International Journal of Bioinformatics Research
ISSN: 0975–3087, E-ISSN: 0975–9115, Vol. 3, Issue 1, 2011, pp-118-134
Available online at http://www.bioinfo.in/contents.php?id=21

INSILICO DRUG ACTIVITY OF N-OXIDES

VALLI G.*, LALITHISWARI T., JOTHIMALAR S. AND RAJESWARI N.
*Department of chemistry, The Standard Fireworks Rajaratnam College for Women, Sivakasi, 626123, Virudhunagar District, Tamil Nadu State, India
*Corresponding author. E-mail: mrs.valliravichandran@gmail.com

Received: August 10, 2010; Accepted: December 30, 2010

Abstract- N-Oxides were found to have antimicrobial activity. In continuation of our work on synthesis, characterization and biological activities (in vitro method) of N-Oxides and knowing their biological activities against micro organisms, we have correlated the biological activity of these N-Oxides against the micro organisms like *Staphylococcus aureus, Salmonella typhi "H", Escherichia Coli, Pseudomonas aeruginosa, Klebsiella aerogenes, Enterobacteraerogenes, Citrobacter, Staphylococcus epidermidis, and Aeromonas hydrophila* by *Insilico* method. The target molecules (microorganism) were taken from Protein data bank. Various soft wares were used to find out the drug likeness properties of these N-Oxides. Online software "Molinspiration" was used to calculate log P (ie) Hydrophobicity of a drug. ACD/ Chemsketch was used to draw the structures of N-Oxides. Hex 4.2, docking software was used to predict the drug activities of these N-Oxides. The drug activities were measured in terms of drug likeness property by recording the E-Total value and compared with the marketed standard drugs for the above micro organism infections. Standard drugs were taken from drug bank. As per the standard norms, it was observed that the compounds that have negative E-Total values could be used as a drug. We have selected Ceftazidime ,Cefepime and Ceftizoxime as standard drugs among the available drugs for these microorganism for correlating the drug activities of these N-Oxides. We observed that some of our N-Oxides were found to have higher drug activities compared to standard drugs.
Keywords: N-Oxides, log P, Hex 4.2, ChemSketch

INTRODUCTION

N-Oxides, have been found extensive use in the field of organic synthesis [1], Pharmaceuticals [2] and corrosion inhibition studies. N-Oxides were found to have antimicrobial [3], insecticidal, miticidal, pesticidal and repellent activities. N-Oxides have received great attention during recent years, because of their utility as important intermediates in organic synthesis. Some N-Oxides have also been used as spin trapping reagents and are utilized in studies concerning detection of radical species. Our work on synthesis, characterization and antimicrobial activities N-Oxides by in vitro method revealed that these N-Oxides were found to have moderate activity. Hence we would like to correlate these activities using *Insilico* method.

Molinspiration

We have drawn the structures of N- Oxides using Molinspiration, which is an Online chemdraw tool and calculated Hydrophobicity (log P value) of these molecules.

Hydrophobic Parameter (*LogP*):

Hydrophobicity of a molecule is measured by its log P value, where P is known as Partition coefficient.

Hydrophobicity affects drug absorption, bioavailability, hydrophobic drug-receptor interactions, metabolism of molecules, as well as their toxicity. The Log P value of a compound, which is the log of its partition coefficient between n-octanol and water, [log ([octanol] / [water])]. It has been shown for compounds to have a reasonable probability of being well absorb, *their log P value must not be greater than 5.0.*

EXPERIMENTAL WORK

A. Calculation of log P value

The structures of 115 N-Oxides of different categories (I to XII series) were drawn in Molinspiration and the calculated log P values were listed in Table I. Log P values indicate the hydrophobicity of a drug. We observed that some of the N-Oxides were found to have negative and very low log P values(less than 5). Hence they may possess the drug activity. We have already reported the in vitro drug activity of these N-Oxides and observed that they were found to have moderate drug activities. Knowing the drug activity of these N-Oxides, we planned to compare their drug activities with the standard drugs available in the market against some microorganism by Insilco method.

ACD/ChemSketch

ACD/ChemSketch is an integrated software package from Advanced Chemistry Development Inc. for drawing chemical structures, reactions, schematic diagrams and other chemistry – related reports and presentations. We have drawn 115 N-

Oxide in ACD/ Chem Sketch. One example is given in the following figure (Fig.I) and saved in pdb file format.
The following three antibiotics were taken as the standard drugs from the drug bank.

1.Ceftazidime
Ceftazidime is a third-generation cephalosporin antibiotic. Like other third- generation cephalosporins, it has broad spectrum activity against Gram-positive and Gram-negative bacteria. Ceftazidime is usually reserved for the treatment of infections caused by *Pseudomonas aeruginosa*.

2. Cefepime
Cefepime has an extended spectrum of activity against Gram-positive and Gram-negative bacteria, with greater activity against both Gram-negative and Gram-positive organisms than third-generation agents. Cefepime has good activity against important pathogens including *Pseudomonas aeruginosa, Staphylococcus aureus,* and multiple drug resistant *Streptococcus pneumoniae*. A particular strength is its activity against *Enterobacteriaceae*.

3. Ceftizoxime
Ceftizoxime is a third generation Cephalosporin antibiotic. It is used for the treatment of lower respiratory tract infections, Urinary tract infections caused by *E.Coli, S.aureus, Enterobacter* and *Klebsiella* species. It has higher activity against *Aeromonas hydrophila*. Ceftizoxime has cross sensitivity with penicillin allergies.

HEX 4.2
Macromolecular Docking was done using HEX 4.2 – software using Spherical Polar Fourier Correlations. In Hex's docking calculations, each molecule is modeled using 3D parametric functions, which are used to encode both surface shape and electrostatic charge and potential distributions. With suitable scaling factors, this docking score can be interpreted as interaction energy. Hex reads protein and DNA molecular structures from PDB- format files. These are treated as receptor.

Docking
In order to run a docking calculation in *Hex*, first we have to load a *receptor* and a *ligand* in *pdb* file format structure using the
File pull-down menu. Then Docking can be carried out using the options.
Controls → Docking → Activate.
To save the Docking Results:
The current docking orientation can be written to a single pdb file by selecting
File → Save → Both.

Docking of N-Oxides
Various steps involved are:

- Structure of the N-Oxides was drawn using the drawing tools in ACD/ChemSketch as given in Fig.I.
- The 3D structure of the receptors (Microorganisms) were obtained from *Protein Data Bank.*
- Docking menu was clicked to carryout Docking process.

The result obtained after docking gets completed were shown in Fig. II as examples.
We have calculated the E-Total value of N-Oxides against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Enterobacter aerogenes, Citrobacter, Staphylococcus epidermidis, Aeromonas hydrophila, Salmonella typhi "H" and Klebsiella Aerogenes* micro-organisms using Hex 4.2 docking software, and observed that some of our N-Oxides have been found to have higher drug activities than the standard drugs

RESULT AND DISCUSSION
All the 115 N-Oxides were made to undergo docking with the selected microorganism and their E-Total were recorded. Some of the N-Oxides were found to possess higher drug activities than the standard and are tabulated as given below with respect to the selected microorganisms.

