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Design, Synthesis, Molecular docking studies, and biological evaluation of 1, 3, 4-oxadiazol-3(2*H*)-yl] ethan-1-one derivatives as antimicrobial agents

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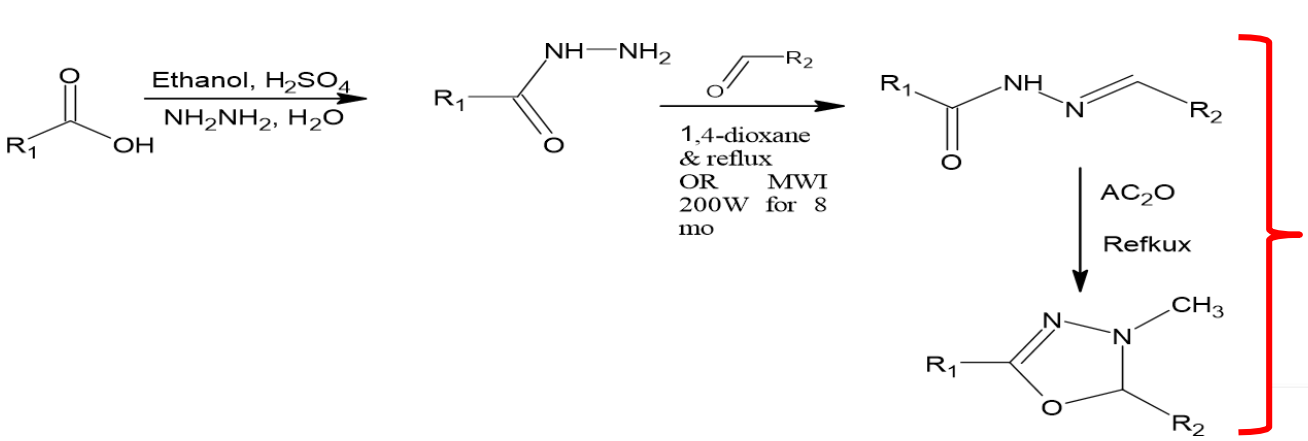
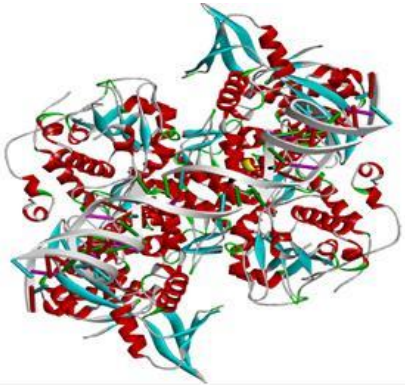
Graphical Abstract





Antimicrobial activity against E.coli DNA gyrase

Abstract:

A number of novel 1, 3, 4-oxadiazole analogues have been designed and synthesized by Condensation of substituted aldehyde/ketone with substituted benzohydrazide to form substituted N'-alkylidene benzohydrazide and then cyclization of N'-alkylidene benzohydrazide to form 1, 3, 4-oxadiazole derivatives. To investigate the antimicrobial data on structural basis, in-silico docking studies of the synthesized compounds (4a-4r) into the crystal structure of E-coli DNA gyrase (Type-2 topoisomerase) using Autodock PyRx virtual screening program were performed to predict the affinity and orientation of the synthesized compounds at the activities by using 6rks PDB. Inhibiting the ATPase activity of gyrase blocks the introduction of negative supercoils in DNA and traps the chromosome in a positively supercoiled state that may have a downstream impact on cell physiology and division. The results indicate that ketone substituted benzohydrazide derivatives show good binding affinity (-8kcal to -9kcal) and electron-withdrawing group such as $–NO_2$ and -Cl present at R1 increases the affinity of scaffold and DNA gyrase receptors and binds into the specificity pocket. In this pocket, the 1, 3, 4-oxadiazole nucleus of these compounds interacts with the amino acid Alanine A: 421, Valine A: 420, Tyrosine A: 478 and Glutamine A: 381 residues of the target. Also, it is verified by in vitro antimicrobial screening, where all the compounds were active against tested bacterial strains. Among these compounds 4(c), 4(d), (4e), (4h), (4i), 4(m), 4(n), 4(o), 4(p), and (4q) showed good bacterial zone inhibition.

