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PREPARATION OF 2H-3-(ARYL)-3, 4-DIHYDRO-1, 3-BENZOXAZINE AND 3-(4'-BROMO PHENYL)-5-(ARYL SUBSTITUTED) ISOXAZOLINES, BIOLOGICAL ACTIVITY AND COMPUTATIONAL STUDIES OF PC MODEL

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ABSTRACT
Diverse activities have been reported to be associated with 2H-3-aryl-3,4-dihydro-1,3-benzoxazines . They are also used in the preparation of polymers. The presence of halogen atom in benzene ring of benzoxazines isoxazolines molecule imparts marked antimicrobial activity to above said compound. So to achieve better therapeutic agents 2H-3-aryl-3,4 dihydro-1,3-methoxy benzoxazines were prepared. These compounds can be prepared in one step by the Mannich reaction of primary amines with the appropriate , phenol in presence of an excess of formaldehyde. However the yields in these methods are somewhat less. Realizing the importance of 1,3-benzoxazines a new route for the synthesis of these compounds was developed . The isoxazolines have seen a vast increase in their use,both as intermediates in the synthesis of natural and unnatural products, and as bioisosteric functionalities in medicinal compounds, along with a survey of 2-isoxazolines in recently discovered medicinal compounds.

Keywords:- *Oxazoles, Isoxazole, Isoxazolines,Benzoxazole.*

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INTRODUCTION

Benzoxazine are unique in their chemical behavior Heterocyclic compounds are a major class of organic chemistry. Compounds, characterized by the fact that the atoms in their molecules are joined into rings or circles containing at least one atom of an element other than carbon. These compounds are of great importance because many of the biochemical materials essential to life belong to this class.Cycloaddition of C,N-diphenylnitrone to x-methylene-y-butyrolactone afforded two diastereomeric 5-Spirosubstituted isoxazole with high selectivity have been reported 4-5-dispirocyclopropane [5] and 3-spirocylobutane isoxazole derivatives have been obtained by cycloaddition of bicyclopropylidene N-methyl cyclobutylidine amine respectively[6-7].

Theoretical calculations on 5-amino-3-methyl isoxazole-4-carboxylic acid hydrazide Schiff base derivatives using polarized continuum model (in order to account for water salvation effects) have been reported. The compounds studied exhibit biological (biological immuno

suppressing or immuno stimulating) activity measured experimentally in various assays [8-13].

MATERIALS AND METHODS: COMPOUNDS 01

Step: - I 1-(aryl substituted)–3–(4'-Bromo phenyl) Prop–1–ene–3–ones

A solution of p–bromo acetophenone (0.01mol.) in ethanol (15 ml), aromatic aldehyde (0.01mol.) was added and stirred well. Later NaOH (35%, 30 ml) was added keeping the temperature below 15^{o}C. The mixture was stirred well and kept at room temperature for 12 hour. Then it was rendered acidic with dil. HCl and poured over crushed ice. The solid thus obtained was washed with water and recrystallized from absolute alcohol.

Step: - II 3–(4'-Bromo phenyl)-5–(aryl substituted) isoxazoles:

Anhydrous sodium acetate (0.01 mol.) dissolved in a minimum amount of hot glacial acetic acid was added to a solution of $NH_2OH.HCl$ (0.01 mol) in ethanol (10 ml). This solution was added to a solution of 1-(aryl substituted) -3-(4'-Bromophenyl) prop-1-ene–3–one (0.01 mol) in ethanol (15 ml). The mixture was refluxed on sand bath for three hours, concentrated and poured over crushed ice and neutralized with NaOH. The precipitate formed was washed with water and recrystallized from absolute alcohol. The yields, melting points, elemental analysis and spectral data are given in tables. The purity of the compounds was checked by TLC.

Step: - III 3-(4'-Bromo phenyl)-5-(aryl substituted) isoxazolines:

A mixture of 1-(aryl substituted)-3-(4'-Bromophenyl)-pop-1-ene-3-ones (0.01 mol), $NH_2OH.HCl$ (0.02 mol) and KOH (0.02 mol) in ethanol (25 ml) were refluxed on water bath for four hours. The reaction mixture was then cooled and acidified with glacial acetic acid. The resulting solid was washed with water and recrystallized from rectified spirit. The yields, melting prints, elemental analysis and spectral data are given in tables. The purity of the compounds was checked by TLC.