I. Against *Staphylococcus aureus*:
A. Comparison with Cefepime:
Among the 115 N-Oxides, XII i (-246.60), XII d (-241.38), XII g (-238.18), XII f (-237.02), XII c (-236.36), XII j (-236.35), XII h (-230.43) were found to have higher value than Cefepime.(Table-II)
B. Comparison with Ceftizoxime:
Twenty one N-Oxides were found to have higher activities than Ceftizoxime against *Staphylococcus aureus*.(Fig.III.) & (Table-III)

II. Against Salmonelle typhi "H":
A. Compared to standard Ceftazidime, compound XII i was found to possess higher drug activity with the energy value -262.17. The standard drug value is -242.45.
B. Comparison with Cefepime:
Compared to Cefepime ten N-Oxides as mentioned in Table-IV have higher drug activities against *Salmonelle typhi "H"*
C. Comparison with Ceftizoxime:
XII i, VI g, XII h, XII f , XII j, XII g, XII e and VII i N-Oxides were observed to have higher drug activity than Ceftizoxime(Table-V)

III. Against *Escherichia Coli:*
A. Comparison with Cefepime:
Seven N-Oxides (listed in Table-VI) were shown higher drug activities than Cefepime**.**
B. Correlation with Ceftizoxime:
Thirty seven N-Oxides were observed to have higher drug activity than Ceftizoxime (Table-VII).

IV. Against *Pseudomonas Aeruginosa:*
A. Comparison with Ceftazidime:
Compounds XII i (-246.32), XII d (-235.14) and XII g (-235.14) were shown higher activities than Ceftazidime(-234.36).
***B.* Correlation with Cefepime**:

Compounds XII i (-246.32), XII d (-235.14), XII g (-235.14) and XII f (-230.54) possessed higher activities than Cefepime(-230.48).

C. Comparison with Ceftizoxime:

Compared to the standard Ceftizoxime , XII i, XII d, XII g, XII f, XI e, XII j, XII h, XII c, VI i, III i , XII b, XII e, VII i, and XII a were having higher activities against *Pseudomonas Aeruginosa* (Table-VIII).

V. Against *Klebsiella Aerogenes:*

A. Comparison with Ceftazidime:

Forty two compounds were found to have higher drug activities. Among these N-Oxides compound VIg possessed greater activity than standard Ceftazidime.(Table-IX).

B. Comparison with Ceftizoxime:

Compared to standard Ceftizoxime, compound VI g was found to possess higher drug activity against *Klebsiella Aerogenes* with the energy value -213.39 which was greater than the standard drug value, -208.84.

VI. Against *Enterobacter Aerogenes:*

***A*. Comparison with Ceftazidime:**

The E-total value of Compounds XII c (-200.18), XII b (-198.91), XII i (-197.09), XII d (-195.20), VI i (-190.19) and Ceftazidime (-185.85) were observed.

B. Comparison with Ceftizoxime:

Compared to Ceftizoxime(-196.73) Compounds XII c (-200.18), XII b (-198.91), XII i (-197.09) were found to possess higher drug activities.

VII. Against *Citrobacter:*

A. Correlation with Ceftazidime and Ceftizoxime:

E-Total for Compounds and the standard were VI i (-210.56), VI g (-204.72), XII a (-204.52) Ceftazidime (-202.49) and Ceftizoxime(-201.84).

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VIII. Against *Staphylococcus Epidermidis:*

A. Correlation with Ceftazidime:

Twenty one N-Oxides were found to have higher drug activities. Among these compounds VI i have higher drug activity than the standard Ceftazidime against *Staphylococcus Epidermidis*. (Table-X)

B. Comparison with Ceftizoxime:

Drug activities of Compounds XII f (-205.44), VI i (-204.36), XII a (-200.08) were higher than Ceftizoxime(-195.89).

IX. Against *Aeromonas Hydrophila:*

A. Comparison with Ceftazidime:

Among the thirty nine N-Oxides given in Table-XI, the compound XII c (2-{(Z)-[(4-hydroxyphenyl)(oxido)-λ5-azanylidene]methyl}phenyl 4-methylbenzene sulfonate) was found to possess higher drug activity than the standard Ceftazidime against *Aeromonas Hydrophila*.

B. Comparison with Cefepime:

From the result given in Table-XII , Compound XII c (2-{(Z)-[(4-hydroxyphenyl)(oxido)-λ5-azanylidene]methyl}phenyl 4-methylbenzenesulfonate) showed higher drug activity than the standard Cefepime against *Aeromonas Hydrophila*.

C. Comparison with Ceftizoxime:

Compounds XII c (-161.75), and XII b (-160.97) were having higher drug activities than the standard Ceftizoxime (-154.55).

CONCLUSION

Insilico drug activity comparison revealed the following observations:

- The compound XII i was found to possess higher drug activity against *Staphylococcus aureus, Salmonella typhi "H", Escherichia Coli and Pseudomonas Aeruginosa.*
- The compound VIg possessed greater drug activity against *Klebsiella Aerogenes.*
- The compound XIIc have shown higher drug activity against *Enterobacter Aerogenes.*
- The compound Vii showed higher drug activity against *Citrobacter* and *Staphylococcus Epidermidis.*
- The compound XIIc observed to have higher drug activity against *Aeromonas Hydrophila*

  than the standard drugs chosen for the comparison of drug activities

We observed that the antimicrobial activity determination by both Invitro and Insilco methods are parallel in their result and revealed that these N-Oxides can be used as an antimicrobial agent.

