A CSD ANALYSIS OF SOME CHLORINATED QUINOLINES

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ABSTRACT

Quinoline and its derivatives, especially the halogenated quinolines, possess a variety of biological activities and exhibit some excellent antimicrobial and anti-cancer activities. The chemical and crystallographic aspects of this class of chemical compounds have been studied in isolation over the years, but there seems to be no attempt in the literature that could present and place together with the comparative crystal structures and their biological aspects for a larger audience comprising of small molecule crystallographers, chemists, biophysicists, etc. In order to fill the gap, a CSD survey of the X-ray structures of some interesting and similar-looking chlorine quinoline derivatives was made for obtaining the comparative crystal data, empirical analysis of the predicted biological activities, and molecular packing interaction analysis. The intermolecular interactions [X-H...A (X=C, N,O; A=O, CL, N, C,F)] and intra-molecular interactions [X-H...A (X=C,N; A=CL, O, C, F, N)] have been computed and analyzed for a better understanding of the molecular packing in halogenated quinolines.

Keywords: Halogenated, Quinoline, Biological Activity, Comparative Analysis, Hydrogen Bonding.

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INTRODUCTION

Quinoline (C₉H₇N) is a heterocyclic aromatic compound (Fig.-1) that is found in natural compounds and biologically active substances, exhibiting a wide range of activity. Many activities of quinoline derivatives such as antimicrobial activity,¹ antimycobacterial activity,² inhibitors for plaque-forming microorganisms,³ anti-cancer activity,⁴ antitubercular and antiamoebic activities,⁵ antileishmanial activity⁶ have been reported in the literature. A careful CSD survey (*version 2.0.5, 2021*) of a few structurally-similar crystal structures of quinoline derivatives revealed that halogenated quinoline derivatives with amino or nitrogen groups present in the ring system exhibits excellent cytotoxic activities and are useful as antimicrobial and anticancer agents.^{7,8} In view of some wide-ranging properties of halogenated quinoline derivatives, we have identified a series of chemically-similar-looking chlorine substituted quinoline derivatives for a close comparative analysis of their crystallographic structures and inter/intra-molecular hydrogen bond interactions. A total of twenty-six such crystal structures have been identified for the analysis and their CCDC codes, IUPAC names/ chemical structures, chemical formulas, and corresponding published references are presented in Table-1.⁹⁻²⁸

Fig.-1: Basic Quinoline Structure with Atomic Labeling

Table-1: CCDC Codes, Chemical Structures / IUPAC Names, Molecular Formula and References of the Selected Compounds

S. No.	CCDC Code	IUPAC Name Compounds	Molecular Formula	References
M-1	BOPSAC	2-Chloro-4-hydrazino-8-methylquinoline	C ₁₀ H ₁₀ ClN ₃	9
M-2	FOXWEW	2-chloro-7-methoxyquinoline-3-carbaldehyde	C ₁₁ H ₈ ClNO ₂	10
M-3	IJIHAL	2-Chloro-3-(chloromethyl)-8-methylquinoline	C ₁₁ H ₉ Cl ₂ N	11
M-4	IYIXUJ	2-Chloro-5-fluoro-6-methoxyquinoline-3-carbaldehyde	C ₁₁ H ₇ ClFNO ₂	12
M-5	IZITUH	2-Chloro-3-(chloromethyl)-6-methylquinoline	C ₁₁ H ₉ Cl ₂ N	13
M-6	IZIVET	2,4-Dichloro-5-methylquinoline	C ₁₀ H ₇ Cl ₂ N	13
M-7	IZIVUJ	(2-Chloro-7-methylquinolin-3-yl)methanol	C ₁₁ H ₁₀ ClNO	13

M-8	PINVEN	<p>2-Chloro-4-chloromethyl-6,7-dimethylquinoline</p>	$C_{12}H_{11}Cl_2N$	14
M-9	PUHFOO	<p>2-Chloro-7-methylquinoline-3-carbaldehyde</p>	$C_{11}H_8ClNO$	15
M-10	PUHFUU	<p>2-Chloro-6-methoxyquinoline-3-carbaldehyde</p>	$C_{11}H_8ClNO_2$	16
M-11	PUHGAB	<p>2-Chloroquinoline-3-carbaldehyde</p>	$C_{10}H_6ClNO$	17
M-12	PUHGEF	<p>2-Chloro-8-methoxyquinoline-3-carbaldehyde</p>	$C_{11}H_8ClNO_2$	18
M-13	PUHGIJ	<p>2-Chloro-7,8-dimethylquinoline-3-carbaldehyde</p>	$C_{12}H_{10}ClNO$	19
M-14	PUHHIK	<p>2-Chloro-6-methylquinoline-3-carbaldehyde</p>	$C_{11}H_8ClNO$	20
M-15	PUKJUB	<p>2-Chloroquinoline-3-carboxylic acid</p>	$C_{10}H_6ClNO_2$	21

