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Synthesis, Characterization, of 2H-3-Aryl-3, 4-Dihydro-1,3-Chlorobenzoxazine Derivatives of Benzoxazoline, antimicrobial activity and PC model Computational Studies

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Abstract

The invention comprises benzoxazole-2-carboxylic acid derivatives of the general formula wherein R represents a chlorine atom or an alkyl radical containing 1 to 4 carbon atoms, n is O or an integer of 1 to 4, and Y represents -OR1 or -NR112, wherein R1 represents an alkyl, aralkyl, cycloalkyl, aryl or chloroaryl radical and R11 represents a hydrogen atom or an alkyl, aralkyl or cycloalkyl radical, or -NR112 represents a heterocyclic ring. They may be prepared by causing a 3-chlorobenzoxazine-(1,4)-one-(2) of the general formula to react with ammonia, a strong basic primary or secondary amine, an alcohol, a phenol or a chlorophenol in the presence of an acid binding agent.; The reaction is expediently performed in an inert organic solvent or diluent at -30 DEG to + 200 DEG C. and when one of the reactants is an alcohol it can advantageously be used in excess as the diluent. Specified acid binding agents are the alkali metal and alkaline earth metal hydroxides, carbonates and bicarbonates, but in the case of the reaction with ammonia or an amine an excess thereof can be used instead of the binding agent.; The compounds of the invention may be isolated from the reaction mixture, which may contain the corresponding 3-substituted-benzoxazine-(1,4)-ones-(2) as by-products (see Specification 1,008,266), by, for example, fractional crystallization or preparative chromatography. ALSO:Herbicidal compositions comprise benzoxazole-2-carboxylic acid derivatives of the general formula wherein R represents a chloric atom or an alkyl radical containing 1 to 4 carbon atoms, n is 0 or an integer of 1 to 4, and 7 represents -OR1 or -NR112, where in R1 represents an alkyl, aralkyl, cycloalkyl, aryl or chloroaryl radical and R11 represents a hydrogen atom or an alkyl, aralkyl or cycloalkyl radical, or -NR112 represents a heterocyclic ring.; The compositions may be in the form of p emulsifiable concentrates, spray powders, pastes, soluble powders, dusts or granulates and contain 0.1 to 95% by weight of the active compounds.

Keywords: Synthesis, characterization, chlorobenzoxazine derivatives, antimicrobial, PC model, computational studies.

Introduction

The present new heterocyclic esters are therapeutically useful as such or can be employed in the form oE sal-ts with a wide variety of acids, inorganic and organic, including therapeutically-acceptable acids. The strobilurins, derived from fermentations of *Strobilurus tenacellus* by Anke and coworkers in 1977, are one of the most important classes of agricultural fungicides[1]. Their primary mechanism of action is the inhibition of mitochondrial respiration by blocking electron transfer at the ubiquinol oxidation center (Qo site) of the cytochrome 1 complex (complex III)[2]. Strobilurin derivatives have attracted significant attention of the agricultural chemists owing to their outstanding characteristics and uniquemode of action, broader antifungal spectrum, long-lasting effects, high antifungal activity, and low toxicity toward mammalian cells[3–6]. The strobilurins were first commercialized in 1996 with the launch of azoxystrobin and kresoxim-methyl (figure-1)[7]. Till date, over ten strobilurin derivatives are commercially available[8–10]. However, following the use of strobilurin fungicides in a short period of field applications, significant increase in resistance to fungicide has been observed[11]. Recently, significant research efforts focusing on structural modification of strobilurins have been devoted to overcoming the above-mentioned problem. Moreover, according to the literature, the methoxyiminoacetate is an effective pharmacophore which is indispensable for antifungal activity of strobilurin fungicides. The aromatic bridge helps to stabilize the molecule and the molecule also exhibits photo stability. Therefore, numerous studies have reported that modification of the side chain is the most effective method to obtain novel strobilurin derivatives with higher biological activities[6, 12–14]. In general, 1,2,4-triazole and similar Schiff bases exhibit diverse biological activities, such as pesticides, fungicides, herbicidal, anticancer, anti-inflammatory, antiviral, and antimicrobial properties[15–22]. So far, over twenty triazole fungicides have been commercialized, like triadimefon and triadimenol. Therefore, based on the active substructure combination and bioisosteric replacement, the intermediate derivatization method was employed to synthesize a series of novel strobilurin derivatives containing 1,2,4-triazole[15-19].