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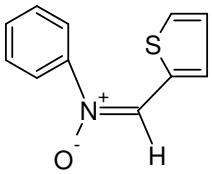
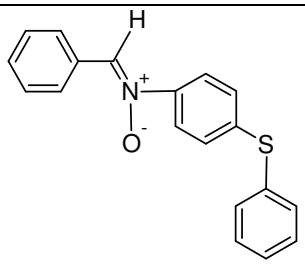
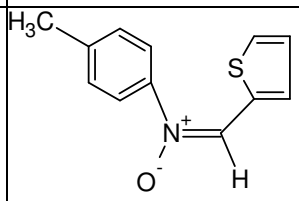
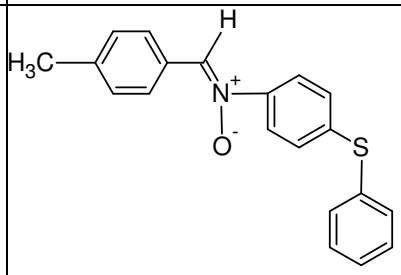
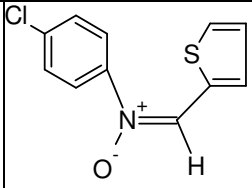
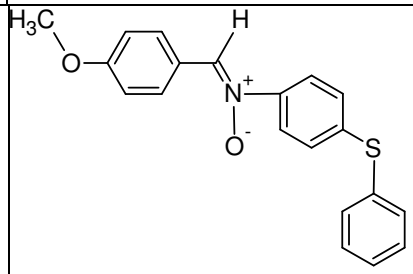
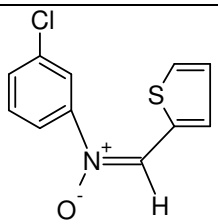
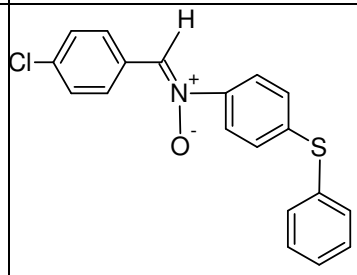
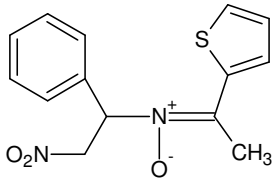
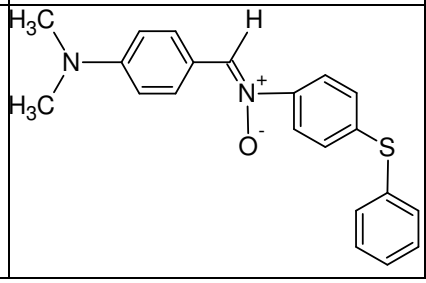
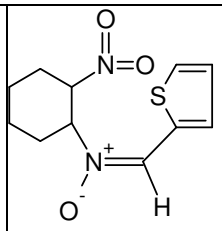
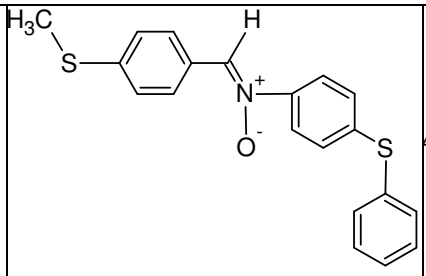
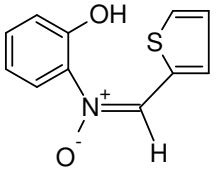
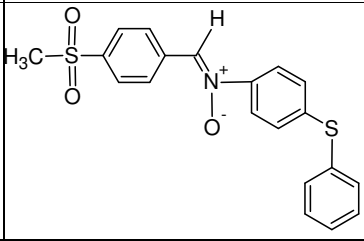
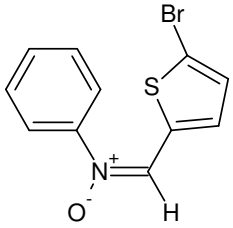
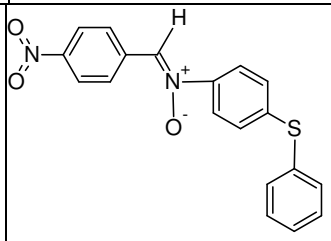
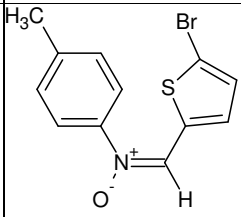
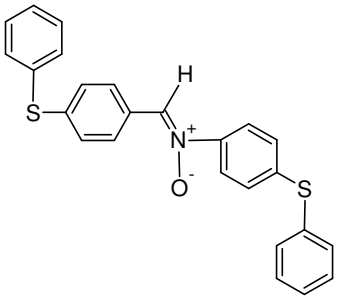
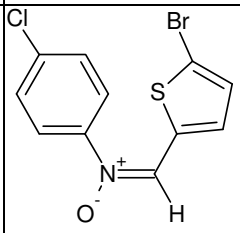
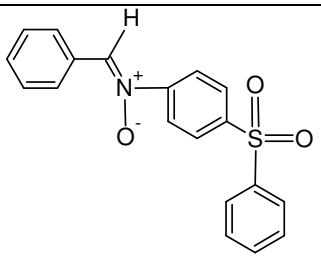
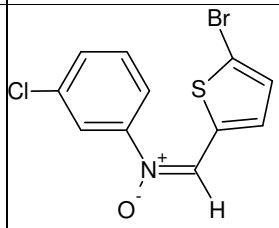
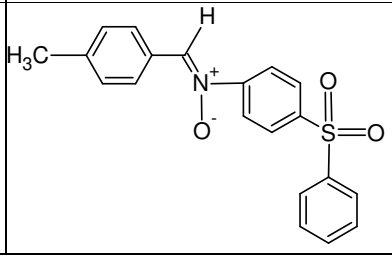
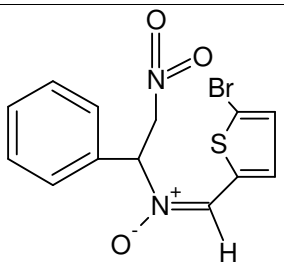
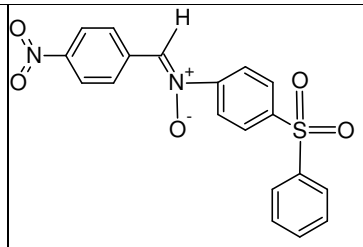
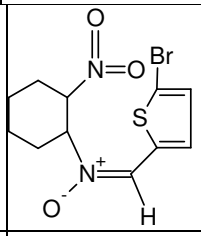
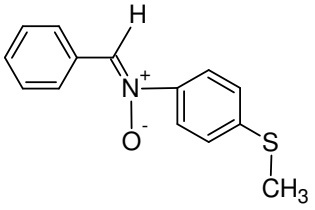
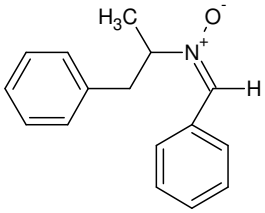
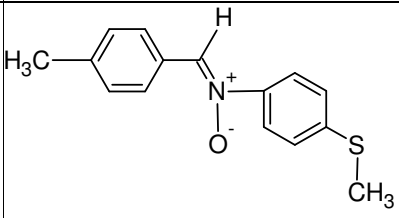
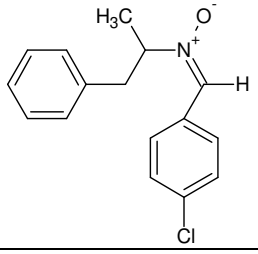
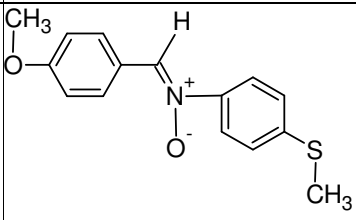
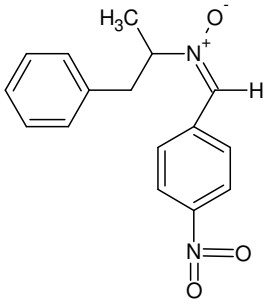
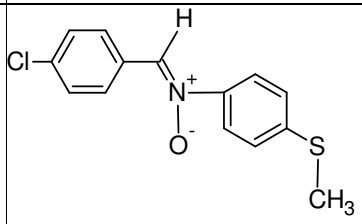
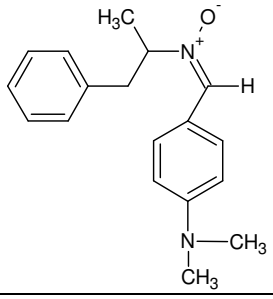
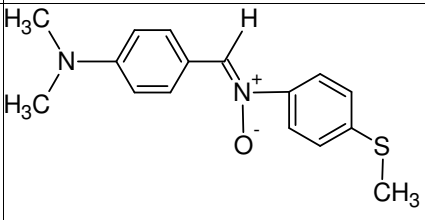
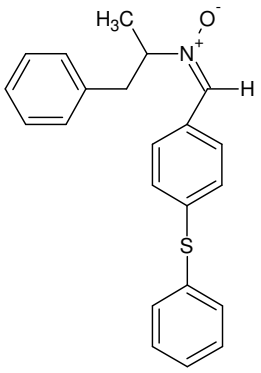
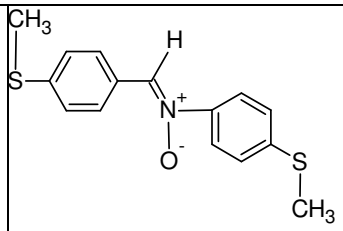
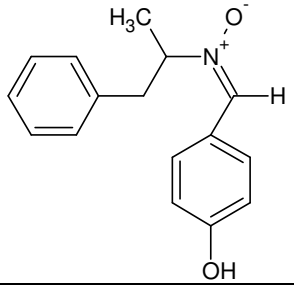
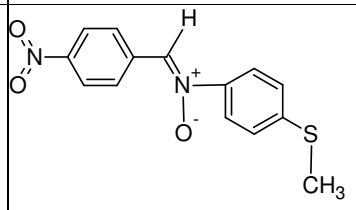
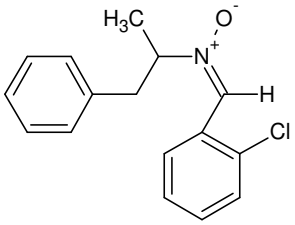
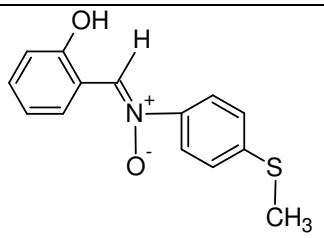
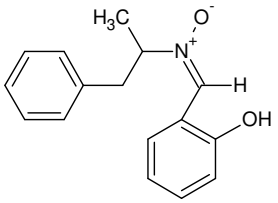
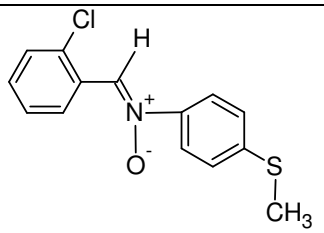
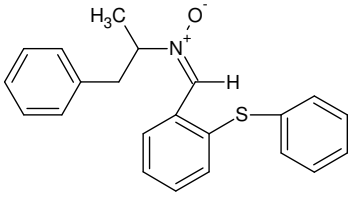
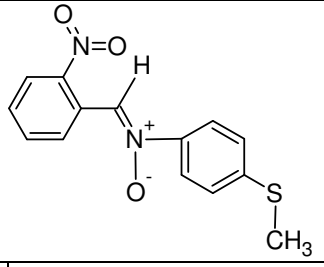
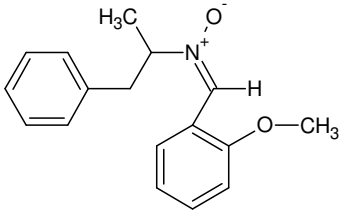
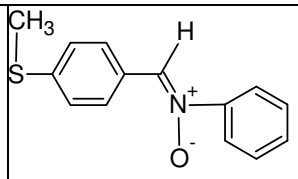
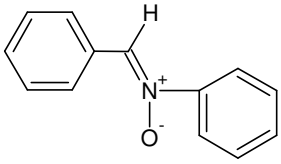
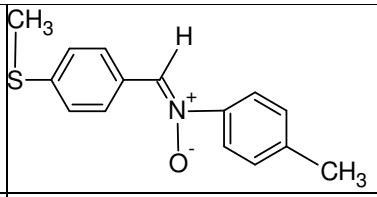
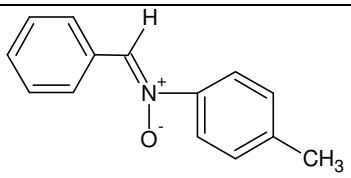
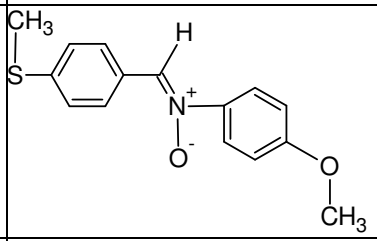
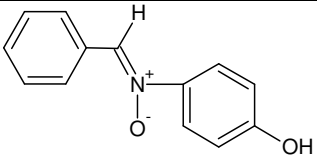
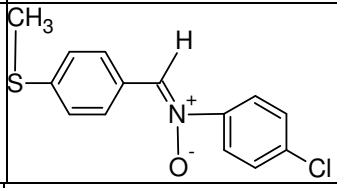
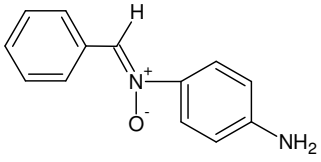
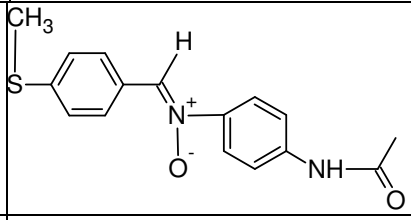
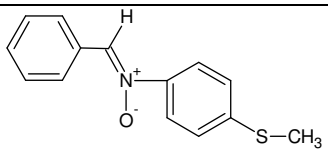
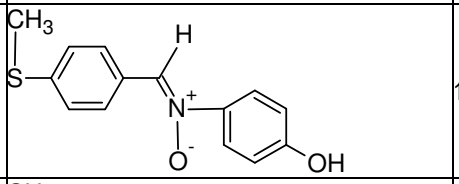
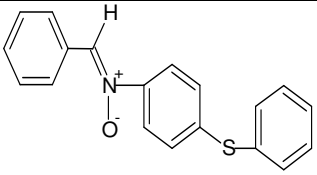
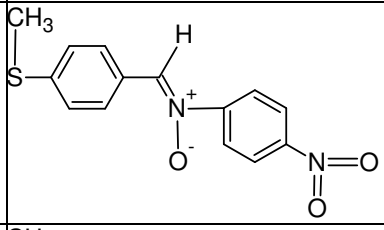
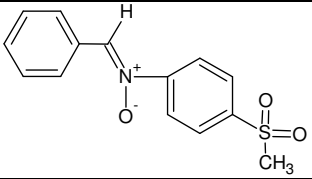
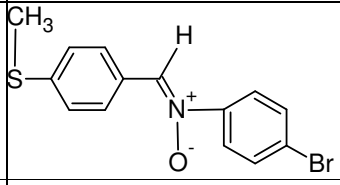
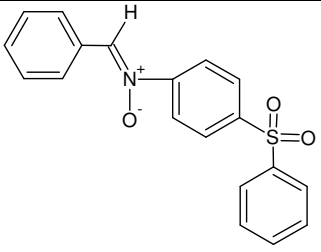
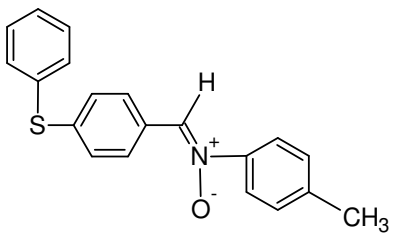
Table-I