M-16	QAMSEC	<p>2-Chloro-4-methylquinoline</p>	$C_{10}H_8ClN$	22
M-17	QOBKOI	<p>2,4-dichloro-6-methylquinoline</p>	$C_{10}H_8Cl_2N$	23
M-18	QUYGIB	<p>2,4-Dichloro-7,8-dimethylquinoline</p>	$C_{11}H_9Cl_2N$	24
M-19	RAGPEX	<p>2-chloro-6,7-difluoroquinoline</p>	$C_9H_4ClF_2N$	25
M-20	RAGPUN	<p>2,6-dichloro-5,7-difluoroquinoline</p>	$C_9H_3Cl_2F_2N$	25
M-21	RAGQEY	<p>2-chloro-6-fluoroquinolin-7-amine</p>	$C_9H_6ClFN_2$	25
M-22	RAGQUO	<p>2,6-dichloro-7-fluoroquinolin-5-amine</p>	$C_{10}H_5Cl_2FN$	25

M-23	RAGREZ	2-chloro-6-fluoroquinolin-8-amine	C ₉ H ₆ ClFN ₂	25
M-24	TUNNIA	2,4-Dichloroquinoline	C ₉ H ₅ Cl ₂ N	26
M-25	YUQRUY	(2-Chloro-8-methylquinolin-3-yl)methanol	C ₁₁ H ₁₀ ClNO	27
M-26	YUQSAF	(2-Chloro-6-methylquinolin-3-yl)methanol	C ₁₁ H ₁₀ ClNO	28

Crystallographic Analysis

A preliminary crystal data of the structures, as given in Table-2, reveals that most of the structures have preferred to crystallize in monoclinic crystal system (~65%), followed by orthorhombic (~27%) and triclinic (~3%), and this observation is in agreement with the findings of Stout and Jensen.²⁹ The incidence of occurrence of the space group P2₁/n (or P2₁/c) is also quite high (58%) and the reliability index for all the structures (i.e. R_{range} = 0.0202 - 0.0852) indicates that all these structures were obtained at a good to moderate level of refinement.

Table-2: The Crystal Systems, Space Groups, Z-Values, Study Temperatures and R-Factors of the Molecules M-1 to M-26.

S. No.	Crystal System	Space Group Symbol	Z Value	Study Temp. (K)	R-factor (%)
M-1	Monoclinic	P2 ₁ /n	8	100	4.85
M-2	Monoclinic	P2 ₁ /n	4	296	6.20
M-3	Monoclinic	P2 ₁ /c	4	100	2.02
M-4	Monoclinic	P2 ₁ /c	4	120	3.81
M-5	Triclinic	P-1	2	295	3.46
M-6	Monoclinic	P2 ₁ /c	4	295	3.28

M-7	Monoclinic	$P2_1/c$	8	290	4.27
M-8	Orthorhombic	$Pca2_1$	4	293	3.50
M-9	Monoclinic	$P2_1/n$	4	290	7.79
M-10	Monoclinic	$P2_1/c$	4	290	3.81
M-11	Monoclinic	$P2_1/n$	4	290	3.30
M-12	Monoclinic	$P2_1/n$	4	290	3.66
M-13	Orthorhombic	$Pnma$	4	290	3.41
M-14	Monoclinic	Pc	2	290	3.40
M-15	Orthorhombic	$P2_1nb$	4	120	3.76
M-16	Orthorhombic	$Pbca$	8	150	4.3
M-17	Triclinic	$P-1$	4	293	5.77
M-18	Orthorhombic	$Pca2_1$	8	295	4.90
M-19	Monoclinic	$C2/c$	8	200	2.92
M-20	Monoclinic	$P2_1/c$	4	296	6.91
M-21	Orthorhombic	$P2_12_12_1$	4	296	3.24
M-22	Monoclinic	$P2_1/c$	4	296	2.96
M-23	Orthorhombic	$P2_12_12_1$	4	296	2.73
M-24	Monoclinic	$P2_1/n$	4	296	4.09
M-25	Monoclinic	$P2_1/c$	4	290	6.06
M-26	Monoclinic	$P2_1/c$	4	295	8.52