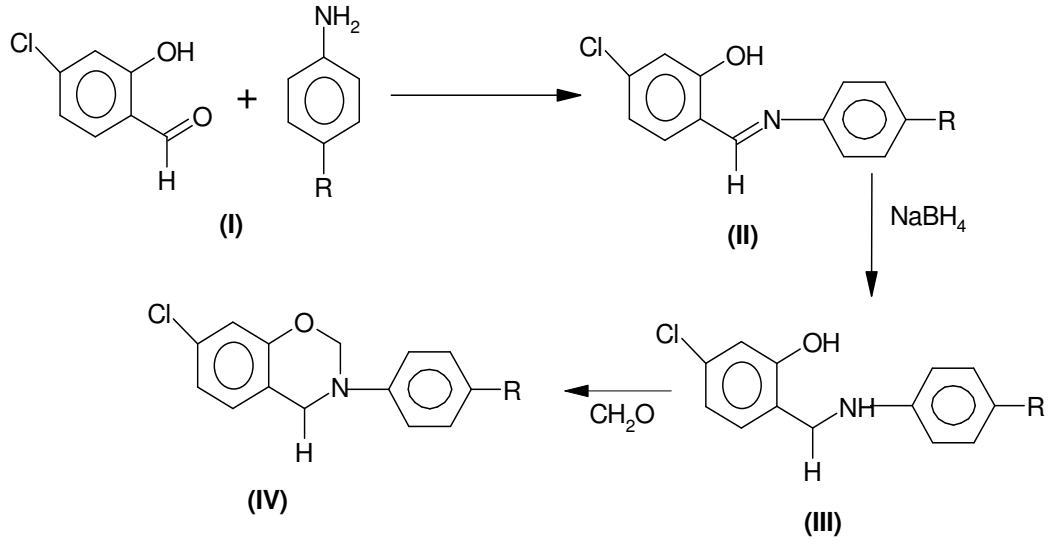
Methodology

Step: I Preparation of 2-(arylimino)-5—Chloromethyl

phenols: 5-Chlorosalicylaldehyde(I) 2 gm and appropriate aromatic amine 2 gm were refluxed in ethanol (20 ml) for 30 min crystalline residue deposited on cooling was further purified by crystallization from chloroform-petroleum ether (2:8 v/v) to Furnish (II) the amines taken were aniline(Clbenz.1), p-Chloro-aniline, (Clbenz.2), o-nitroaniline, (Clbenz.3), m-nitro aniline (Clbenz.4),,p-nitro aniline and(Cbenz.5), p-bromo-aniline.

Step II Preparation of 2-(Arylamino-5-Chloromethyl phenols: Sodium borohydride (0.5 gm) was added to solution of 2-(arylimino)-5-Chloromethyl phenol (2 gm) in methanol (10 ml) and the mixture stirred for 30 min at room temperature. The residue obtained on pouring the solution in to cold water was further crystallized from ethanol to afford (III).

Step III Preparation of 2H-3-Aryl-3, 4-Dihydro-1,3-Chlorobenzoxazine: 2-(aryl amino)-5-Chloromethyl phenol 2 gm and formalin (35% 10 ml) were refluxed in ethanol (10 ml) for 6 h. The residue obtained after pouring the reaction mixture into cold water was crystallized from ethanol to give the yields and melting points of the 1, 3-oxazines are given in table-1. The molecular formulae of these compounds were calculated from their elemental analysis (table-2). The structure of 1,3-oxazines were confirmed by their IR spectra. IR spectra of compounds have been scanned with Perkin-Elmer spectrophotometer using KBr pellets.