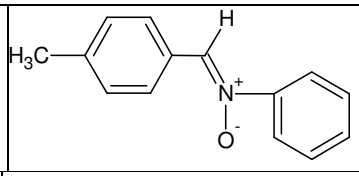
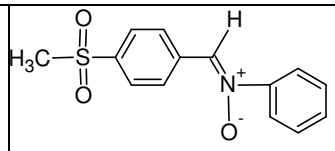
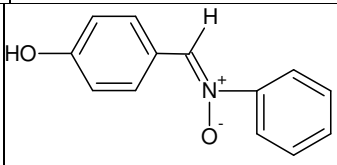
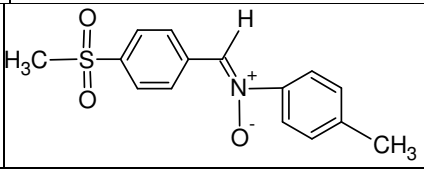
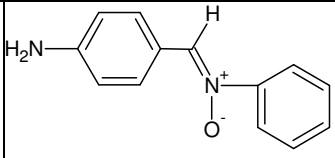
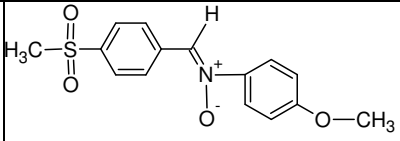
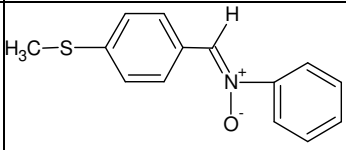
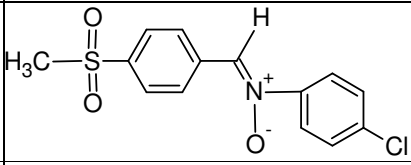
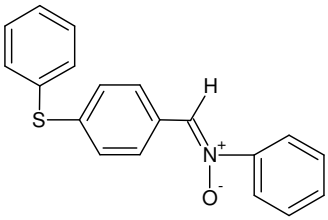
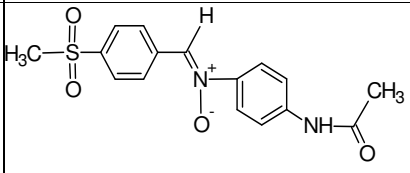
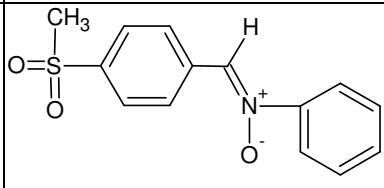
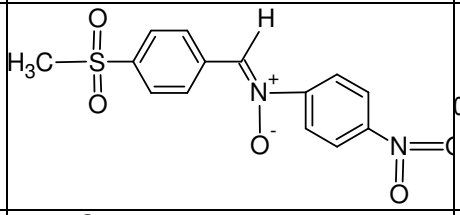
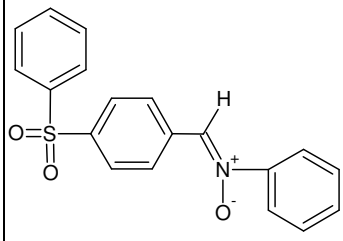
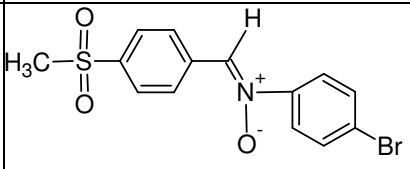
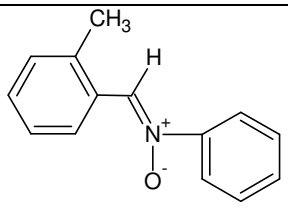
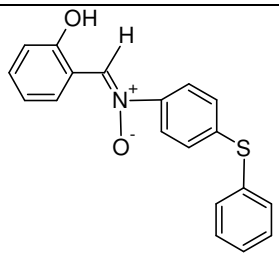
No	N-Oxides	Log P Value	No	N-Oxides	Log P Value
I a		1.595	VIIa		3.663
I b		2.044	VIIb		4.111
I c		2.273	VIIc		3.72
Id		2.249	VIId		4.341
I e		1.469	VIIe		3.765