The precise data in terms of various bond distances between C-N (sp^3-sp^2 / sp^2-sp^3), C-C (sp^3-sp^2 / sp^2-sp^3), C-Cl (sp^2-sp^3), are presented in Table-3. The C2-N1 bond distance, ranging between 1.274 – 1.308 Å (average, 1.296 Å) is much shorter than the standard value of 1.336 Å.³⁰ In all the structures of the series, this bond distance is shorter compared to the corresponding value (1.319 Å) of the simple quinoline structure.³¹ Similarly, the bond distance N1-C8a (sp^3-sp^2 / sp^2-sp^3) lies in the range of 1.361 – 1.389 Å (average value 1.372 Å), the average value bond distance in all structures is in agreement with the standard literature value (1.374 Å).³¹ The bond distance C2-C3 (sp^3-sp^2 / sp^2-sp^3), lies in the range 1.389 – 1.433 Å (average being 1.413 Å). This bond distance in most of the structures, except M-1 (1.389 Å), M-6 (1.398 Å), M-17 (1.394 Å) and M-20 (1.391 Å), is slightly longer than the corresponding reported value of 1.400 Å.³¹

Table-3: Selected Bond Distances and Bond Angles around C2 of the Molecules M-1 to M-26.

S.No.	Selected Bond Distances (Å)				Selected Bond Angles Around C2 (°)		
	N1-C2 (sp^3-sp^2 Sp^2-sp^3)	N1-C8a (sp^3-sp^2 Sp^2-sp^3)	C2-C3 (sp^3-sp^2 Sp^2-sp^3)	C2-Cl (sp^2-sp^3)	N1-C2-C3	N1-C2-Cl	C3-C2-Cl
M-1	1.308	1.377	1.389	1.755	128.60	115.22	116.53
M-2	1.292	1.376	1.410	1.749	126.21	115.00	118.79
M-3	1.303	1.372	1.425	1.742	126.04	116.19	117.77
M-4	1.297	1.375	1.422	1.754	125.78	115.06	119.15
M-5	1.295	1.371	1.419	1.750	126.48	115.44	118.06
M-6	1.289	1.371	1.398	1.745	125.48	117.09	117.43
M-7	1.308	1.373	1.413	1.747	127.22	115.12	117.81

M-8	1.290	1.367	1.425	1.746	126.59	116.76	116.62
M-9	1.293	1.374	1.422	1.753	125.71	115.70	118.59
M-10	1.302	1.362	1.414	1.746	125.38	114.07	119.62
M-11	1.288	1.372	1.423	1.752	126.16	115.13	118.71
M-12	1.294	1.365	1.423	1.754	125.95	114.99	119.05
M-13	1.290	1.378	1.419	1.754	126.60	115.19	118.21
M-14	1.299	1.366	1.409	1.748	126.42	114.65	118.93
M-15	1.306	1.389	1.424	1.736	124.91	113.58	121.52
M-16	1.293	1.375	1.410	1.750	126.21	116.55	117.23
M-17	1.297	1.361	1.394	1.737	125.98	116.47	116.73
M-18	1.274	1.383	1.421	1.720	125.58	115.92	115.78
M-19	1.306	1.372	1.412	1.742	126.38	116.74	116.88
M-20	1.307	1.372	1.391	1.745	126.46	115.84	117.69
M-21	1.299	1.376	1.403	1.742	126.24	116.15	117.61
M-22	1.297	1.368	1.403	1.743	125.83	116.19	117.98
M-23	1.295	1.361	1.407	1.746	125.57	115.75	118.68
M-24	1.300	1.374	1.410	1.745	126.50	116.79	116.77
M-25	1.307	1.373	1.419	1.735	125.97	116.18	117.85
M-26	1.276	1.376	1.433	1.751	127.95	115.88	116.14
Largest	1.308	1.389	1.433	1.755	128.6	117.09	121.52
Smallest	1.274	1.361	1.389	1.720	124.91	113.58	115.78
Average	1.296	1.372	1.413	1.746	126.24	115.68	117.93