R= 1 p- chloro-aniline, 2 =o-nitro-aniline, 3 = m-nitro-aniline, 4 = p-nitro-aniline, 5 = p-bromo- aniline.

Scheme-1
Reaction Sequences

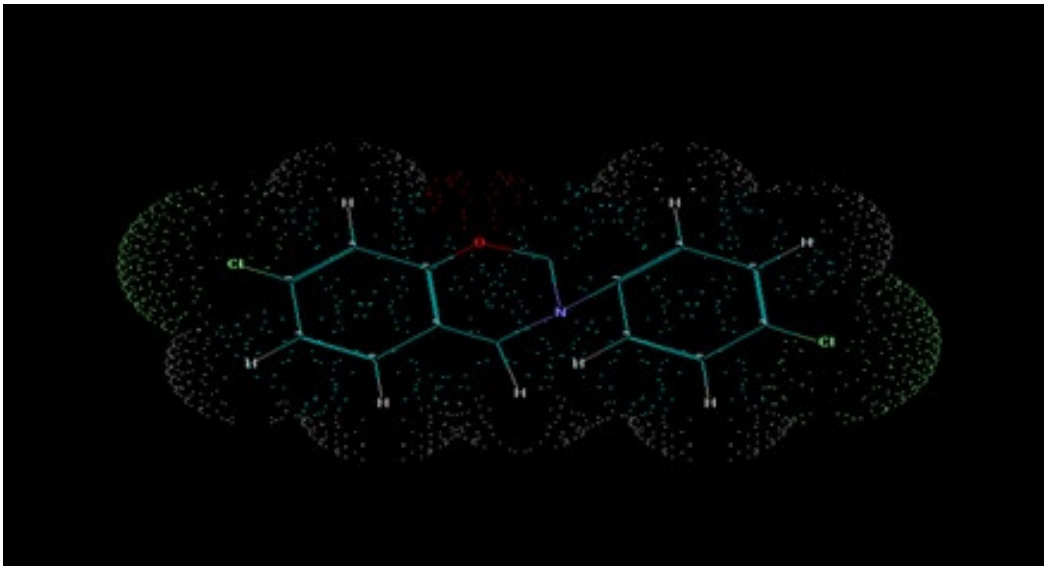


Figure-1
Ball and stick model Chloro-Benzoxazine

Table-1
Physical Data Compound Code Clbenzx

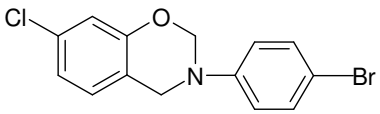
Name	2H-3(p-bromophenyl)-3,4-dihydro-Chloro-1,3-benzoxazine					
Mol. Wt.	356.7					
M.P.°C	165					
Yield (%)	75					
Mol. For.	$C_{14}H_{11}NO_3ClBr$					
Elemental Analysis	**C %**		**H %**		**N %**	
	Found	**Calcu.**	**Found**	**Calcu.**	**Found**	**Calcu.**
	47.10	47.12	3.06	3.08	13.44	13.46

Table-2
Characterization of IR data

Group type	**Vibration mode**	**Frequency (cm^{-1})**
Oxazine ring	-CH (str.) in–OCH_2	2916.64
	-CH (str.) in –NCH_2	2842.54
	-C-N (str.) in –NCH_2	1278.78
	C-O(str.) in –OCH_2	1062.96
	-CH (bend.) in–OCH_2	1510.65
	-CH (bend.) in –NCH_2	1473.97
Aromatic ring	-CH (str.)	3056.54,3012.13
	C=C (str.)	1597.60
	-CH (bend.)	1026.65
Ar-Cl	C-Cl(str.) in Ar-Cl	760.90
Ar-Br	C-Br(str.) in Ar-Br	621.80