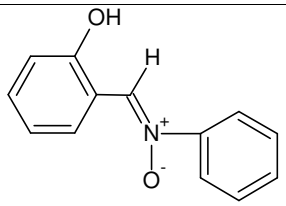
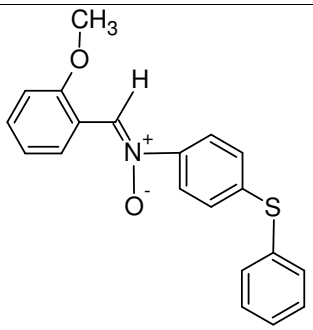
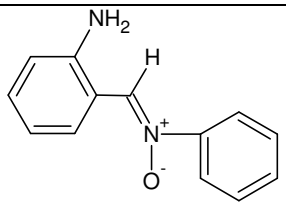
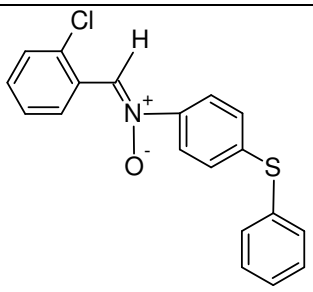
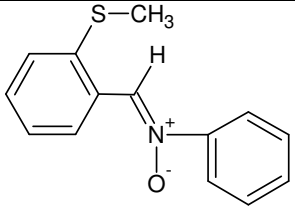
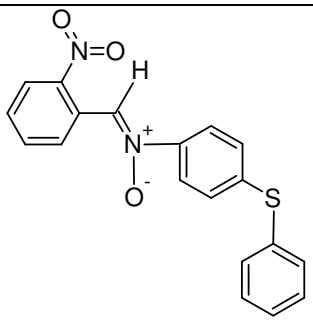
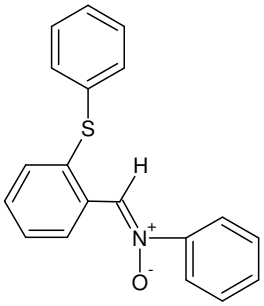
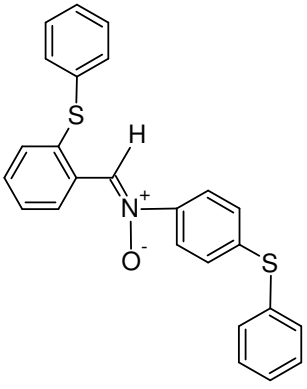
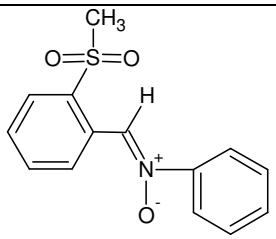
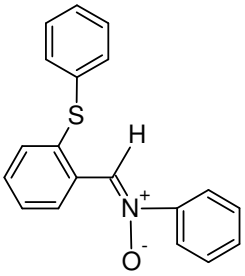
If		1.274	VIIf		4.097
I g		1.328	VIIg		2.532
II a		2.528	VIIh		3.622
II b		2.977	VIIi		5.63
II c		3.206	VIIj		2.538
II d		3.182	VIIk		2.987