The shortening and lengthening of bond distances N1-C2 and C2-C3 could possibly be due to the presence of a highly electronegative chlorine atom located at C2 position and its involvement in the formation of hydrogen bond interactions. The carbon-chlorine bond distance [C2-Cl (sp^2-sp^3)], lying in the range of 1.720 – 1.775 Å (average being 1.746 Å), shows a slight departure from the standard value 1.739 Å.³⁰ The bond angle N1-C2-C3 lies in the range of 124.91° – 128.60°. The average value (126.19°) for this bond angle in the basic quinoline structure is 124.49°, indicating a slight but not very significant deviation. The other bond angles of interest, viz. N1-C2-Cl and C3-C2-Cl, lie in the range 113.58° – 118.11° (average = 115.76°) and 115.78° – 121.52° (average = 117.93°), respectively.

Biological Activity Prediction

Activities are the intrinsic properties of chemical compounds and the activity spectrum forms the basis for the prediction of biological activities, which depend only on their chemical structures. The Prediction of Activity Spectra for chemical Substances (PASS *software*³²), a large database housing chemical structures of a huge number of organic compounds as described by the original descriptor called Multilevel Neighbourhoods of Atoms (MNA),³³ has been employed to show that the MNA descriptors are capable of representing various structure-property relationships, including many types of biological activity³⁴ and drug-likeness,³⁵ with the structural formula of the compound in *.mol* file as the input and the output represents a list of probable activities, i.e., Pa(probability of being active) and Pi (probability of being inactive), respectively, on a scale of 0-1. Though most of the structures have shown enormous biological activities, yet we have retained those with Pa ≥ 0.5 (Table-4).

Table-4: Comparison Table of Some Biological Activities as predicted by PASS Online Software

S.No.	Anti-inflammatory	Membrane permeability Inhibitor	Antiviral (Rhinovirus)	Complement Factor D inhibitor	Phobic Disorders Treatment
M-1	-	-	-	0.455>0.092	-
M-2	-	0.321>0.238	0.394>0.097	0.557>0.050	0.414>0.224
M-3	0.605>0.061	-	0.369>0.131	0.563>0.049	0.533>0.156
M-4	-	-	0.306>0.241	0.375>0.144	-
M-5	-	0.281>0.255	0.386>0.108	0.517>0.064	0.497>0.175

M-6	0.538>0.046	0.523>0.134	0.411>0.079	0.666>0.024	0.697>0.077
M-7	0.314>0.148	0.465>0.169	0.427>0.065	-	0.536>0.154
M-8	-	-	-	0.484>0.078	0.382>0.249
M-9	-	0.447>0.179	0.389>0.104	0.532>0.059	0.492>0.178
M-10	0.793>0.006	0.303>0.245	-	0.572>0.046	0.370>0.259
M-11	0.235>0.135	0.342>0.229	0.358>0.146	0.661>0.025	0.638>0.105
M-12	0.248>0.215	-	0.378>0.118	0.543>0.055	0.455>0.200
M-13	0.287>0.174	-	0.369>0.140	0.532>0.059	0.492>0.178
M-14	-	0.396>0.205	0.390>0.103	0.524>0.061	0.499>0.174
M-15	0.405>0.093	0.549>0.118	0.485>0.030	0.670>0.024	0.709>0.072
M-16	-	0.495>0.152	0.429>0.063	0.696>0.019	0.676>0.087
M-17	-	0.547>0.119	0.426>0.066	0.628>0.032	0.665>0.092
M-18	0.582>0.036	0.474>0.164	0.417>0.073	0.669>0.024	0.701>0.075
M-19	-	0.369>0.218	0.337>0.181	0.616>0.034	0.658>0.096
M-20	-	0.287>0.252	0.328>0.198	0.626>0.032	0.670>0.090
M-21	0.241>0.200	-	-	0.520>0.063	0.577>0.144
M-22	-	0.370>0.217	-	0.563>0.049	0.623>0.112
M-23	0.217>0.163	-	-	0.520>0.063	0.557>0.144
M-24	0.517>0.052	0.568>0.106	0.423>0.068	0.781>0.008	0.791>0.037
M-25	0.318>0.145	-	0.414>0.076	0.432>0.105	0.578>0.134
M-26	0.294>0.166	0.417>0.195	0.428>0.064	-	0.543>0.151

The antiviral activity has extensively been demonstrated by most of the molecules with $P_a > P_i$. The anti-inflammatory activity has been found in molecules M-3, M-6, M-10, M-18 and M-24, while the molecules M-6, M-15, M-17 and M-24 indicate their relevance as membrane permeability inhibitors.