Keywords: *1, 3, 4-oxadiazole, Molecular docking, In vitro Antimicrobial activity*

Introduction

- Oxadiazole being a very weak base has less electron density carbon; however its nitrogen is attacked by electrophile with electron-releasing groups.
- Literature survey has revealed that many compounds bearing a five membered heterocyclic ring containing nitrogen and oxygen like oxadiazole; have been synthesized and reported to have antibacterial, anticancer, anti-inflammatory and analgesic effects etc.
- The 1,3,4-oxadiazole ring also acts as a bioisosteres for carbonyl containing compounds such as esters, amides and carbamates. It acts like a flat aromatic linker to provide the appropriate orientation of the molecule. Derivatives of this type have antibacterial antimalarial , anti-inflammatory, antidepressive , anticancer , analgesic and antiviral effect.

Methodology

I. Synthesis of 1,3,4 Oxadiazole Derivatives

Includes two steps reaction.

(i) Synthesis of substituted hydrazide

(ii) Synthesis of Substituted 1,3,4 Oxadiazole

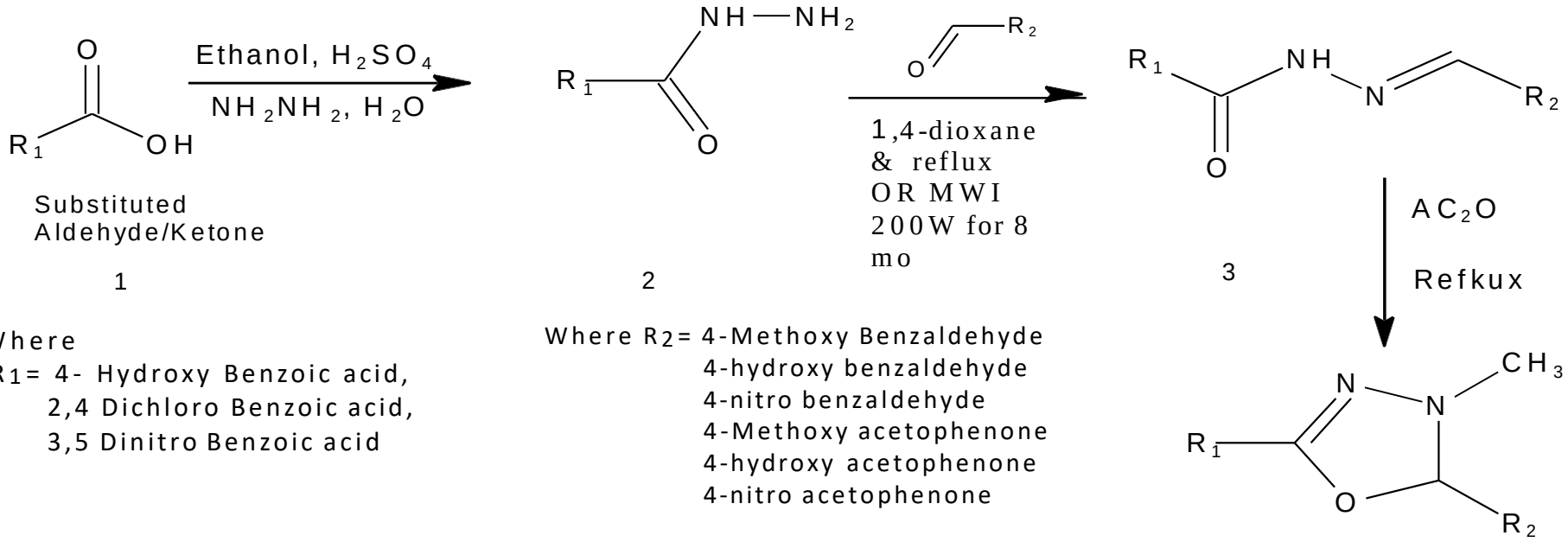
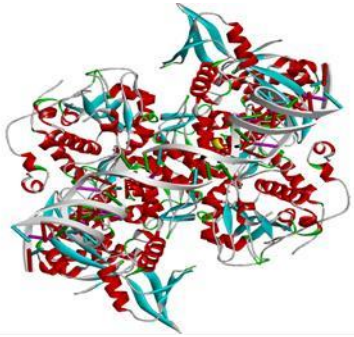


Figure. 1

3X6 Combination will lead us 18 Substituted 1,3,4 Oxadiazole Derivatives (4a-4r).