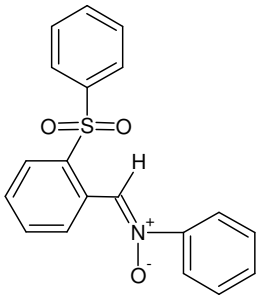
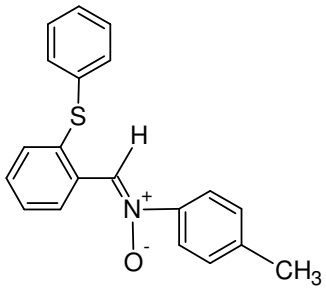
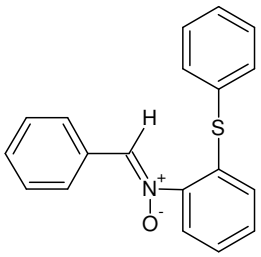
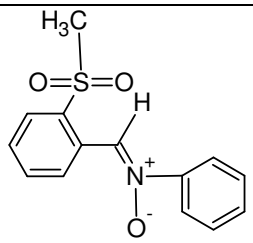
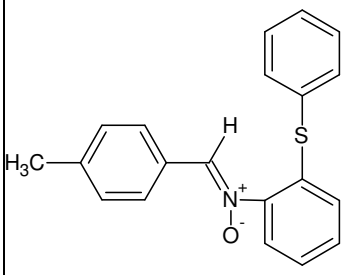
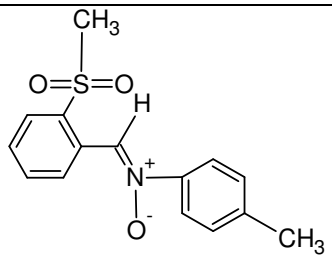
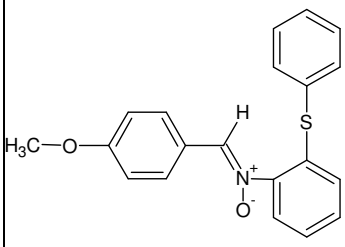
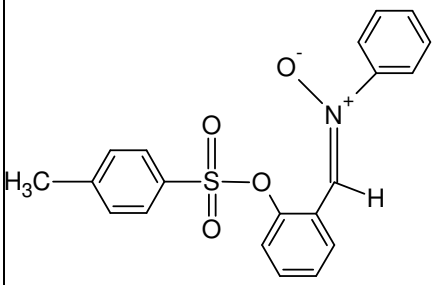
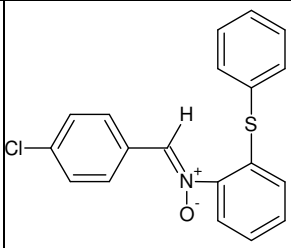
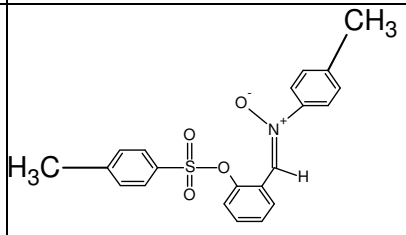
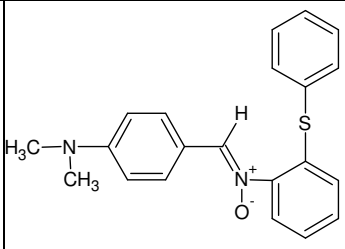
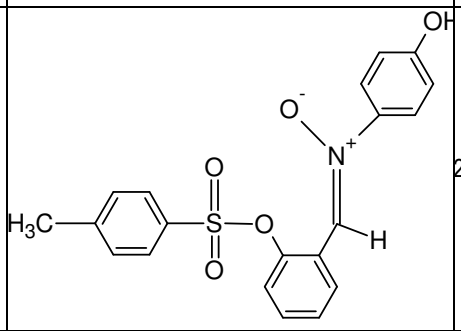
II e		2.402	VIII		2.497
II f		2.207	VIIIa		2.13
III a		2.338	VIIIb		2.578
III b		3.016	VIIIc		2.186
III c		2.297	VIIId		2.808
III d		2.441	VIIIe		2.232

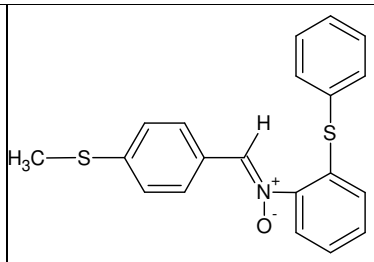
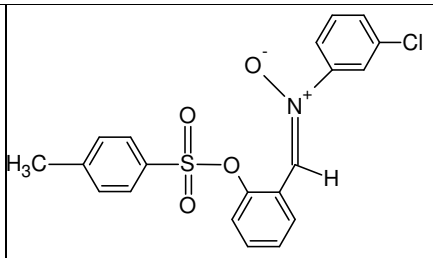
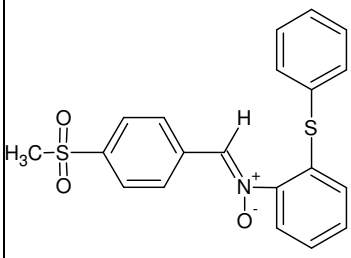
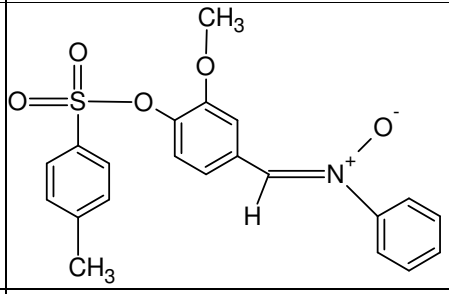
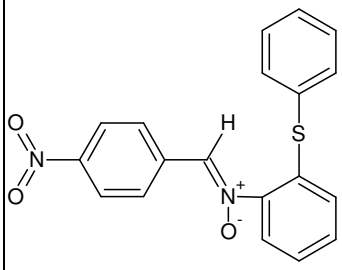
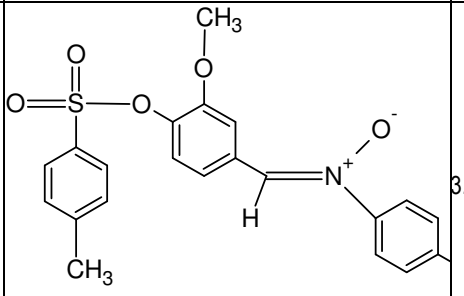
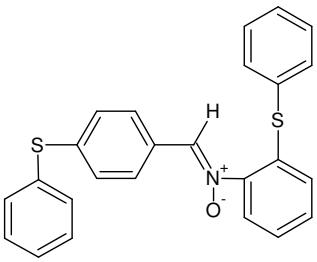
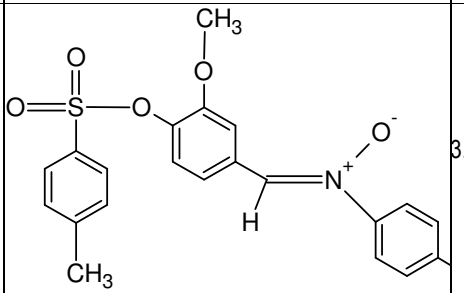
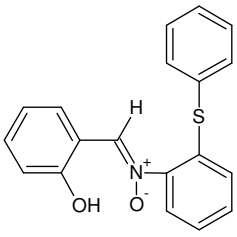
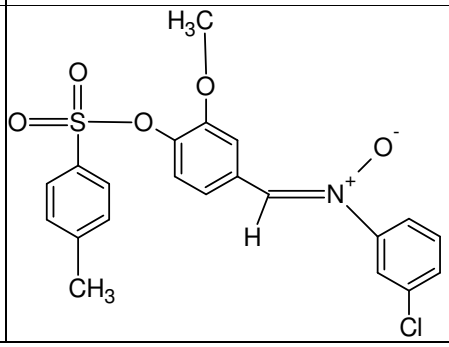
III e		4.305	VIIIf		2.563
III f		1.859	VIIIg		2.089
III g		2.968	VIIIh		2.07
III h		2.279	VIIIi		2.76
III i		4.257	VIIIj		2.041
III j		2.347	IXa		2.13