Hydrogen Bonding Interactions Analysis

Hydrogen bonding has been described by chemists and crystallographers in a variety of ways, but a recent article defines it as “an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation”.³⁶ Intermolecular hydrogen bond interaction is the most important interaction type because it combines strength with directionality and in crystal engineering, it plays a key role in molecular association with biological systems. It acts as a key to predicting the structural features of enzymes and proteins.³⁷ Geometrically, the hydrogen bond X–H...A is usually described by three parameters, viz. $d(H...A)$, $D(X...A)$, and angle $\theta(X-H...A)$, to help analyze the strength and directionality of the hydrogen bond interactions. A classical hydrogen bond places the bridging proton squarely between a proton-donor and acceptor atom, as might occur, for example, between the two O atoms of the water dimer. While such geometry might, in fact, represent a preferred structure, there have been numerous observations of what has come to be termed bifurcated hydrogen bonds. The Halogen bonds are influenced by the surrounding media and the solvent indeed plays a role, opening the door for a multitude of applications, including, for instance, the design of macromolecular hosts capable of recognizing and binding anions. Since a great deal has been learned about the halogen bond in recent years and its parallels to the hydrogen bond, we investigated these interactions with intent to (i) find out the number and nature of hydrogen bonding present in the chlorine substituted quinoline derivatives and strength of these interactions, (ii) understand the role of hydrogen bond interactions in crystal structures and (iii) analyze different types of H-bonded interactions by employing graphical means.

Intermolecular Hydrogen Bonding

The bonds between independent molecules in a crystal structure are termed intermolecular hydrogen bonds. They play a vital role in lending stability to molecular packing in the unit cell. In order to compute and analyze intermolecular interactions in each molecule (M-1 to M-26), the Mercury software³⁸ was used and the interactions thus observed are presented in Table-5.

Table-5: The Geometry of Intermolecular Hydrogen Bonding Interactions

S. No.	X-H...A	d(H...A) Å	D(X...A) Å	∠(X-H...A)°
M-1 Donor = 5 Acceptor = 3	N2A-H2A1...N3B	2.230	3.012	152.20
	N3A-H3A...C11A	2.728	3.337	126.93
	N3A-H3B...C11B	2.860	3.527	132.73
	C10B-H10F...C11A	2.911	3.601	128.32
	C5B-H5B...C11A	2.930	3.588	127.53
M-2 Donor = 4 Acceptor = 3	C9-H9B...N1	2.675	3.542	150.55
	C6-H6...O2	2.623	3.429	145.46
	C10-H10...O2	2.559	3.389	148.88
	C9-H9A...C9	2.891	3.827	165.23
M-3 Donor = 4 Acceptor = 4	C4-H4...C11	2.759	3.680	143.38
	C5-H5...C11	2.850	3.763	142.61
	C10-H10B...C12	2.780	3.866	173.11
	C7-H7...C7	2.718	3.786	171.21
	C7-H7...C8	2.855	3.828	150.27
M-4 Donor = 3 Acceptor = 4	C8-H8...N1	2.622	3.526	160.63
	C11-H11...F	2.614	3.505	161.99
	C11-H11...O2	2.652	3.334	131.16
	C11-H112...O1	2.610	3.199	118.73
M-5 Donor = 1 Acceptor = 1	C10-H10A...C11	2.867	3.745	151.16
M-6 Donor = 1 Acceptor = 1	C7-H7...N1	2.613	3.530	169.00
M-7 Donor = 5 Acceptor = 4	O1-H1O...N1	2.152	2.922	161.08
	O2-H2O...N2	2.211	2.978	159.95
	C11-H11C...N1	2.678	3.609	163.47
	C11-H11A...O1	2.651	3.421	137.49
	C15-H15...O2	2.691	3.454	140.09
M-8 Donor = 5 Acceptor = 4	N4-H4...N1	2.608	3.521	141.72
	C8-H8...C11	2.827	3.897	167.84
	C9-H9...C12	2.864	3.878	156.15
	C10-H10...C11	2.780	3.816	160.60
	C11-H11...C10	2.839	3.867	158.31
M-9 Donor = 2 Acceptor = 1	C4-H4...O1	2.604	3.436	149.09
	C5-H5...O1	2.634	3.453	147.19
M-10 Donor = 4 Acceptor = 4	C8-H8...N1	2.569	3.498	176.13
	C10-H10...O2	2.516	3.403	159.54
	C7-H7...O1	2.708	3.619	166.70
	C4-H4...C11	2.830	3.754	172.23
M-11 Donor = 2 Acceptor = 1	C4-H4...O1	2.643	3.493	152.35
	C6-H6...O1	2.720	3.560	150.64
M-12 Donor = 3 Acceptor = 3	C4-H4...O1	2.667	3.504	150.09
	C5-H5...O1	2.706	3.523	147.08
	C11-H11A...O2	2.635	3.361	132.73
	C11-H11A...N1	2.665	3.598	163.66
M-13 Donor = 1 Acceptor = 1	C11-H11A...O1	2.536	3.467	163.73
M-14 Donor = 1 Acceptor = 1	C7-H7...O1	2.694	3.489	142.94

