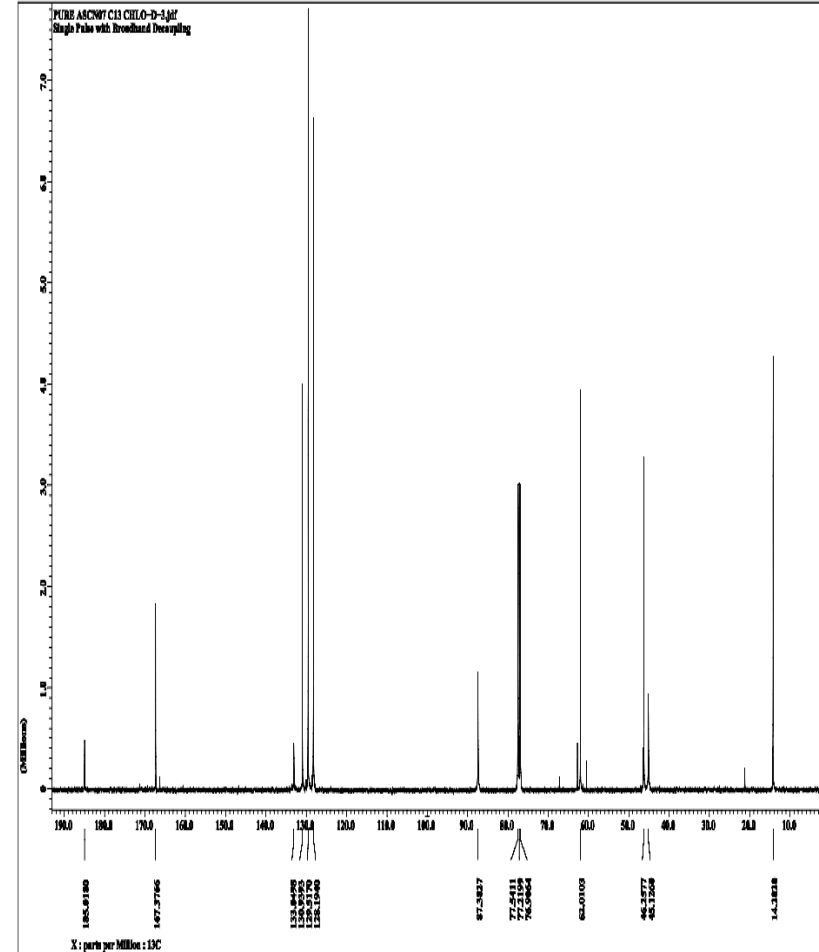
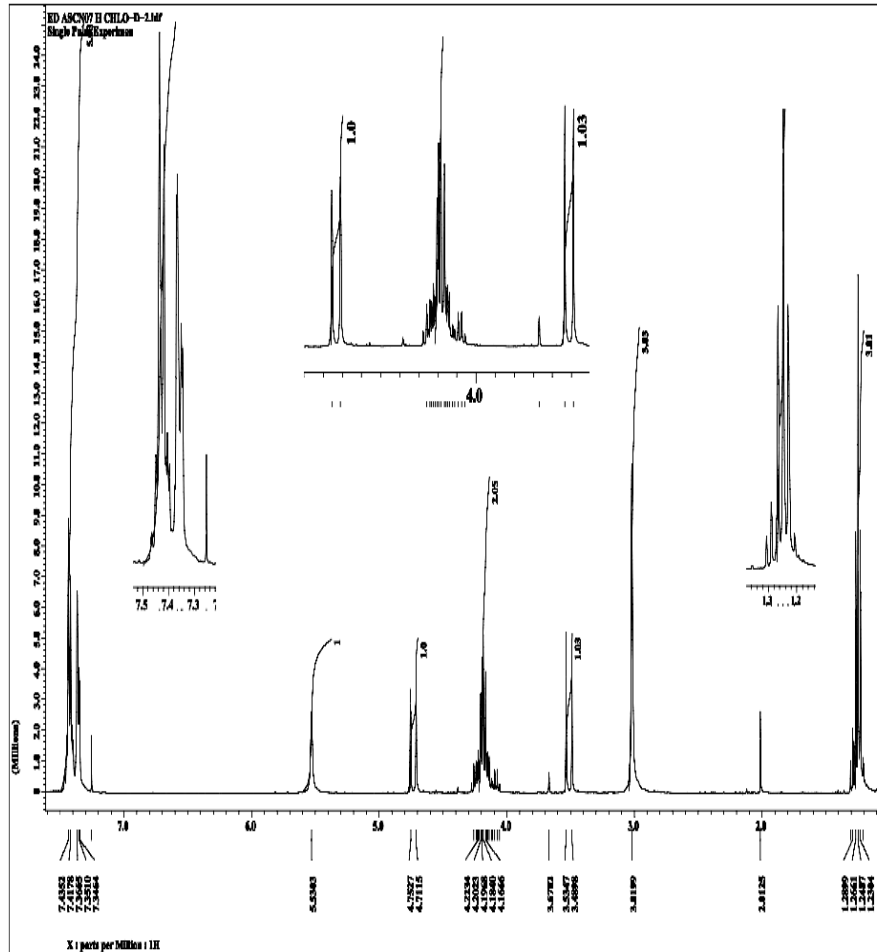
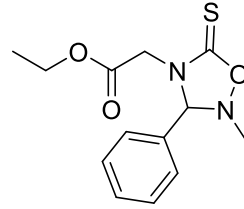


