International Journal of Research in Engineering and Science (IJRES)
ISSN (Online): 2320-9364, ISSN (Print): 2320-9356
www.ijres.org Volume 9 Issue 7 ǁ 2021 ǁ PP. 30-41

Halogen Bonding: Types and Role in Biological Activities of Halogenated Molecules

Sither Dorji[1], Surendra Kumar Nayak[*1]
[*1]*Department of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India*
Corresponding Author: surendra_niper@yahoo.com

Abstract
Halogen bonding has received the attention few years back for optimization and for improving drug-target binding affinity and it is far anticipated to have a potential for reforming drug discovery. The replacement of H-atom with halogen-atom offers special pharmacokinetic and pharmacodynamic properties to drug molecules. Therefore, in present study, we systematically analyzed and classified the types of halogen bonds. Additionally, it also includes updated information about binding interactions through halogen bond and its effect on biological outcomes of some important drugs and other molecules such as thyroidal drugs, chloroquine, hydroxychloroquine, aripiprazole, avanafil, vorasidenib and halomitoxantrones, chloramphenicol, tetracyclines, chlorzoxazone and diclofenac. As a specific example DDT is included due to its significant impact on environment and biota. The careful analysis of literature data indicated that present or absence of halogen in a molecular structure not only changes the physiochemical properties but also affect the pharmacokinetic and pharmacodynamic properties. The change in biological properties is dominantly associated with formation of different types of halogen bonds with target site. This study will help in making decision for selection of suitable halogen-atom (Cl/Br/I) for replacement during the designing of targeted ligands.

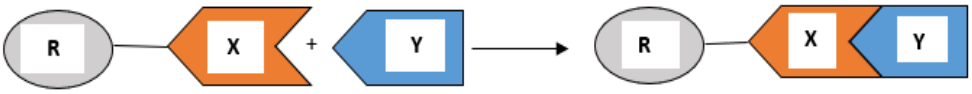
Keywords: *Halogen bond, classification, molecules, interactions.*

Date of Submission: 25-06-2021 Date of acceptance: 08-07-2021

I. INTRODUCTION

Halogens are generally considered as sites of extreme electron density because of their excessive electronegativity. The halogen atom forms outstanding interactions by means of functioning as electron donor websites called nucleophiles. The capability of halogen atoms to function as hydrogen bond acceptors becomes familiar in early 1920s. The creation of halogen bond takes place when there is contact between an electrophilic spot linked with a halogen atom and a nucleophilic region in a molecular entity [1].

In 2009, International Union of Pure and Applied Chemistry started the project (project no. 2009-032-1-100) with the aim, "to take a complete look at intermolecular contact involving halogens as electrophilic species and organize them" decided that development of halogen bond occurs when there is desirability among electrophilic region linked with nucleophilic sites in molecular unit of halogen atom (Fig. 1) [2].



R = C, halogen, N; X = I, Br, Cl, F; Y = N, O, S, Se
Figure 1: Schematic representation of halogen bond formation.

Halogen bonds have been found to arise in many different ways like inorganic, organic, and a biological system. In protein-ligand binding situations, halogen bonds are formed between halogenated ligand and accessible Lewis base in binding area, [3-4] Halogen bonding is predicted to have a capability for transforming drug discovery. It is assumed that pharmaceutical applicability is more than one third of all drugs on the current marketplace and they are halogenated, involving the halogen bonding inside the molecule of drugs. There are many examples of successful application of halogen bond in the growth of new drugs, halogen bond formation between already prevailing drug and their target protein has been shown to occur in several cases, for example, between diclofenac and the cyclooxygenase COX-2 (Ser530) [5].

1.1 NATURE OF HALOGEN BOND

The σ-hole idea was conceptualized by Clark *et al.* to describe the noncovalent interactions of halogen atoms as electrophiles and hetero-atom as nucleophile [6]. However, there are documented examples of