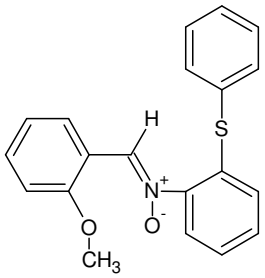
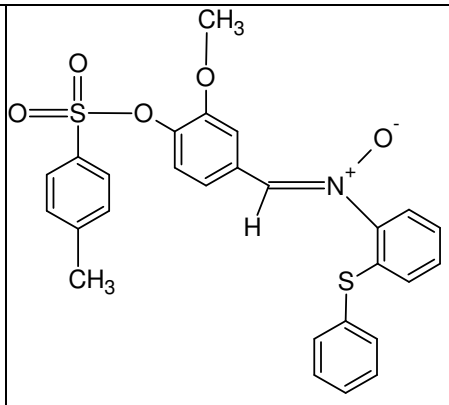
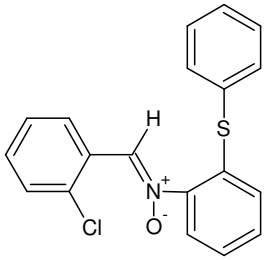
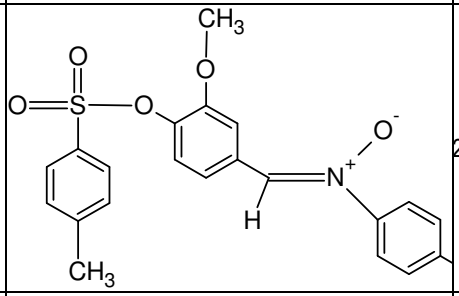
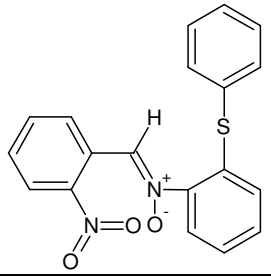
IV a		1.696	IXb		2.578
IV b		2.145	IXc		2.186
IV c		1.217	IXd		2.808
IV d		0.772	IXe		1.348
IV e		2.13	IXf		1.65
IV f		3.663	IXg		2.089
IV g		0.566	IXh		2.939
IV h		2.538	Xa		4.111

V a		2.145	Xb		0.566
V b		1.217	Xc		1.014
V c		0.772	Xd		0.622
V d		2.13	Xe		1.244
V e		3.663	Xf		0.216
V f		0.566	Xh		0.524
V g		2.538	Xi		1.375
V h		2.097	XIa		3.603

V i		1.636	XIb		3.672
V j		1.131	XIc		4.293
V k		2.082	XId		3.574
V l		3.615	XIe		5.582
V m		0.957	XIf		3.615

V n		2.49	XIg		4.063
VI a		3.615	XIh		0.957
VI b		4.063	XIi		1.405
VI c		3.672	XIIa		3.062
VI d		4.293	XIIb		3.51
VI e		3.717	XIIc		2.582

VI f		4.048	XIId		3.716
VI g		2.485	XIIe		4.692
VI h		3.574	XIIf		3.575
VI i		5.582	XIIg		3.551
VI j		3.555	XIIh		4.816

VI k		3.624	XIIi		2.418
VI l		4.245	XIIj		2.897
VI m		3.526			

I. Against *Staphylococcus aureus*:

Table-II

Compound	E-Total	Compound	E-Total	Compound	E-Total
XII i	-246.60	XII f	-237.02	XII h	-230.43
XII d	-241.38	XII c	-236.36	Cefepime	-228.92
XII g	-238.18	XII j	-236.35		

Table-III

Compound	E-Total	Compound	E-Total	Compound	E-Total
XII i	-246.60	XII b	-227.75	XI a	-209.94
XII d	-241.38	XI e	-226.67	X f	-207.16
XII g	-238.18	XII a	-219.03	XI f	-206.52
XII f	-237.02	VI i	-218.20	XI e	-205.53
XII c	-236.36	XI d	-217.93	XI g	-204.75
XII j	-236.35	XI b	-215.34	Ceftizoxime	-201.69
XII h	-230.43	XI c	-211.17		
XII c	-228.35	VI h	-210.56		

II. Against *Salmonelle typhi "H":*

Table-IV.

Compound	E-Total	Compound	E-Total	Compound	E-Total
XII i	-262.17	XII j	-233.77	V g	-223.04
VI g	-241.37	XII g	-233.52	XII c	-219.29
XII h	-239.66	XII e	-232.77	Cefepime	-219.22
XII f	-235.05	VII i	-224.03		

Table-V.

Compound	E-Total	Compound	E-Total	Compound	E-Total
XII i	-262.17	XII f	-235.05	XII e	-232.77
VI g	-241.37	XII j	-233.77	VII i	-224.03
XII h	-239.66	XII g	-233.52	Ceftizoxime	-223.18

III. Against *Escherichia Coli:*

Table-VI.

Compound	E-Total	Compound	E-Total	Compound	E-Total
XII i	-255.66	XII g	-241.38	XII j	-235.72
XII f	-254.61	VII i	-237.31	Cefepime	234.04
XII h	-243.21	XI e	236.65		

Table-VII.

Compound	E-Total	Compound	E-Total	Compound	E-Total
XII i	-255.66	VII i	-217.55	VII d	-201.35
XII f	-254.61	VII k	-216.25	III e	-198.48

Compound	E-Total	Compound	E-Total	Compound	E-Total
XII h	-243.21	V g	-214.40	VI h	-198.45
XII g	-241.38	VII g	-212.87	I f	-198.44
VII i	-237.31	X f	-211.77	X g	-198.11
XI e	-236.65	XII a	-211.59	X d	-198.06
XII j	-235.72	VII e	-207.55	VII b	-197.56
XII e	-232.17	XI d	-207.41	X h	-197.15
VII l	-231.36	XI f	-206.44	XI b	-195.94
XII c	-228.24	VI g	-204.04	III i	-195.56
VI i	-228.07	VII c	-204.00	X a	-194.89
XII b	-223.68	VII h	-203.70	Ceftizoxime	-193.92
XII d	-221.92	IV h	-201.36		

IV. Against *Pseudomonas Aeruginosa:*

Table-VIII.

Compound	E-Total	Compound	E-Total	Compound	E-Total
XII i	-246.32	XII j	-224.37	XII b	-210.83
XII d	-235.14	XII h	-223.87	XII e	-210.32
XII g	-235.14	XII c	-212.91	VII i	-204.66
XII f	-230.54	VI i	-212.87	XII a	-203.29
XI e	-227.14	III i	-211.37	Ceftizoxime	-202.78

V. Against *Klebsiella Aerogenes*

Table-IX.