Methodology



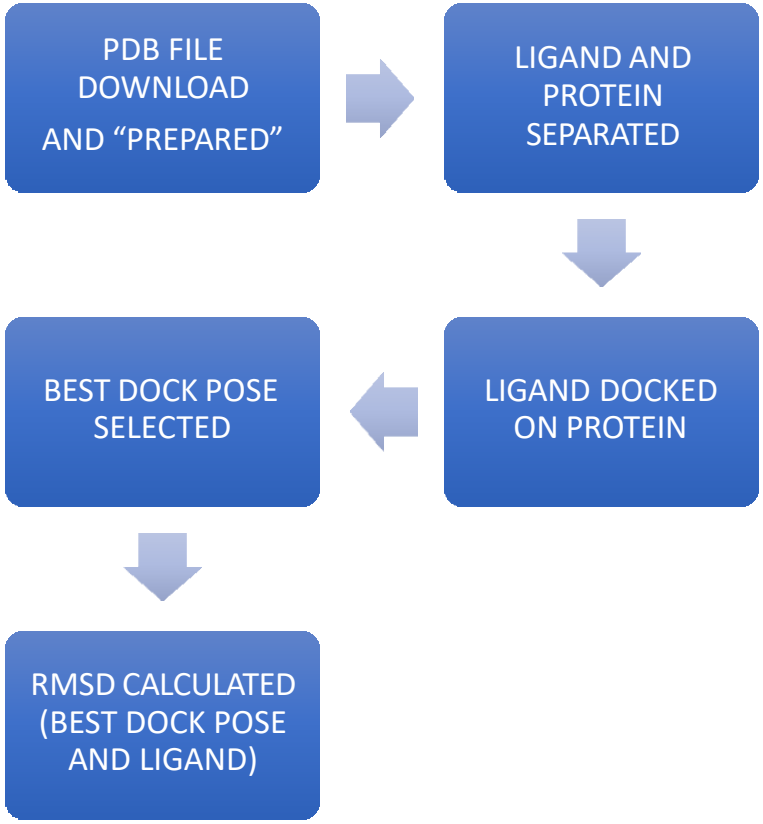
II. Auto docking studies

(i) Protein ligand docking studies by Autodock vina 4.2.

(ii) Discovery studio visualiser is used to visualize output.

Docking studies by Autodock vina 4.2

- PDB PROTEIN CODE: 6RKS
- receptor = Protein.pdbqt
- DOCKING PROTOCOL
  - center_x = 156.22
  - center_y = 148.07
  - center_z = 117.23
  - size_x = 69.2493
  - size_y = 69.5864
  - size_z = 91.4490



Methodology

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(i) Protein ligand docking studies by Autodock vina 4.2.