MATERIALS AND METHODS: COMPOUNDS 02

Step-1: Preparation of 2-(Arylimino)-Methyl Phenol

A mixture of salicyladehyde 2.44 gm (0.02 mole) and appropriate aromatic amine (0.02mole) in ethanol (20ml) was refluxed on water bath for 30 min. crystalline residue was obtained on cooling the reaction mixture. The product was dried and recrystallized from chloroform-petrol (1:4v/v] to furnish 2-(arylimino) methyl phenol. The amines taken at-R_1 PS-09-16

Step-2: Preparation of 2-(Arylamino)-Methyl Phenol

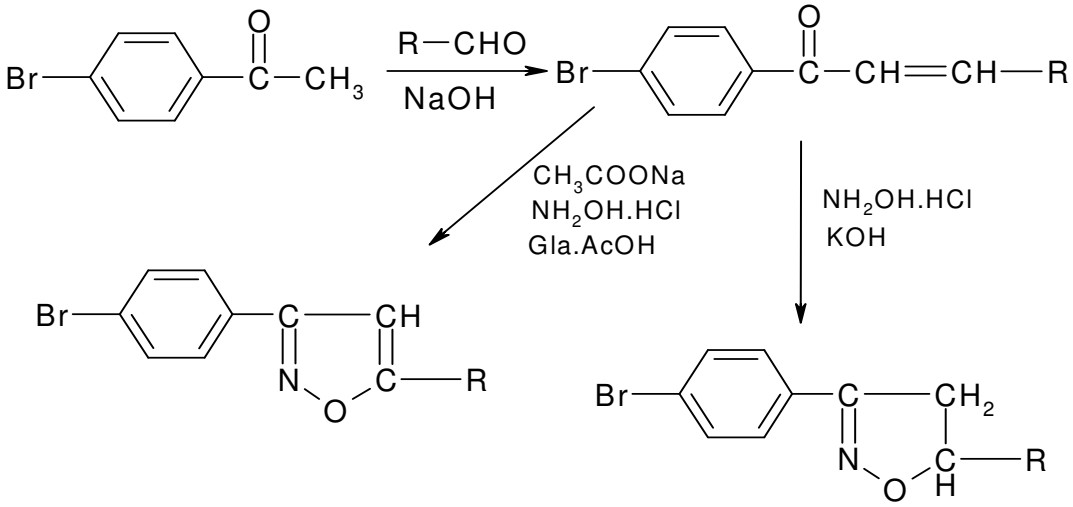
Sodium borohydride (0.3gm) was added to a solution of 2-(aryl amino) methyl phenol (0.05mole) in methanol and the mixture was stirred for 30 minute at room temperature. The mixture was then poured in to ice cold water. The compound separated, was filtered off and recrystallized from ethanol to yield (2-arylamino)-methyl phenol.

Step-3: Preparation of 2H-3-(aryl)-3, 4-Dihydro-1, 3-Benzoxazine

3, 2-(aryl amino) methyl phenol (0.05mole) and formalin 37 % (1ml) were refluxed in ethanol (20ml) for 6 hrs. The product separated out after pouring the reaction mixture in to ice cold water and then filtered and recrystallized using ethanol to yield 2H -3 – (aryl) -3, 4 –dihydro -1, 3 – benzoxazines.

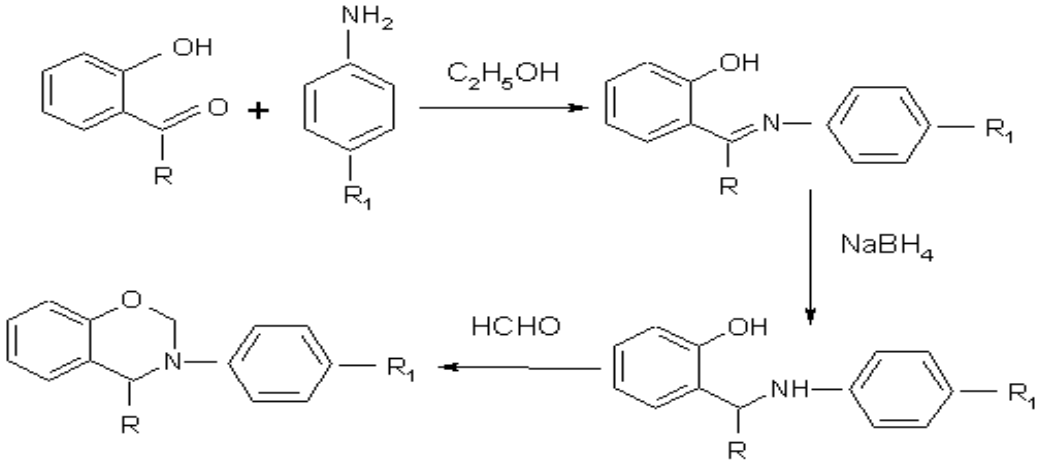
Spectrophotometer and ^{1}H,^{13}C-NMR spectra on a Bruker 80 MHz instrument (CDRI, Lucknow). Elemental analysis was found satisfactory for the compounds. Physical data of the compounds are given in Table.