M-15 Donor = 4 Acceptor = 3	O2-H2...N1 C8-H8...O1 C6-H6...O1 C4-H4...C6	1.950 2.370 2.635 2.891	2.768 3.290 3.226 3.660	164.00 163.00 120.79 138.77
M-16 Donor = 2 Acceptor = 2	C8-H8...N1 C41-H42...C8	2.613 2.756	3.517 3.606	160.00 145.34
M-17 Donor = 1 Acceptor = 1	C11A-H11F...Cl2B	2.774	3.701	162.65
M-18 Donor = 4 Acceptor = 4	C5A-H5A...Cl2 C11B-H11AB...N1 C5B-H5B...Cl4 C11B-H11AB...N2	2.732 2.410 2.763 2.251	3.094 2.825 3.135 2.744	104.01 106.00 105.20 111.00
M-19 Donor = 2 Acceptor = 2	C3-H3...F2 C4-H4...Cl1	2.663 2.759	3.428 3.661	138.00 158.88
M-20 Donor = 2 Acceptor = 2	C8-H8...N1 C3-H3...F2	2.695 2.623	3.607 3.243	166.85 124.63
M-21 Donor = 2 Acceptor = 2	N2-H2...N1 C8-H8...C8	2.301 2.837	3.142 3.715	171.16 157.99
M-22 Donor = 1 Acceptor = 1	N2-H2...N1	2.253	3.051	154.48
M-23 Donor = 1 Acceptor = 1	N2-H2...N2	2.530	3.353	165.24
M-24 Donor = 3 Acceptor = 3	C3A-H3AA...Cl4 C7B-H7BA...N1 C8B-H8BA...Cl1	2.883 2.600 2.950	3.719 3.511 3.729	148.30 161.96 140.50
M-25 Donor = 1 Acceptor = 1	O1-H1O...O1	1.895	2.712	173.92
M-26 Donor = 2 Acceptor = 2	O1-H1O...O1 C4-H4...Cl1	1.929 2.866	2.716 3.781	176.89 167.74

A variety of intermolecular H-bonded interactions of the type C-H...O, C-H...Cl, C-H...N, C-H...C, N-H...N, C-H...F, O-H...N, O-H...O, N-H...Cl, C-H...Br and N-H...F have been observed. The frequency of occurrence of the stated class of interactions and their distance-angle scatter plots are presented in Fig.-2 and 3, respectively. A critical analysis of the plots indicates that the C-H...O interactions are quite dominant (frequency of occurrence ~ 27.5%) and that it significantly contributes to the molecular packing. Based on the range of values as obtained in the case of the geometrical parameters, viz. $d[(H...A)] = 2.37 - 2.72 \text{ \AA}$, $D[(X...A)] = 3.19 - 3.62 \text{ \AA}$ and $\theta[(X-H...A)] = 118 - 167^\circ$, it is suggested that the C-H...O type intermolecular interactions lead to the category of *weak* H-bonding.³⁹ Further, the bifurcated C-H...O interactions (with O being a bifurcated acceptor) are equally significant as they exist in quite a good number of structures (M-2, M-9, M-11, M-12 and M-15).