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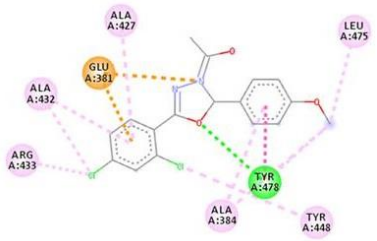
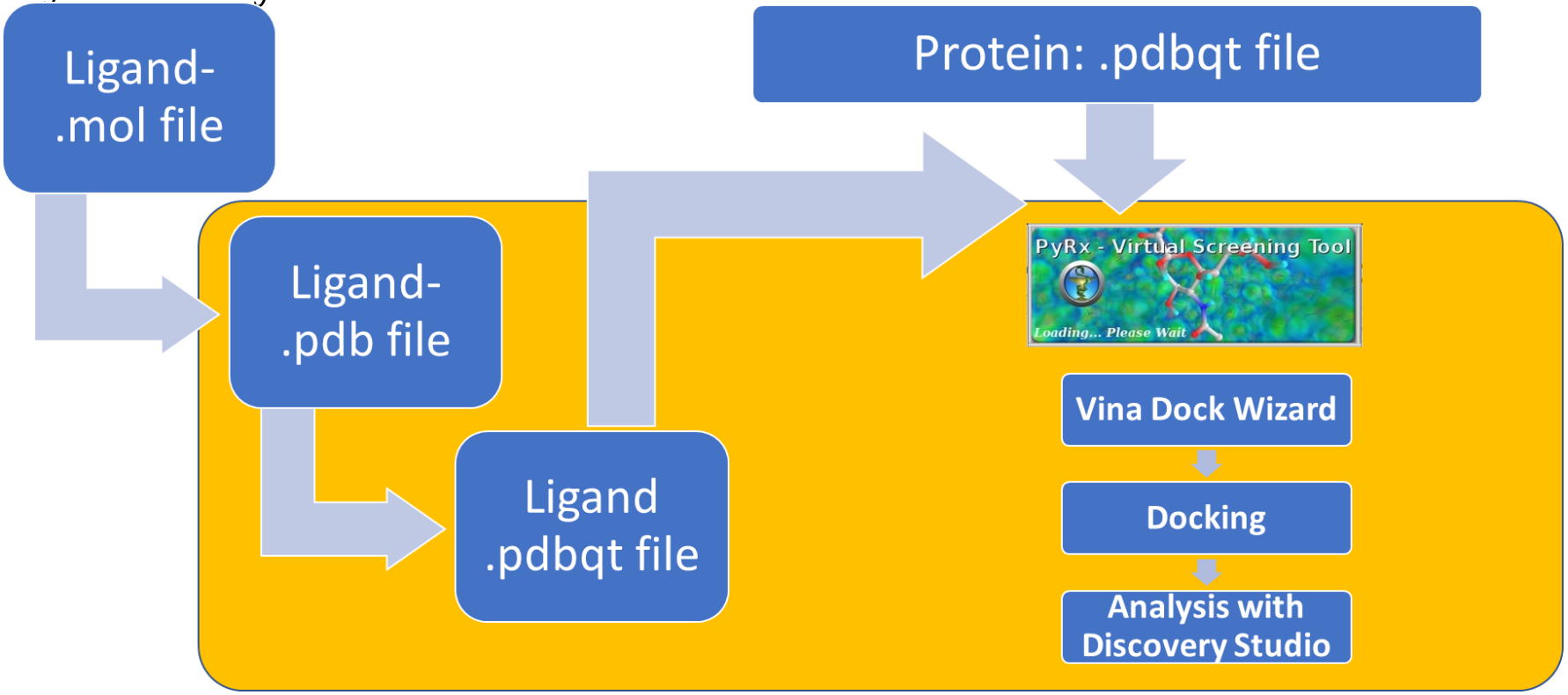
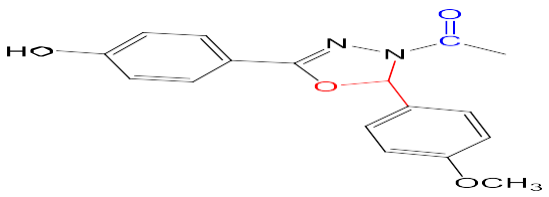
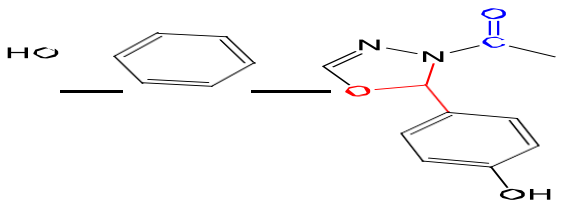
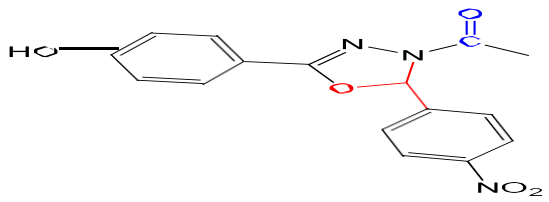