Figure 7: ¹H & ¹³C NMR spectra of compound 2c

of Peaks 436
Raw Spectrum 11.139 (scan: 878)
Background No Background Spectrum
Exact mass 280

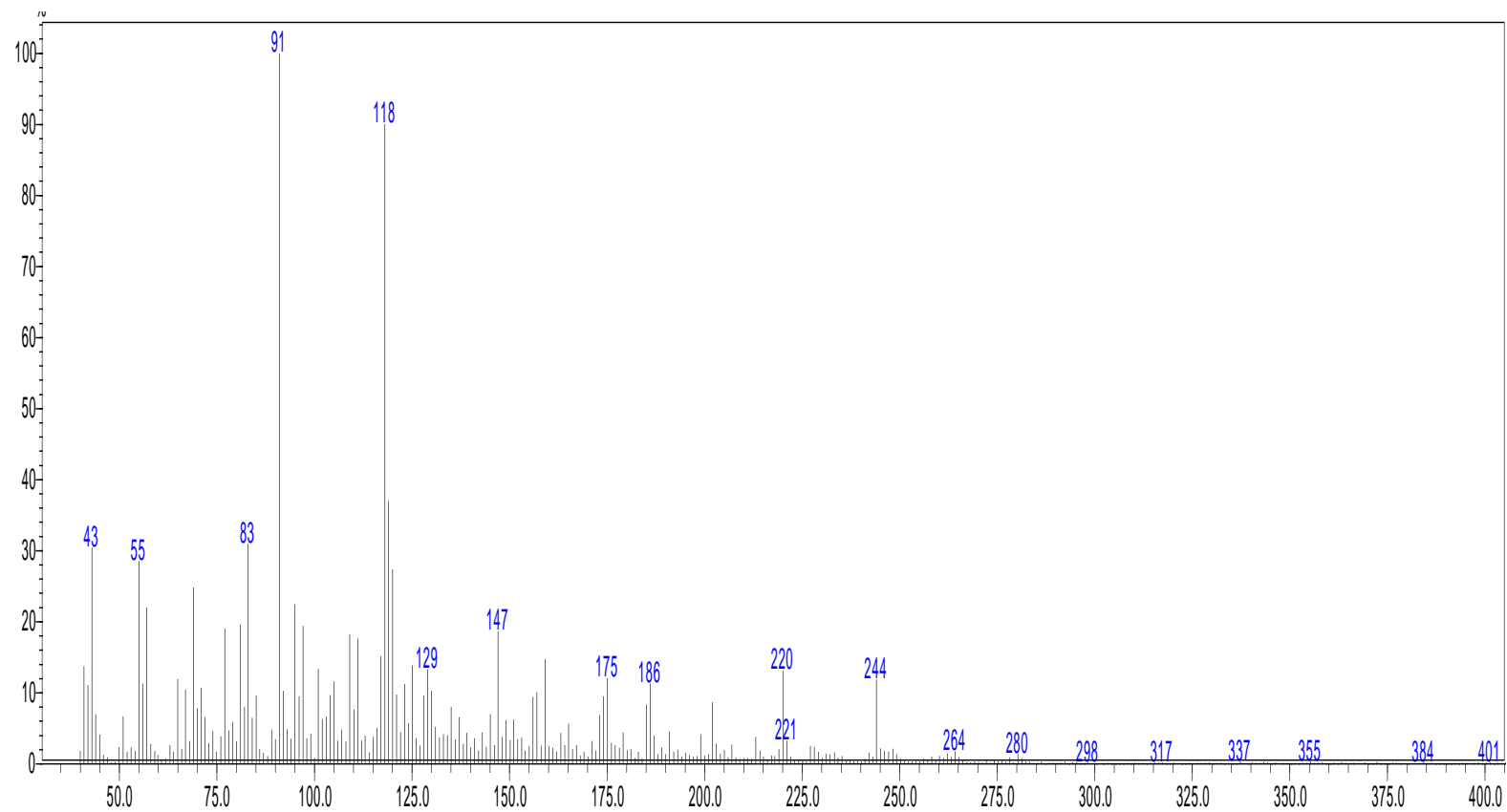
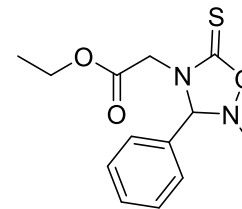