An illustration of the bifurcated C-H...O bond network (for M-11 and M-12) is shown in Fig.-4. The frequency of occurrence of halogenated hydrogen bond-like C-H...Cl is equally significant (incidence of occurrence ~ 23.2%) and comparable with the corresponding population of C-H...O interactions. However, the range of values like $d[(H...A)] = 2.73-2.95 \text{ \AA}$, $D[(X...A)] = 3.095-3.897 \text{ \AA}$ and $\theta[(X-H...A)] = 104^\circ - 173^\circ$, for halogen interactions further vindicate the findings as suggested above that such

interactions are simply the *weak* hydrogen bonds³⁹ but they do play a very significant role in molecular packing by forming molecular chains along with different unit cell directions (Fig.-5).

Fig.-2: Frequency of Occurrence of Various Types of Intermolecular Interactions

Fig.-3: Scattered Plots for d vs. X-H...A and D vs. X-H...A, in Intermolecular Interaction

The molecular packing for M-7 and M-15 is accompanied by a strong O-H...N network, while it is mainly stabilized by strong O-H...O bonds in the case of M-25 and M-26, respectively. A view of crystal packing involving C-H...O, C-H...N and C-H...Cl bonds forming three-dimensional networks in M-10

are presented in Fig.-6. The number of other interactions [C-H...N and N-H...N, N-H...Cl, O-H...N] is too small to merit any specific consideration.

Fig.-4: View of C-H...O bifurcated H-bonding network in M-11¹⁷ and M-12¹⁸

Fig.-5: Formation of C-H...Cl Chains in M-5¹³ and M-19²⁵

Fig.-6: Molecular Packing involving C-H...O, C-H...N and C-H...Cl H-bonds in M-10¹⁶

Intramolecular Hydrogen Bonding

The intramolecular hydrogen bond is said to be happening within the isolated molecule and such bonds are reportedly useful in the stability of molecular conformations.⁴⁰ A great deal of intra-molecular H-bonded interactions, viz. C-H...Cl, C-H...O, C-H...C, N-H...F, C-H...N, C-H...F, N-H...Cl and N-H...N, have been observed in such molecules and their geometrical parameters and geometrical range for $d[(H...A)] = (1.392-2.796)\text{\AA}$, $D[(X...A)] = (2.684-3.114)\text{\AA}$ and $\theta[(X-H...A)] = 96^\circ-117.13^\circ$ are presented in Table-6.

Table-6: The Geometry of Intramolecular Hydrogen Bonding Interactions

S.No.	X-H....A	d(H....A) Å	D(X.....A) Å	$\Theta(X-H....A)^\circ$
M-2	C11-H11...Cl1	2.746	3.088	102.18
Donor = 3	C3-H3...C1	2.500	2.793	98.51
Acceptor = 2	C10-H10...O2	2.572	2.838	96.87
M-3				
Donor = 1	C10-H10A...Cl1	2.686	3.054	99.07
Acceptor = 1				
M-4				
Donor = 2	C1-H1...Cl	2.738	3.131	105.63
Acceptor = 2	C7-H7...Cl1	2.521	2.825	98.46
M-5				
Donor = 1	C10-H10B...Cl1	2.725	3.063	101.35
Acceptor = 1				
M-8				
Donor = 2	C8-H8...C10	2.419	2.960	109.42
Acceptor = 2	C10-H10...C8	1.392	2.960	111.20
M-9				
Donor = 2	C10-H10...Cl1	2.689	3.088	106.77
	C3-H3...O1	2.571	2.842	97.25