Docking of Ligands and Analysis by Discovery studio Visualiser



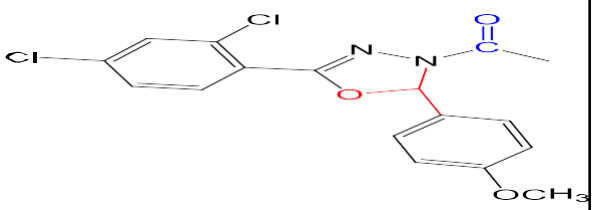
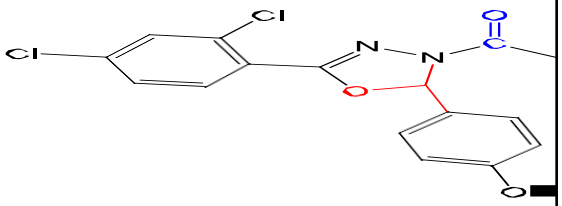
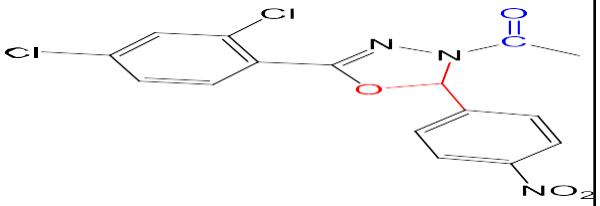
Results and discussion

Table 1: List of synthesized derivatives

Sr. No	R_1	R_2	IUPAC Name	Structure	Melting point°C	TLC studies Mobile Phase and Rf value	Appearance	Yield
IV-a	4-OH-C_6H_4	4-OCH_3-C_6H_4	1-(5-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethenone		132-134	Hexane :Ethyl acetate: 3::2 Rf=0.82	Yellowish-powder	65%
IV-b	4-OH-C_6H_4	4-OH-C_6H_4	1-(2,5-bis(4-hydroxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone		142-144	Hexane :Ethyl acetate: 3::2 Rf=0.80	Yellowish-powder	63%
IV-c	4-OH-C_6H_4	4-NO_2-C_6H_4	1-(5-(4-hydroxyphenyl)-2-(4-nitrophenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone		136-138	Hexane :Ethyl acetate: 3::2 Rf=0.79	Yellowish-powder	56%

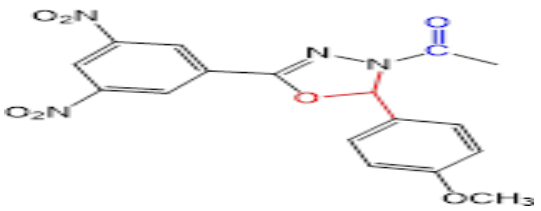
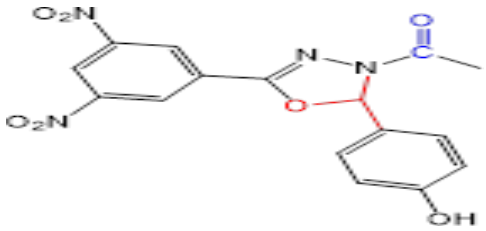
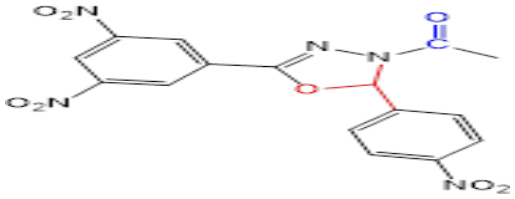
Results and discussion

Table 1: List of synthesized derivatives cont….

Sr. No	R_1	R_2	IUPAC Name	Structure	Melting point°C	TLC studies Mobile Phase and Rf value	Appearance	Yield
IV-d	2,4-Cl_2-C_6H_3	4-OCH_3-C_6H_4	1-(5-(2,4-dichlorophenyl)-2-(4-methoxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone		156-169	Hexane :Ethyl acetate: 3::2 Rf=0.81	Yellowish-powder	65%
IV-e	2,4-Cl_2-C_6H_3	4-OH-C_6H_4	1-(5-(2,4-dichlorophenyl)-2-(4-hydroxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone		180-183	Hexane :Ethyl acetate: 3::2 Rf=0.78	Yellowish-powder	63%
IV-f	2,4-Cl_2-C_6H_3	4-NO_2-C_6H_4	1-(5-(2,4-dichlorophenyl)-2-(4-nitrophenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone		182-185	Hexane :Ethyl acetate: 3::2 Rf=0.83	Yellowish-powder	56%