Reaction Sequence: - **1**



R = C_6H_5, 4-Cl, 4-OH, 4-OH-3-OCH_3, 4-OCH_3 , 3,4-OCH_3 , 3-NO_2 , - $N(CH_3)_2$ .C_6H_4

Reaction Sequence: - **2**



1= o-chloro-aniline, 2 = m-chloro-aniline, 3 = p-chloro-aniline, 4=o-nitro aniline, 5= m-nitro-aniline, 6 = p-nitro-aniline, 7= o,m-di-nitro-aniline, 8 = p-bromo- aniline

Table 1. : Physical Data Compound PS-01 Derivatives.

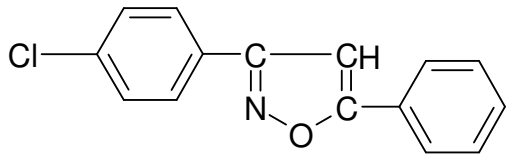
Name	3-(4'-chlorophenyl)-5-(phenyl) isoxazole					
Mol.Wt.	265.14					
M.P.°C	130					
Yield (%)	80 %					
Mol.For.	$C_{15}H_{10}NOCL$					
Elemental Analysis	**C %**		**H %**		**N %**	
	Found	**Calcu.**	**Found**	**Calcu.**	**Found**	**Calcu.**
	62.07	61.02	4.34	4.36	4.67	4.30

Table 2: Characterization of infra red data

Type	Vibration mode	Frequency (cm^{-1})
oxazole ring	C=N Str.	1438.0
	N—O Str.	1383.8
	C=C Str.	1589.9
	β—C—H Str.	1179.1
Aromatic ring	Ar—Br	434.9
	C=C bend	693.7
	1,4 —Disubstituted Benzene ring	
	—C—H bending	727.3
	—C=C Str.	1670.5

Table 3: Characterization of NMR data

Signal No.	Chemical shift in δ ppm	Multiplicity	Relative no. of protons	Inference
1.	6.3446	Multiplet	04	Br substituted ring
2.	6.5324	Multiplet	05	Benzene ring
3.	4.4378	Singlet	01	-CH of Isoxazole ring

Table.4: Compound Physical PS-09 Derivatives

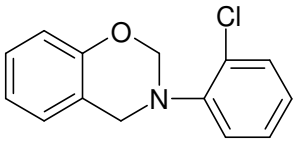
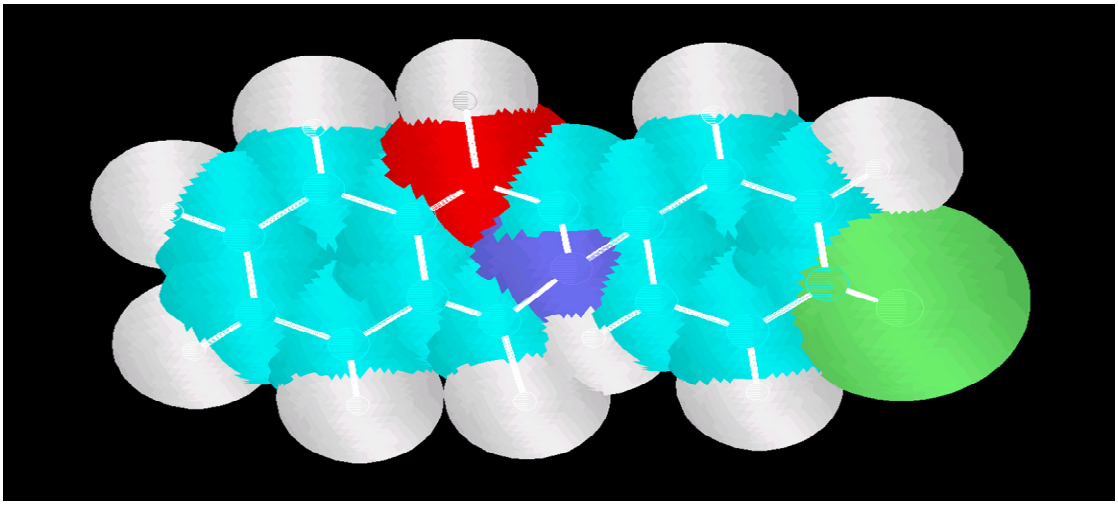
Name	2H-3(o-Chlorophenyl)-3,4-dihydro-1,3-benzoxazine					
Mol.Wt.	246					
M.P.°C	135					
Yield (%)	84					
Mol.For.	$C_{14}H_{12}NOCl$					
Elemental Analysis	C %		H %		N %	
	Found	Calcu.	Found	Calcu.	Found	Calcu.
	68.31	68.29	4..63	4.88	5.67	5.69