Figure 8: GC-MS spectrum of compound **2c**

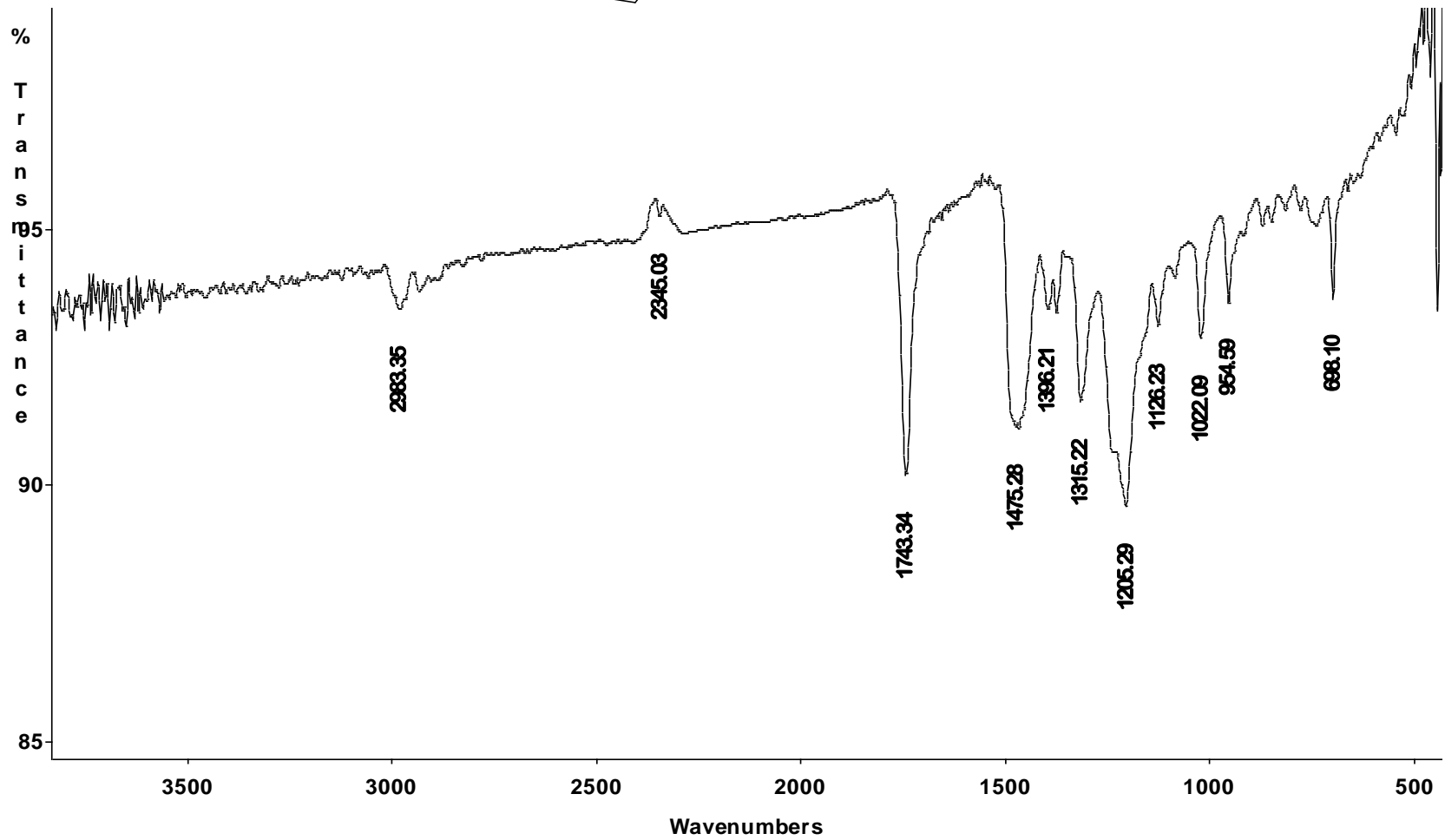
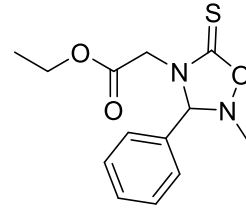