Table-3
Characterization of H^1 NMR data

Signal No.	**Chemical shift (in δ ppm)**	**Multiplicity**	**Relativeno. of protons**	**Inference**
1.	7.16-7.71	Multiplet	7	Ar-H
2.	4.68	Singlet	2	-OCH_2 of Benzoxazine ring
3.	3.63	Singlet	2	-NCH_2 of Benzoxazine ring

Table-4
Variation in PC Model simulated data for substituted Chlorobenzoxazine derivatives of series

Compound Code	**Position**	**Substit.**	**B.L. N-C**	**B.A. C-N**	**Dihed. Angle C-N-C**	**Mol.Volu.**	**VDW**	**Dip. Mom.**
Clbenzx.1	13	4 – Cl	1.463	120.82	165.82	280	9.24	1.89
Clbenzx 2	11	2-NO_2	1.459	112.26	156.94	276	11.7	5.03
Clbenzx 3	12	3-NO_2	1.457	111.60	160.096	276	11.7	3.93
Clbenzx 4	13	4-NO_2	1.464	120.81	166.19	275	10.1	2.51
Clbenzx .5	13	4 – Br	1.463	120.82	165.82	356	9.36	1.95

Table-5
Z-matrix in PC Model simulated data for substituted Chlorobenzoxazine derivatives of series

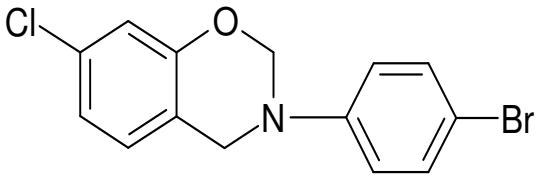
20	**Compound code Clbenz** – 20	**PC Model Values**	
		MMXEnergy	**27.582**
	Structure:	Str	0.642
		Bnd	1.32
		Str Bnd	0.052
		Tor	14.47
		VDW	9.363
		QQ	1.743
		DM	1.954
		HF	16.85
		SE	3.15

Table-6
IR Characterization data for specific bonds in substituted Chlorobenzoxazine derivatives

Compound code	**Substituent**	**benzoxazine ring**				**Disubstituted Ring**	
		C=N	**C-O**	**C-H(str)inNCH$_2$**	**C-H(bend)inN-CH$_2$**	**C=C**	**Ar-Cl**
Clbenzx.-1	4-Cl	1279.5	1056.8	2846.1	1472.4	1610.7	767.4
Clbenzx.-2	2-NO$_2$	1269.6	1062.8	2843.1	1441.4	1605.6	769.9
Clbenzx.-3	3-NO$_2$	1271.5	1056.7	2840.2	1452.4	1608.7	770.9
Clbenzx-.4	4 –NO$_2$	1277.5	1058.6	2838.12	1456.4	1604.7	774.8
Clbenzx.-5	4 - Br	1278.6	1062.8	2842.2	1473.5	1597.7	621.4

The deviations may be due to the steric hinderance in these cases. On similar lines, the NMR shift values showed the following trend. 4-Br, 2-NO$_2$, 3-NO, 4-NO$_2$, 4-Cl

Table-7
Variation in the ^{1}H-NMR spectra for substituted Chlorobenzoxazine derivatives of series III

Compound code	**Substituent**	**Cl-Subs ring**	**- OCH$_2$ of benzoxazine ring**	**-NCH$_2$ of benzoxazine ring**
Clbenzx.-1	4 -Cl	7.19-7.77	4.60	3.59
Clbenzx.-2	2-NO$_2$	7.00-7.73	4.66	3.56
Clbenzx.-3	3-NO$_2$	7.02-7.72	4.62	3.52
Clbenzx-.4	4-NO$_2$	7.39-7.64	4.63	3.67
Clbenzx.-5	4 – Br	7.16-7.71	4.68	3.63

This may be the expected trend on account of the PC Model data obtained for these compounds (table-7)

Table-8
Computer simulated PC Model data for marked bonds and their subsequent angles Series III