Table.5: Characterization of IR data

Group type	Vibration mode	Frequency (cm^{-1})
Oxazine ring	-CH (str.) in–OCH_2	2910.54
	-CH (str.) in –NCH_2	2844.12
	-C-N (str.) in –NCH_2	1276.59
	C-O(str.) in –OCH_2	1050.88
	-CH (bend.) in–OCH_2	1511.23
	-CH (bend.) in –NCH_2	1468.41
Aromatic ring	-CH (str.)	3036.51,3016.10
	C=C (str.)	1597.71
	-CH (bend.)	1022.42
	C-Cl (str.)	763.31

Table.6: Characterization of H^1 NMR data

Signal No.	Chemical shift (in δ ppm)	Multiplicity	Relative no. of protons	Inference
1.	7.22-7.61	Multiplet	8	Ar-H
2.	4.68	Singlet	2	-OCH_2 of Benzoxazine ring
3.	3.53	Singlet	2	-NCH_2 of Benzoxazine ring



Ball and Stick model for Benzoxazine

[1]

A test of the above statement can be made using the corresponding IR spectra. A general perusal of IR spectral frequencies obtained for different types of stretching and bending frequencies exhibit almost similar sequence with respect to the phenyl substitution at fifth position in isoxazole ring. Records the IR frequencies for various bonds.

Table.7: IR Characterization data for specific bonds in substituted isoxazole derivatives

Compound code	Substituent	Isoxazole Ring				Br-Substituted Ring	
		C=N	N-O	C=C	β C-H	Ar-Br	C=C bend
PS01	4-H	1446	1274.8	1582.9	1279.1	334.9	593.7
PS-02	4-Cl	1486.8	1382.5	1583.6	1248	531.3	682.3
PS-03	4-OH	1483.4	1270.5	1585.9	1148	553.2	684.5
PS-04	4-OH,3-OCH_3	1416.5	1273.7	1578.7	1125.9	512.5	662.9
PS-05	4-OCH_3	1459.8	1253.8	1591.4	1172.4	534.7	663.5
PS-06	3-NO2	1438.6	1253.9	1583.4	1170.1	501.3	683.7
PS-07	3,4-OCH_3	1414.6	1264.1	1564.1	1243.3	523.5	644.5
PS-08	4-N(CH3)	1424.1	1234.5	1588.7	1371.7	552.4	670.6
PS-09	2-Cl	1448.3	1273.8	1583.9	1179.1	534.9	693.7
PS-10	3-Cl	1487.8	1282.1	1588.6	1148.2	531.3	682.1
PS-11	4-Cl	1483.4	1272.5	1585.9	1148.1	553.2	684.5
PS-12	2-NO2	1413.5	1274.7	1578.7	1125.9	512.5	662.9

PS-13	3-NO2	1459.8	1253.8	1593.4	1173.4	534.7	663.5
PS-14	4-NO2	1438.6	1250.9	1583.4	1170.1	501.3	683.7
PS-15	o-m,di NO2	1415.6	1264.1	1565.1	1141.3	523.5	644.5
PS-16	P-Br	1424.1	1222.5	1581.7	1176.1	524.4	676.6

The above values are in good agreement with the electron release ability of the substituents and the related stability as stated above. Further, verification of this may be obtained from the NMR shift values for substituted ring, disubstituted benzene ring and H of C-H in isoxazole ring.