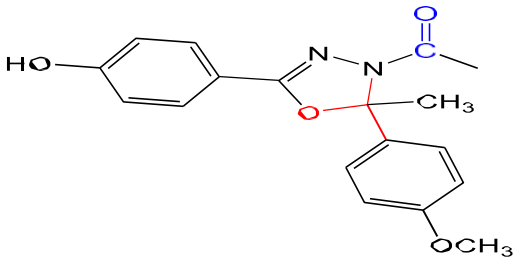
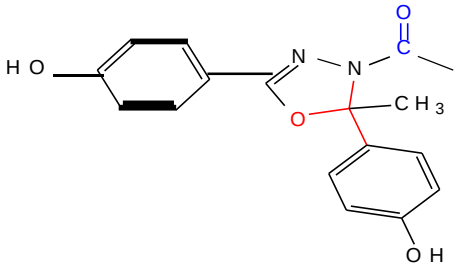
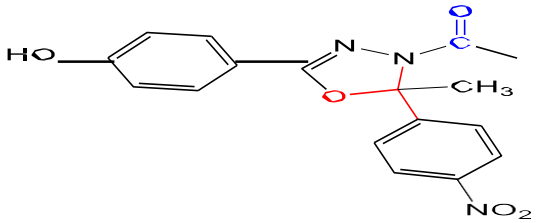
Results and discussion

Table 1: List of synthesized derivatives cont….

Sr. No	R_1	R_2	IUPAC Name	Structure	Melting point°C	TLC studies Mobile Phase and Rf value	Appearance	Yield
IV-g	3,5-$(NO_2)_2$-C_6H_3	4-OCH_3-C_6H_4	1-(5-(3,5-dinitrophenyl)-2-(4-methoxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone		168-170	Hexane :Ethyl acetate: 3::2 Rf=0.81	Yellowish-powder	65%
IV-h	3,5-$(NO_2)_2$-C_6H_3	4-OH-C_6H_4	1-(5-(3,5-dinitrophenyl)-2-(4-hydroxyphenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone		163-165	Hexane :Ethyl acetate: 3::2 Rf=0.77	Yellowish-powder	63%
IV-i	3,5-$(NO_2)_2$-C_6H_3	4-NO_2-C_6H_4	1-(5-(3,5-dinitrophenyl)-2-(4-nitrophenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone		201-205	Hexane :Ethyl acetate: 3::2 Rf=0.78	Yellowish-powder	56%

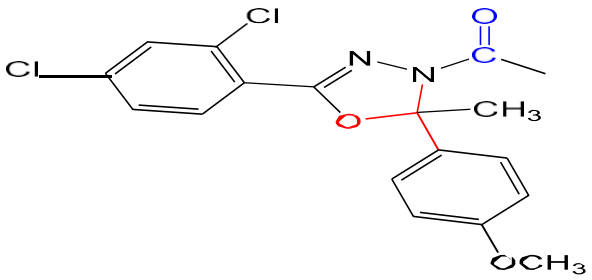
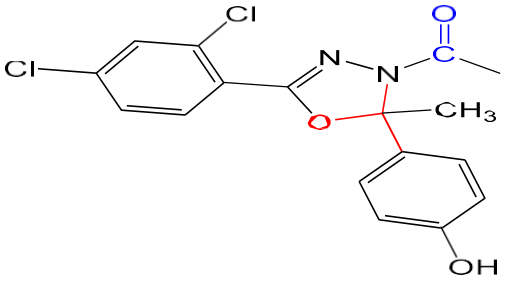
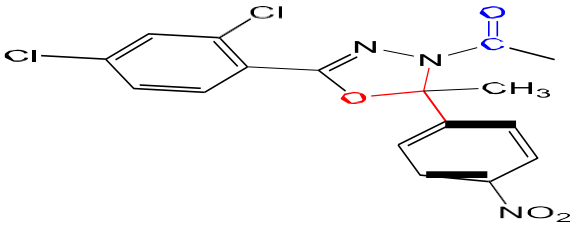
Results and discussion

Table 1: List of synthesized derivatives cont….

Sr. No	R_1	R_2	IUPAC Name	Structure	Melting point°C	TLC studies Mobile Phase and Rf value	Appearance	Yield
IV-j	4-OH-C_6H_4	4-OCH_3-C_8H_7	1-(5-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-2-methyl-1,3,4-oxadiazol-3(2H)-yl)ethenone		156-158	Hexane :Ethyl acetate: 3::2 Rf=0.80	Yellowish-powder	65%
IV-k	4-OH-C_6H_4	4-OH-C_8H_7	1-(2,5-bis(4-hydroxyphenyl)-2-methyl-1,3,4-oxadiazol-3(2H)-yl)ethanone		138-141	Hexane :Ethyl acetate: 3::2 Rf=0.77	Yellowish-powder	63%
IV-l	4-OH-C_6H_4	4-NO2-C_8H_7	1-(5-(4-hydroxyphenyl)-2-(4-nitrophenyl)-2-methyl-1,3,4-oxadiazol-3(2H)-yl)ethanone		205-210	Hexane :Ethyl acetate: 3::2 Rf=0.80	Yellowish-powder	56%