Figure 9: IR spectra of compound 2c

Demonstration of cycloaddition

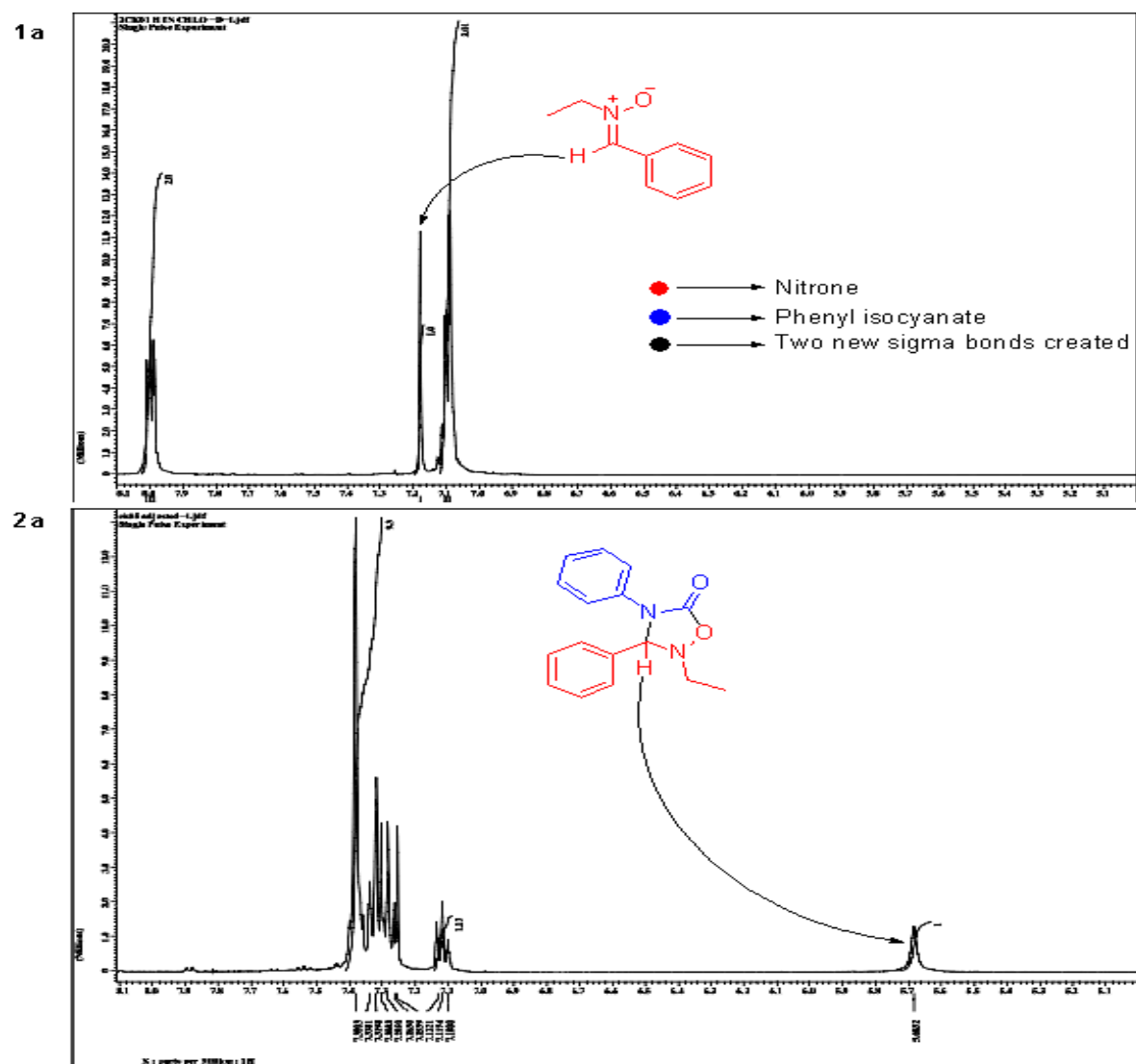