Table.8: Variation in the chemical shift values for sub.isoxazoline derivatives

Compound Code	Substituent	Br-Subs Ring	Benzene Subs Ring	C-H of Isoxazole Ring		
PS01	4-H	6.384	6.512	4.426		
PS-02	4-Cl	6.425	6.661	4.396		
PS-03	4-OH	6.253	6.658	4.316	O-H 9.218	
PS-04	4-OH,3-OCH_3	6.168	5.681	4.166	O-H 9.007	OCH3 2.561
PS-05	4-OCH_3	6.237	6.65	4.253	OCH3 2.985	
PS-06	3-NO2	6.198	6.253	4.618		
PS-07	3,4-OCH_3	6.234	6.168	4.611	2-OCH3 2.659	
PS-08	4-N(CH3)	6.238	6.439	4.463	2-CH3 2.896	
PS-09	2-Cl	6.384	6.512	4.426	6.384	
PS-10	3-Cl	6.425	6.661	4.396	6.425	
PS-11	4-Cl	6.253	6.658	4.316	6.253	
PS-12	2-NO2	6.168	5.681	4.166	6.168	
PS-13	3-NO2	6.237	6.65	4.253	6.237	
PS-14	4-NO2	6.198	6.253	4.618	6.198	
PS-15	o-m,di NO2	6.234	6.168	4.611	6.234	
PS-16	P-Br	6.238	6.439	4.463	6.238	
PS-09	2-Cl	6.384	6.512	4.426	6.384	

A comparison of the ^{1}HNMR protons of disubstituted benzene ring shows a downfield shift for 3–NO_2, 4-OCH_3 and 4-N$(CH_3)_2$ as compared to the upfield shift for the corresponding 4-OH, 4-Cl, 4-OH,3-OCH_3, showing a increase in the proton relaxation for the said substitution. Similarly, a comparison for the proton of the isoxazole ring show a reverse trend i.e. upfield shift for 3–NO_2, 4-OCH_3 and 4-N$(CH_3)_2$ and downfield shift for 4-OH, 4-OH, 3-OCH_3.

- 4-CL,3,4-OCH_3,4-Cl, 4-OH,'H', 3-NO_2, 4-OCH_3,4-N$(CH_3)_2$
  upfield down field
- 4-N$(CH_3)_2$, 4-OCH_3, 3-NO_2,H, 4-OH,4-OH,4-CL,3,4-OCH_3
  upfield down field

The above values are quiet encouraging and vary almost regularly following the sequence of electron release and strain estimated due to phenyl substitution at 5- positions. The computer simulated data on PC model also justify the steric/spatial arrangements extended by the substituents. Records the PC model values (Bond length, Bond angle Dihedral angle molar volume, VDW, Dipole moment) for the present set of Isoxazole and Benzoxazole derivations.

A perusal of the dipole moment values and the maximum minimization energy values shows the following trend.

D.M.	3-NO_2	4-Cl	4-OH	H	4-OH,3-OCH_3	4-N$(CH_3)_2$	3,4-OCH_3
	2.44	2.44	2.99	3.79	3.43	3.67	3.92
MMXEnergy	4-Cl	4-N$(CH_3)_2$	4-OH	H	3-NO_2	4-OCH_3	4-OH,3-OCH_3
	174.3	186.4	186.4	174.1	184.4	194.2	191.2

Downfield Upfield

To examine the reliability of the values obtained from PC Model these values are correlated with the sum of the electrical polarizability values obtained from the theoretical values quoted by Hansch for various substituents at various positions for the present set of synthesized compounds. the electrical polarizability for the said substituent's along with their dipole moment values.

Table.9: Computer simulated PC model data for the marked bonds and their subsequent angles.

Compound code	Substituent	Dihed. Ang	Mol. Vol.	VDW	Dip. Mom	MMX Energy
PS01	4-H	3.14	301.15	15.12	3.60	108.1
PS-02	4-Cl	3.19	334.50	14.43	2.918	170.4
PS-03	4-OH	1.88	316.44	13.24	2.434	146.9
PS-04	4-OH,3-OCH_3	2.105	346.17	16.11	4.53	196.0
PS-05	4-OCH_3	1.831	331.17	16.62	3.64	191.2
PS-06	3-NO_2	2.153	345.14	14.66	2.33	189.4
PS-07	3,4-OCH_3	3.431	360.2	25.61	3.51	256.74
PS-08	4-N(CH_3)	2.462	343.20	17.31	3.64	183.31
PS-09	2-Cl	3.04	300.15	15.32	3.79	188.93
PS-10	3-Cl	13.04	334.59	14.42	2.908	179.42
PS-11	4-Cl	21.838	316.14	14.24	2.414	186.51
PS-12	2-NO2	12.105	346.17	16.11	4.53	190.80
PS-13	3-NO2	11.831	330.17	16.62	2.66	193.22
PS-14	4-NO2	13.152	345.14	14.66	2.33	189.41
PS-15	o-m,di NO2	15.43	361.21	25.61	3.51	456.90
PS-16	P-Br	22.46	343.21	17.33	3.64	186.23