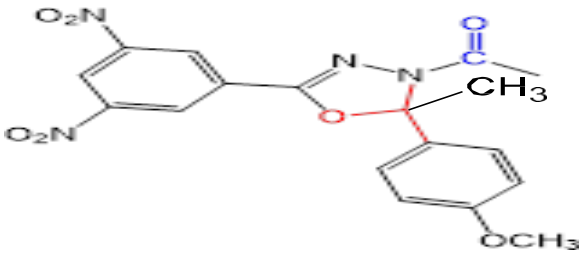
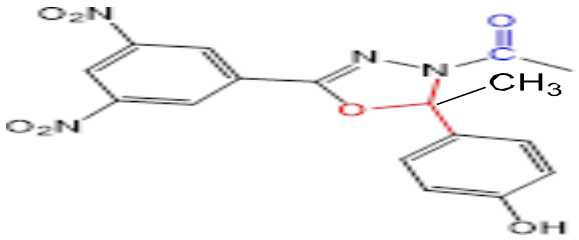
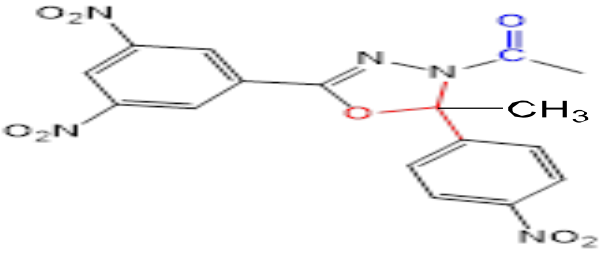
Results and discussion

Table 1: List of synthesized derivatives cont….

Sr. No	R_1	R_2	IUPAC Name	Structure	Melting point°C	TLC studies Mobile Phase and Rf value	Appearance	Yield
IV-m	2,4-Cl_2-C_6H_3	4-OCH_3-C_8H_7	1-(5-(2,4-dichlorophenyl)-2-(4-methoxyphenyl)-2-methyl-1,3,4-oxadiazol-3(2H)-yl)ethanone		186-189	Hexane :Ethyl acetate: 3::2 Rf=0.79	Yellowish-powder	65%
IV-n	2,4-Cl_2-C_6H_3	4-OH-C_8H_7	1-(5-(2,4-dichlorophenyl)-2-(4-hydroxyphenyl)-2-methyl-1,3,4-oxadiazol-3(2H)-yl)ethanone		210-215	Hexane :Ethyl acetate: 3::2 Rf=0.78	Yellowish-powder	63%
IV-o	2,4-Cl_2-C_6H_3	4-NO2-C_8H_7	1-(5-(2,4-dichlorophenyl)-2-(4-nitrophenyl)-2-methyl-1,3,4-oxadiazol-3(2H)-yl)ethanone		160-165	Hexane :Ethyl acetate: 3::2 Rf=0.78	Yellowish-powder	56%

Results and discussion

Table 1: List of synthesized derivatives cont….

Sr. No	R_1	R_2	IUPAC Name	Structure	Melting point °C	TLC studies Mobile Phase and Rf value	Appearance	Yield
IV-p	3,5-$(NO_2)_2$-C_6H_3	4-OCH_3-C_8H_7	1-(5-(3,5-dinitrophenyl)-2-(4-methoxyphenyl)-2-methyl-1,3,4-oxadiazol-3(2H)-yl)ethanone		170-180	Hexane :Ethyl acetate: 3::2 Rf=0.81	Yellowish-powder	65%
IV-q	3,5-$(NO_2)_2$-C_6H_3	4-OH-C_8H_7	1-(5-(3,5-dinitrophenyl)-2-(4-hydroxyphenyl)-2-methyl-1,3,4-oxadiazol-3(2H)-yl)ethanone		188-193	Hexane :Ethyl acetate: 3::2 Rf=0.80	Yellowish-powder	63%
IV-r	3,5-$(NO_2)_2$-C_6H_3	4-NO2-C_8H_7	1-(5-(3,5-dinitrophenyl)-2-(4-nitrophenyl)-2-methyl-1,3,4-oxadiazol-3(2H)-yl)ethanone		243-245	Hexane :Ethyl acetate: 3::2 Rf=0.83	Yellowish-powder	56%