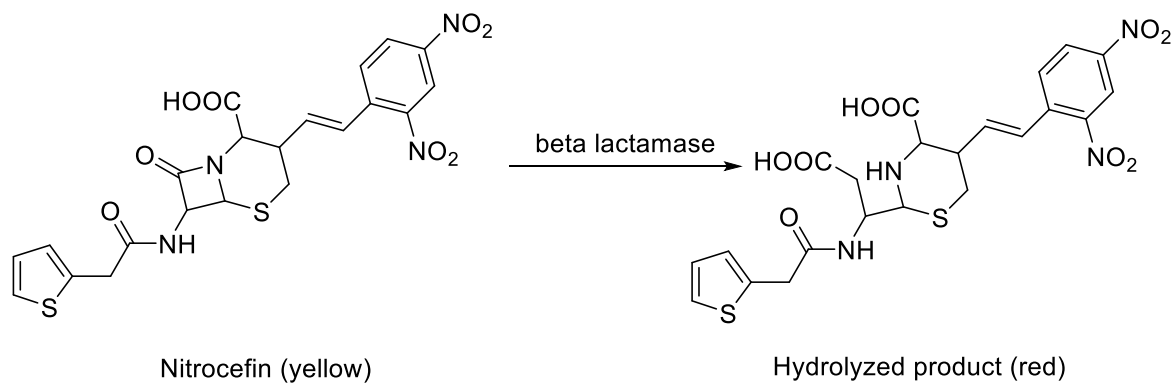
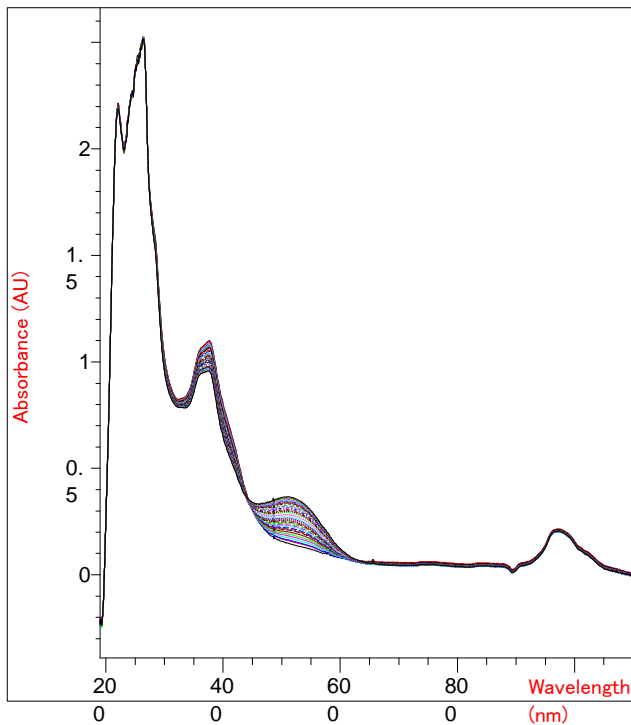
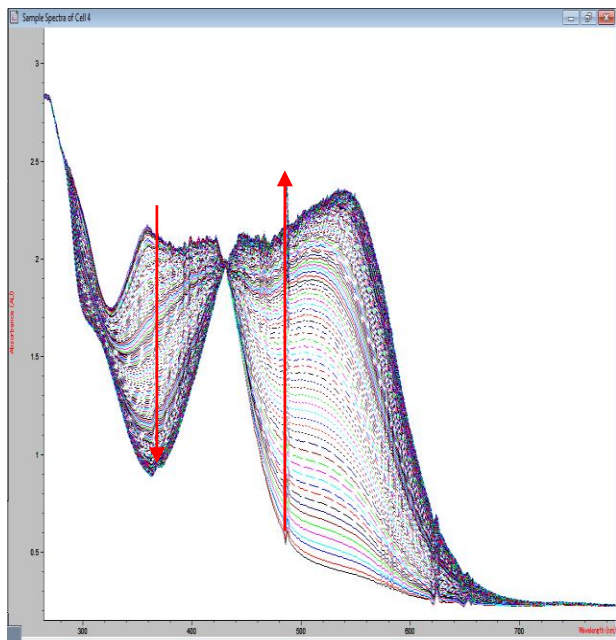