Compound	E-Total	Compound	E-Total	Compound	E-Total
VI g	-213.39	XII a	-181.34	VI m	-176.94
XII i	-207.80	VI d	-181.06	VI i	-176.63
XII j	-189.87	XII b	-180.77	XI b	-176.65
XII h	-189.16	VI e	-180.68	VI a	-175.84
III e	-188.89	X b	-180.63	XI f	175.36
III i	-187.49	VI h	-179.83	XI c	-174.89
XII c	-184.51	VI l	-179.21	X c	-174.10
XII d	-184.34	VI b	-179.09	VII i	-173.67
IV h	-183.84	V g	-179.04	VII k	-172.65
XII e	-183.57	X i	-178.83	X h	-172.05
VI f	-183.22	X e	-178.83	II b	-171.96
VII l	-182.81	III c	-177.47	XI g	-171.77
VI k	-182.75	III d	-177.47	Ceftazidime	-170.94
VII d	-182.43	X g	-176.88		
VI c	-181.46	X a	-176.82		

VIII. Against *Staphylococcus Epidermidis:*

Table-X.

Compound	E-Total	Compound	E-Total	Compound	E-Total
VI i	-205.44	VI f	-189.01	V e	-182.07
XII f	-204.36	VI c	-186.14	V n	-181.20
XII a	-200.08	VI m	-184.14	VI j	-179.83
XII i	-192.06	VI e	-183.81	XII c	-179.04
VI g	-191.36	VI k	-182.83	VI d	-179.24
VI h	-189.92	XII d	-182.62	XII b	-179.04
XII h	-189.64	VI l	-182.40	Ceftazidime	-176.47
V g	-189.62				

IX. Against *Aeromonas Hydrophila*:

Table-XI

S.No	Compound	E-Total	S.No	Compound	E-Total
1.	XII c	-161.75	21.	VI d	-132.89
2.	XII b	-160.97	22.	X g	-132.30
3.	VI i	-153.24	23.	XII g	-131.21
4.	VI g	-148.33	24.	XII j	-131.20
5.	V g	-144.20	25.	VI h	-131.05
6.	II f	-141.38	26.	X c	-130.87
7.	VI k	-139.93	27.	V l	-130.85
8.	VI m	-137.51	28.	VIII j	-130.38
9.	VI l	-137.17	29.	VI c	-129.91
10.	VI j	-136.83	30.	III f	-129.86
11.	XII i	-136.79	31.	VIII d	-129.81
12.	VIII e	-135.38	32.	XII e	-129.19
13.	III b	-135.08	33.	XI i	-128.94
14.	III i	-134.93	34.	II a	-128.77
15.	XII h	-134.17	35.	V k	-128.68
16.	VI f	-133.85	36.	III g	-128.42
17.	VIII f	-133.75	37	XII d	-128.36
18.	VI e	-133.55	38.	III e	-127.40
19.	X i	-133.49	39.	VIII b	-127.05
20.	X e	-133.49	40.	Ceftazidime	-126.37

Table-XII.

Compound	E-Total	Compound	E-Total	Compound	E-Total
XII c	-161.75	VI g	-148.33	VI k	-139.93
XII b	-160.97	V g	-144.20	VI m	-137.51
VI i	-153.24	II f	-141.38	Cefepime	-137.39

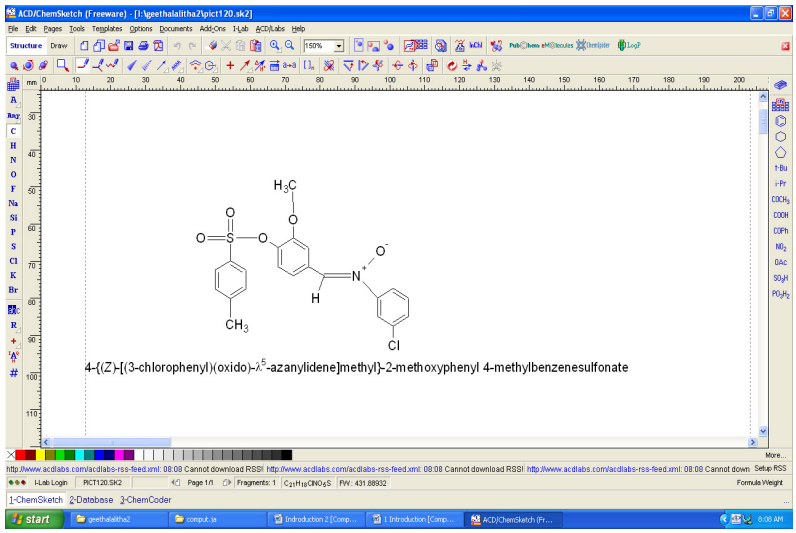


Fig. I

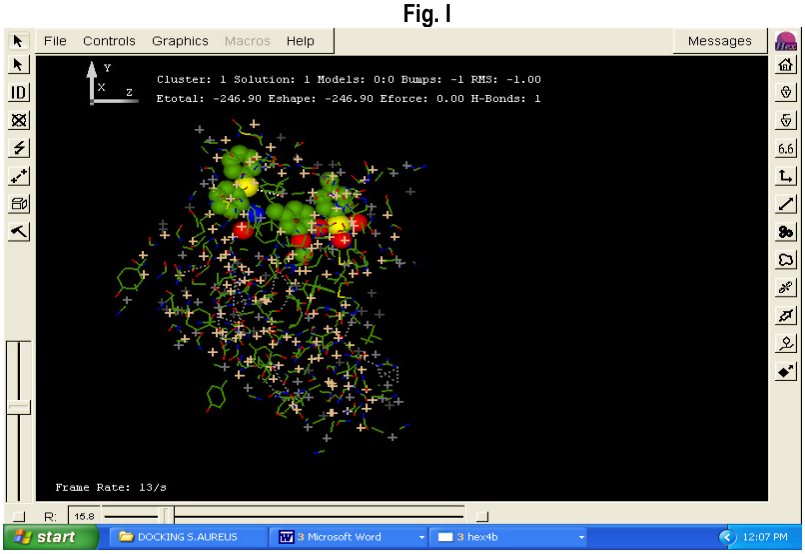


Fig. II

Against *Staphylococcus aureus*

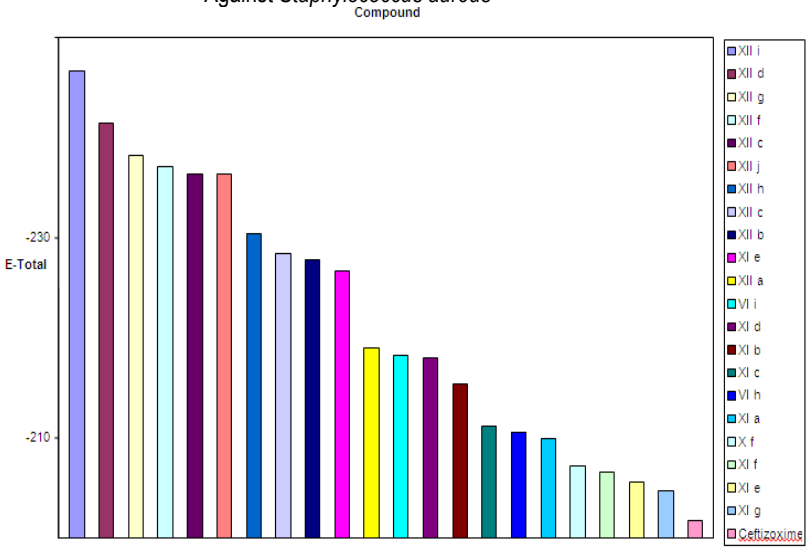


Fig. III.