Results and discussion

Table 2: Visualisation and Evaluation (Minimum binding energy)

Sr.No	Minimum binding energy (kcal/mol)	Hydrogen bonding	Sr. No	Minimum binding energy (kcal/mol)	Hydrogen bonding
4-a	-8.6	Leu474	**4-j**	-8.3	Leu474
4-b	-7.9	His471	**4-k**	-7.6	Gly442
4-c	-7.8	Ser464	**4-l**	-7.5	Tyr478
4-d	-8.4	Arg433	**4-m**	-7.8	Val420
4-e	-8.6	Val420	**4-n**	-8	Val420
4-f	-7.6	Tyr478	**4-o**	-8.4	Tyr478
4-g	-7.5	Arg433	**4-p**	-8	Arg433
4-h	-7.9	Ala427	**4-q**	-8	Ala427
4-i	-8.1	Gln267	**4-r**	-7.4	Gln267

Results and discussion

Table 3: Antimicrobial study against E. coli DNA gyrase

Comp	Zone of inhibition in mm	Average zone of inhibition in mm	Minimum inhibitory concentration (MIC) in µg/ml	Comp	Zone of inhibition in mm	Average zone of inhibition in mm	Minimum inhibitory concentration (MIC) in µg/ml
IV-a	17	17	25	IV-d	20	20	12.5
	17				20		
	18				21		
IV-b	20	21	12.5	IV-e	25	24	6.25
	21				23		
	22				23		
IV-c	22	21	25	IV-f	20	20	25
	21				21		
	21				20		

Results and discussion

Table 3: Antimicrobial study against E. coli DNA gyrase cont….

Comp	Zone of inhibition in mm	Average zone of inhibition in mm	Minimum inhibitory concentration (MIC) in µg/ml	Comp	Zone of inhibition in mm	Average zone of inhibition in mm	Minimum inhibitory concentration (MIC) in µg/ml
IV-g	19	19	50	IV-j	21	21	25
	19				21		
	20				22		
IV-h	22	23	25	IV-k	20	20	100
	22				21		
	24				20		
IV-i	23	23	12.5	IV-l	20	17	100
	24				18		
	22				17		

Results and discussion

Table 3: Antimicrobial study against E. coli DNA gyrase cont…..

Comp	Zone of inhibition in mm	Average zone of inhibition in mm	Minimum inhibitory concentration (MIC) in µg/ml	Comp	Zone of inhibition in mm	Average zone of inhibition in mm	Minimum inhibitory concentration (MIC) in µg/ml
IV-m	19	19	25	IV-p	21	20	25
	19				21		
	20				19		
IV-n	21	20	12.5	IV-q	21	20	25
	20				22		
	20				20		
IV-o	21	20	12.5	IV-r	18	19	50
	21				19		
	19				19		

Results and discussion

Table 3: Antimicrobial study against E. coli DNA gyrase

Comp		Zone of inhibition in mm	Average zone of inhibition in mm	Minimum inhibitory concentration (MIC) in µg/ml
Std	**Ciprofloxacin**	27	27	2
		28		
		26		
Std	**Gentamycin**	26	26	2
		25		
		27		

Conclusions

- 18 heterocyclic derivatives of 1,3,4-Oxadiazole of substituted Aldehyde/Ketone [Figure 1 and Table 1] were successfully synthesized.
- Among the newer analogs, ten compounds exhibited promising antimicrobial activity against DNA gyrase.
- In silico studies results indicate that $–NO_2$, -Cl substituted benzohydrazide derivatives show good binding affinity which is also confirmed by in-vitro antimicrobial activity against E.coli.[Table 2 and Table 3].

Acknowledgments

The authors are thankful to LSHGCT Gahlot Institute of Pharmacy, Koperkhairane, Navi Mumbai and SVKMs Dr.Bhanuben Nanavati college of Pharmacy, Vile parle , Mumbai for providing facilities to synthesis and antimicrobial activity of compounds reported herein.