Compound code	**Substituent**	**B.L. C-N**	**B.A N-C**	**Dihed. Ang**	**Mol. Volu**	**VDW**	**Dip. Mom**	**MMX Energy**
Clbenzx.-1	4 -Cl	1.463	120.82	165.82	280	9.245	1.899	27.338
Clbenzx.-2	2-NO$_2$	1.459	112.26	156.94	276.5	11.76	5.033	44.908
Clbenzx.-3	3-NO$_2$	1.457	111.60	160.96	276.5	11.74	3.938	29.41
Clbenzx-.4	4-NO$_2$	1.464	120.81	166.19	275	10.13	2.516	22.208
Clbenzx.-5	4 - Br	1.463	120.82	165.82	356.7	9.363	1.954	27.582

B.L. –Bond Length, B.A.- Bond angle, D.A.-Dihedral angle

Results and Discussion

The overall, correlation between the experimental characterization and PC model data justify the results obtained in spectral characterization and also certify the potential of the PC model simulation. The reliability of the PC model simulated data was further justified by correlating PC model values with the electrical polarizability values as described by Hansch for different substituents at different positions (ortho, Meta, para) for the present series of synthesized compounds. The following table (table-8) records the electrical polarizability for the set substituents of series III along with their dipole moment values.

Biological Studies: A general perusal of the biological studies made on four bacteria (*E. coli, Bacillus subtalis, Pseudomonas alcaligens, Salmonella* sp.) and four fungi (*penicillium citrinum, Aspergillus flavus, Rhizoctonia bataticola*, *Aspergillus niger)* for 8 different samples indicates a significant biological activity for the synthesized compounds with respect to a common fungal (Griseofulvin) and bacterial (Streptomycin) control taken for the present study. This indicates that the synthesized samples possess good bactericidal and fungicidal activity.

The biological activities for these samples have been compared within the series. In persuation with the results obtained in QSPR, the author is of the opinion that a greater asymmetry in the molecule may lead to greater distribution of charges leading to higher dipole values which are responsible for the higher hydrophobicity values. The hydrophobicity (lipophilicity) on its turn is responsible for the penetration of the drug through the biological (lipid) membrane thereby causing the exact cidal activity. Therefore, a direct dependence in biological activity and dipole moment values may be sort.

Variations in the biological activities (measure of the zone of inhibition in mm) with the dipole moment values have been attempted. The following tables record the dipole and zone of inhibition for some selected cases (where the activity is significant and large) for the azine and chlorobenzoxazine compound

Table-9
Electrical polarizability as obtained by Hansch table for various derivatives of series and their dipole moment values

Compound No.	Clbenzx.17	Clbenz.18	Clbenz.19	Clbenz.20	Clbenz.21
Elec.pol.	2.78	2.34	3.03	3.23	2.78
Dip. Mom.	1.899	5.033	3.938	2.516	1.954

The almost linear dependence between the electrical polarizability values and dipole moment values justifies the various correlations carried out in present study.

Table-10
Antibacterial activity of chlorobenzoxazine derivatives and its variation with Dipole moment values

Compound code	Dip.Mom	*E. coli*		*Klebsiella pneumoniae*		*Pseudomonas alcaligens*		*Salmonella* sp.	
		2%	4%	2%	4%	2%	4%	2%	4%
Clbenzx.1	1.899	10	13	8	11	13	15	10	12
Clbenzx.2	1.954	12	14	15	19	14	17	16	20
Clbenzx. 3	2.516	14	17	17	21	16	19	18	21
Clbenzx. 4	3.938	9	11	13	16	10	14	12	15
Clbenzx. 5	5.033	11	13	12	14	9	11	15	16