Figure 10: ^1H NMR spectra of **1a** and corresponding oxadiazolidinone **2a**

Table 1: The cytotoxicity assay (%) of **2a** on relative control (100%) against IGROV1, OVCAR-4, HS 578T, BT-549, A498, UO-31, UACC-62, SK-MEL-28

Cancer types	Cell line	Growth %	% Inhibition
Ovarian Cancer	IGROV1	95.59	4.41
	OVCAR-4	95.84	4.16
Breast Cancer	HS 578T	93.06	6.94
	BT-549	99.50	0.50
Renal Cancer	A498	82.27	17.73
	UO-31	86.72	13.33
Melanoma	UACC-62	93.93	6.07
	SK-MEL-28	99.89	0.11

Enzyme Inhibition Kinetics



Final concentration & volume of Enzyme (TEM-1) = 3 μ L (0.45 nM),
 Substrate (NCF) = 12 μ L (100 μ M)
 0.1 % BSA in MOPS buffer = 562 μ L (0.02 mM, pH – 7.5)
 Inhibitor (in 3 % ACN) = 20 μ L (500 μ M)

Table 2: Residual Activity and Percent Inhibition of TEM-1 for 3 minutes, 30°C Utilizing Potential Synthesized Inhibitors*

Compound	Molecular Weight (g/mol)	Initial Rate $V_o \pm SD (\Delta A, \text{sec}^{-1}) \times 10^{-3}$	Initial Rate +Inhibitor $V_i \pm SD (\Delta A, \text{sec}^{-1}) \times 10^{-3}$	Residual Activity (%)	% Inhibition
2a	268.31	1.6870 ± 0.01531	1.2930 ± 0.03163	76.47	23.53
2b	254.28	2.9367 ± 0.26697	2.1840 ± 0.34975	74.37	25.63
2C	280.00	1.159 ± 0.01139	1.0139 ± 0.02758	87.48	12.52
3	252.29	2.0411 ± 0.01252	1.2465 ± 0.01698	61.07	38.93
3 (P99)	252.29	7.1434 ± 0.15520	5.5067 ± 0.15981	77.09	22.91

Conclusion

- In this work, oxadiazolidinone derivatives (**2a**, **2b**, **2c**, and **3**), were prepared using commercially available isocyanate derivatives with synthesized nitrene **1a** and **1b**. The synthesized inhibitors were characterized using ^1H and ^{13}C NMR, GC-MS, and IR.
- Afterwards, there were tested against TEM-1 and P99 serine β -lactamase. Compound **2a**, **2b**, **2c**, and **3** showed inhibition ranging from 12-38% and **3** showed 22% inhibition against P99
- MTT Essay was used to test the in vitro cytotoxicity of oxadiazolidinone **2a** on cancer cell lines. **2a** had more activity on renal cancer, decreasing the cell viability of 786-0 by about 18%. The activity on other cell lines ranged from 4-14%.

Acknowledgement

- God almighty,
- My parents,
- Dr. Abbas G. Shilabin,
- David Mingle, Noah Lyon, Austin Miller, Joseph Osazee.
- Department of Chemistry and the School of Graduate Studies at ETSU.