A perusal of the dipole moment values and the maximum minimization energy values shows the following trend.

Table.10: Electrical polarizability as obtained by Hansch table for various derivatives and their dipole moment values

Compound No.	01	02	03	04	05	06	07	08
Elec.pol	4.15	4.38	3.78	3.90	3.88	3.44	4.00	3.32
Dip.Mom	3.79	2.90	2.41	4.53	2.66	2.33	3.51	3.63

An almost linear dependence in the theoretical sum of electrical polarizability values to that of the dipole moment values obtained from the PC simulation supports the said correlation in the present study.

Table.11: Characterization and Chemical Shift of C^{13}NMR data

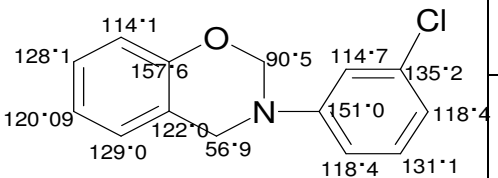
Compound code Isoxazole,Benzx.2, Cl –ph	Inference	Relative no.of carbon(δ ppm)
Stru. 	(O-C-N) (C-Cl) (N-C)	(C),90.5 (C), 135.2 (C), 56.9
	Cl-Ar Benzene Ring	(C), 118.4,131.1,118.4,151.0,114.7 (C), 114.1, 128.1, 120.09,129.0,122.0, ,157.6

Table 12: Antibacterial Activity of the Isoxazole Benzox. Derivatives

Comp. Code	*Bacillus subtilis*		*Escherichia Coli*		*Klebsiella pneumoniae*		*Staphylococcus aureus*	
	2%	**4%**	**2%**	**4%**	**2%**	**4%**	**2%**	**4%**
PS01	18	10	07	19	11	12	19	13
PS-02	09	11	09	11	10	14	10	12
PS-03	12	10	10	12	13	14	10	14
PS-04	10	11	10	12	08	11	10	12
PS-05	12	10	11	10	12	13	11	12
PS-06	12	11	12	14	10	14	10	14
PS-07	09	10	12	15	11	10	12	16
PS-08	10	13	12	14	12	12	9	14
PS-09	08	10	07	9	10	12	21	16
PS-10	09	11	09	11	11	14	10	12
PS-11	12	10	10	12	13	14	10	11
PS-12	10	11	10	12	18	11	10	12
PS-13	12	10	11	10	12	13	11	12
PS-14	12	11	12	14	17	14	10	14
PS-15	09	10	12	15	11	10	12	16
PS-16	10	13	12	14	16	12	13	14
Std:	15	17	14	15	17	10	16	18

Table 13: Antifungal Activity of the Isoxazole, Benzoxazole Derivatives:

Comp. Code	*Aspergillus niger*		*Aspergillus Flavus*		*Trichoderma viride*		*Cadida albicans*	
	2%	**4%**	**2%**	**4%**	**2%**	**4%**	**2%**	**4%**
PS01	08	10	07	10	16	12	19	10
PS-02	09	11	09	11	13	14	12	12
PS-03	12	10	10	12	13	14	14	11
PS-04	10	11	10	12	08	11	15	12
PS-05	12	10	11	11	12	13	11	12
PS-06	16	11	12	14	10	14	14	14
PS-07	13	13	12	15	11	12	12	16
PS-08	11	13	12	14	8	12	9	14
PS-09	09	10	07	9	10	12	09	10
PS-10	14	11	09	11	10	14	10	12
PS-11	12	10	10	12	13	14	10	16
PS-12	10	11	10	12	08	11	10	12
PS-13	12	10	11	10	12	13	11	13
PS-14	12	11	12	14	12	14	11	14
PS-15	09	10	12	15	11	13	12	16
PS-16	10	13	12	14	8	12	19	24
Std:	15	17	13	19	20	21	20	23

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