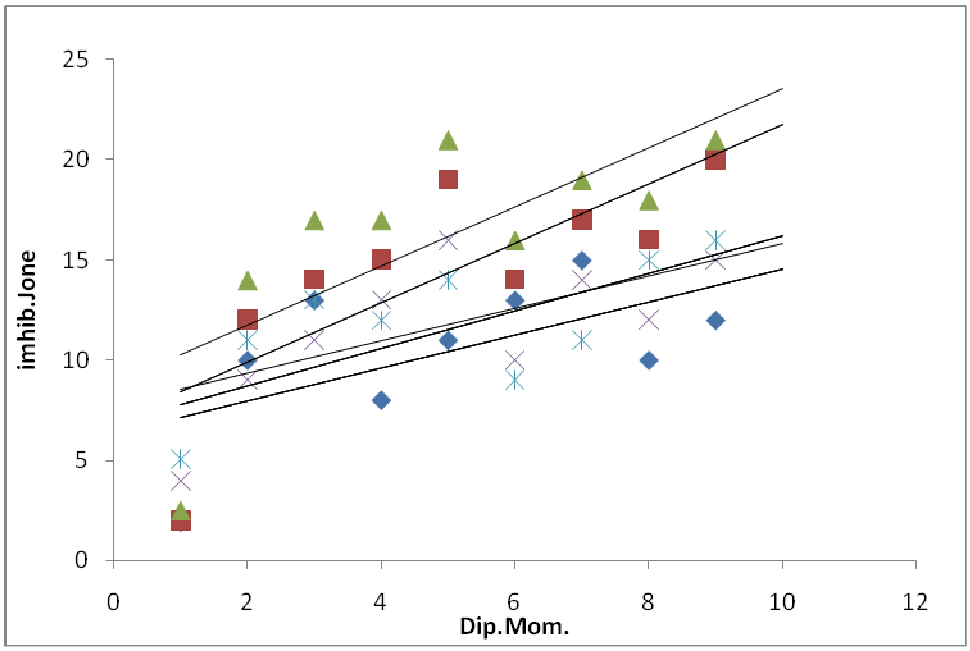


Figure-1
Variations in the biological activities (measure of the zone of inhibition in mm) with the dipole moment

Table-11
Antifungal activity of Clbenzoxazine derivatives and its variation with Dipole moment values

Compound code	Dip.Mom	*Penicillium citrinum*		*Aspergillus flavus*		*Rhizoctonia bataticola*		*Aspergillus niger*	
		2%	4%	2%	4%	2%	4%	2%	4%
Clbenzx.1	1.899	10	12	13	14	10	13	15	19
Clbenzx.2	1.954	15	16	13	15	18	19	17	20
Clbenzx.3	2.516	18	20	16	19	16	20	20	21
Clbenzx.4	3.938	9	11	12	15	15	18	11	13
Clbenzx.5	5.033	12	15	14	16	9	11	13	16