Acceptor = 2				
M-10 Donor = 2 Acceptor = 2	C10-H10...Cl1 C3-H3...O1	1.739 2.539	3.125 2.825	105.99 98.18
M-11 Donor = 2 Acceptor = 2	C10-H10...Cl1 C3-H3...O1	2.703 2.571	3.100 2.841	106.63 97.13
M-12 Donor = 2 Acceptor = 2	C10-H10...Cl1 C7-H7...Cl1	2.730 2.545	3.117 2.836	106.04 98.54
M-13 Donor = 2 Acceptor = 2	C10-H10...Cl1 C3-H3...O1	2.688 2.577	3.095 2.850	107.36 97.41
M-14 Donor = 1 Acceptor = 1	C10-H10...Cl1	2.703	3.084	105.46
M-15 Donor = 1 Acceptor = 1	C3-H3...O2	2.337	2.684	100.90
M-16 Donor = 1 Acceptor = 1	C5-H5...C41	2.679	3.003	100.63
M-17 Donor = 1 Acceptor = 1	C5A-H5AA...Cl2A	2.704	3.092	104.79
M-18 Donor = 2 Acceptor = 2	C5-H5...Cl2 C11-H11B...N1	2.727 2.405	3.094 2.825	104.49 106.04
M-20 Donor = 1 Acceptor = 1	C4-H4...F1	2.552	2.817	96.81
M-21 Donor = 1 Acceptor = 1	N2-H2...F1	2.357	2.699	104.44
M-22 Donor = 1 Acceptor = 1	N2-H2...Cl2	2.555	2.961	109.93
M-23 Donor = 1 Acceptor = 1	N2-H2...N1	2.343	2.700	105.92
M-24 Donor = 1 Acceptor = 1	C5-H5A...Cl2	2.740	3.114	104.32

Among the various intra-molecular interactions, the concentration of C-H...Cl type interactions are quite large (41.38%) and that of C-H...O and C-H...C bonds is 20.69% each. The incidence of occurrence for N-H...N, N-H...Cl, O-H...N, N-H...F, C-H...F and C-H...N type of interactions is quite low, though not

insignificant (Fig.-7). From the d - θ scatter plots, viz. $d(\text{H}\dots\text{A})$ vs $\theta(\text{X-H}\dots\text{A})$ and $D(\text{X}\dots\text{A})$ vs $\theta(\text{X-H}\dots\text{A})$, for intra-molecular H-bonds(Fig.-8), maximum spot density has been observed in case of C-H...Cl type interactions, followed by C-H...C intramolecular interactions. A substantial number of halogen-based intramolecular C-H...Cl and C-H...C bonds are found to exist in the range [$d(\text{H}\dots\text{A}) = 2.700\text{\AA}$ - $2.750\text{\AA}$ and $D(\text{X}\dots\text{A}) = 3.000\text{\AA}$ - $3.200\text{\AA}$ for $\theta(\text{X-H}\dots\text{A})$ range $\sim 97^\circ$ - 108°] and [$d(\text{H}\dots\text{A}) = 2.400\text{\AA}$ - $2.600\text{\AA}$, $D(\text{X}\dots\text{A}) = 2.800\text{\AA}$ - $3.000\text{\AA}$ and $\theta(\text{X-H}\dots\text{A})$ range $\sim 98^\circ$ - 112°], respectively. A close examination of their geometrical parameters conveniently places these interactions in the category of weak hydrogen bonds.⁴¹

Fig.-7: Frequency of Occurrence of Various Types of Intramolecular Interaction

Fig.-8: Scatter Plots for d vs. $\text{X-H}\dots\text{A}$ and D vs. $\text{X-H}\dots\text{A}$, in Intramolecular Interaction

CONCLUSION

Preliminary crystallographic analysis shows that most of the chlorine quinolines prefer to crystallize in a monoclinic crystal system with $P2_1/n$ space group. The variation observed in bond distances and bond angles around C2 is most likely due to the involvement of the chlorine atom at C2 position. The predictions for chlorine quinoline derivative possessing biological activities and their comparative analysis reveal that most of these derivatives are quite active for anti-inflammatory, membrane

permeability inhibitor, antiviral, complement factor D inhibitor and phobic disorders treatment. Most of the structures in the present investigation are found to be quite rich in forming a sizeable number of inter- and intra-molecular C-H...O and C-H...Cl hydrogen bonds. A careful analysis of the scatter plots depicts that such interactions are weak hydrogen bonds contributing effectively to defining the crystal packing effects. It is pertinent to mention that the participation of Cl atom (at C2) leads to the formation of intra and inter-molecular hydrogen bonds in most of the structures and hence plays a significant role in the characterization of molecular packing of chlorine quinoline structures. Another important feature observed from the graphical presentations is the existence of bifurcated C-H...O hydrogen bonding in several structures of the halogenated quinoline structures. Since the work of this kind is going on to take into its fold some other related halogen quinoline derivatives, the findings, as such, thus be considered empirical till comprehensive research is compiled and reported.

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