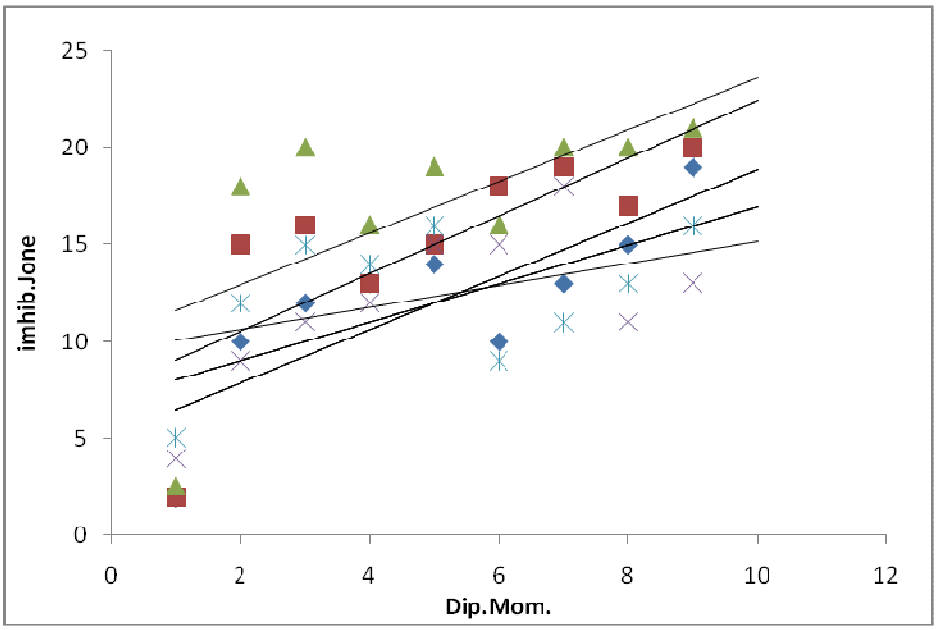


Figure-2
Variations in the biological activities (measure of the zone of inhibition in mm) with the dipole moment

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Conclusion

The biological activities for these samples have been compared within the series. In persuation with the results obtained in QSPR, the author is of the opinion that a greater asymmetry in the molecule may lead to greater distribution of charges leading to higher dipole values which are responsible for the higher hydrophobicity values. The hydrophobicity (lipophilicity) on its turn is responsible for the penetration of the drug through the biological (lipid) membrane thereby causing the exact cidal activity. Therefore, a direct dependence in biological activity and dipole moment values may be sort.

Variations in the biological activities (measure of the zone of inhibition in mm) with the dipole moment values have been attempted. The following tables record the dipole and zone of inhibition for some selected cases (where the activity is significant and large) for the azine and chlorobenzoxazine compound

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Table-12
Z-Matrix Parameters for Compounds of Series- I as obtained from Table; III-21.3 PC Model precisegnorm=0.01 Clbenzx.21

1	C	0.000000 0 0.000000 0 0.000000 0	0 0 0
2	C	1.400825 1 0.000000 0 0.000000 0	1 0 0
3	C	1.399224 1 120.008614 1 0.000000 0	2 1 0
4	C	1.400654 1 119.988037 1 0.000000 1	3 2 1
5	C	1.399190 1 120.020996 1 0.000000 1	4 3 2
6	C	1.400848 1 119.984909 1 0.000000 1	5 4 3
7	C	1.103120 1 120.012054 1 -180.000000 1	5 4 3
8	O	1.103110 1 119.992371 1 -180.000000 1	6 5 4
9	N	1.256616 1 117.430664 1 180.000000 1	7 5 4
10	C	1.315408 1 123.193077 1 0.000000 1	8 6 5
11	C	2.958651 1 178.238083 1 180.000000 1	9 7 5
12	C	1.400826 1 179.198380 1 0.000000 1	11 9 7
13	C	1.399224 1 59.189938 1 0.000000 1	11 9 7
14	C	1.400649 1 119.988472 1 180.000000 1	13 11 9
15	C	1.399192 1 120.020851 1 0.000000 1	14 13 11
16	C	1.400847 1 119.984856 1 0.000000 1	15 14 13
17	H	2.541224 1 130.424652 1 -114.839020 1	1 2 3
18	Cl	1.099999 1 119.938950 1 180.000000 1	2 3 1
19	H	1.100000 1 119.955330 1 -180.000000 1	3 2 1
20	H	1.100000 1 120.041451 1 180.000000 1	4 3 2
21	H	1.110107 1 105.008102 1 55.221573 1	7 5 4
22	H	1.110107 1 105.008095 1 -55.221600 1	7 5 4
23	H	1.110107 1 111.363617 1 -121.582977 1	10 8 6
24	H	1.110107 1 111.363617 1 121.583160 1	10 8 6
25	H	1.100000 1 120.059540 1 180.000000 1	12 11 9
26	H	1.100000 1 119.955238 1 0.000000 1	13 11 9
27	H	1.100000 1 120.041260 1 -180.000000 1	14 13 11
28	Br	3.845640 1 117.276375 1 -113.195656 1	15 14 13
29	H	1.100000 1 120.052635 1 -180.000000 1	16 15 14

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