halogen-bonded complexes whose characteristics cannot be explained on the basis of the σ-hole and the profile of the character of the halogen. Formation of σ-hole results from the 3 pairs of lone-pair electrons on the halogen atoms which make a cylindrical cloud of higher electron density around the atom. The electronic cloud generates positive electrostatic potential or low electron density regions along the bond axis of halogen known as 'σ-hole' (Fig. 2). These σ-holes are originated when half filled p-orbital of halogen-atom participates in the covalent bonding result in electron deficiency in outer lobe of p-orbital [7]. Further, electropositive strength of σ-hole depends on polarity of halogen atom such as F < Cl < Br < I. Fluorine has very less electropositive intensity of σ-hole than iodine. Thus, iodine forms more strong halogen-bonds that other members of the group. The important factors for strength of halogen-bond is electron withdrawing ability of atom or group to which halogen is covalently attached and charge transfer ability of donor or hetero-atom. Strong electron withdrawing or easy charge transferring atom or group increases the electro-positivity of σ-hole and strength of halogen-bond [7, 8]. Later, studies indicated existence of σ-holes with negative electrostatic potential and participation in halogen-bond formation such as $CH_3Cl\cdots O{=}CH_2$ bond with stability of 1.17 Kcal/mol [9].

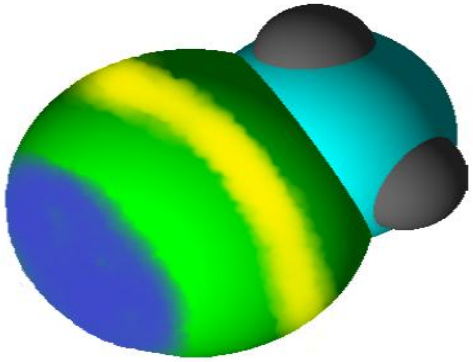


Figure 2: Charge distribution and generation of σ-hole on chlorine atom in the methyl chloride (Gray = hydrogen, Cyan = carbon, Green = chlorine, Blue = σ-hole).

1.2 CLASSIFICATION OF HALOGEN BONDS

Halogen bonding is a noncovalent interaction, in a few methods, it's analogous to hydrogen bonding, taking place among a halogen atom in a single molecule and negative site in another. Halogens contributing in halogen-bond includes: iodine, bromine, chlorine, and fluorine. All four halogens are able to act as electron acceptor and follow the overall order: F < Cl < Br < I, with iodine classically forming the toughest interactions. Di-halogens (I_2, Br_2) tends to form strong halogen bonds compared to mono halogens (Cl, F) [10].

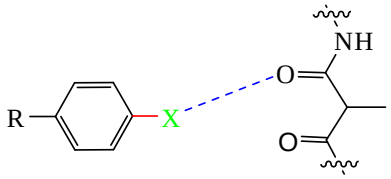
Halogen bond are particularly directional and specific that acts much like classical hydrogen bond and fashioned between a covalently bonded halogen atom and a nucleophile [11]. Due to the anisotropy of the fee distribution of halogen atoms, a certainly charged electrostatic location on the extension of C−X bonds interacts attractively with the nucleophile [12]. Halogen bonds are classified into following classes:

1. Simple halogen bond
2. Symmetrical Bifurcated Halogen Bond,
3. Asymmetric Bifurcated Halogen Bonds
4. Double Charge-Assisted Halogen Bridge bond

The influence and effectiveness of chlorine and fluorine in halogen bond formation depend upon the nature of the electron contributor. If the halogen is bonded to an electronegative (electron withdrawing) moiety, it results in stronger halogen bonds formation. Halogen bonds are sturdy, precise, and directional interactions that supply upward push to properly-defined structures which depends on charge distribution on the halogen atom and have bond strength varies from 5-180 kJ/mol [13].

1.2.1 Simple halogen bond

Simple halogens are the type of interaction in which a bond formed is in between nucleophile atoms and any halogen atom present in the particular reacting medium. Non-covalent interaction of nucleophile and halogen atom leads to the formation of single bond formation so called simple halogen bond (Fig. 3) [14].

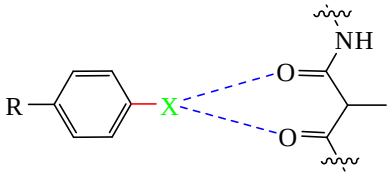


R = Any substituent
X = Cl/Br/I

Figure 3: Representation of formation of simple halogen bond between organic compound and amino acid shown by dotted bond.

1.2.2 Symmetrical bifurcated halogen bond

Symmetrical bifurcated halogen bond is the type of bond in which there is interaction of two nucleophile atoms with a halogen atom in a molecular unit and formation of di-coordinate bond in symmetrical manner (Fig. 4). This involves noncovalent interaction involving a halogen atom as an acceptor of electron density, due to the presence of an electropositive crown called σ-hole at the upper side of the halogen atom and leads to the electron contribution [15].



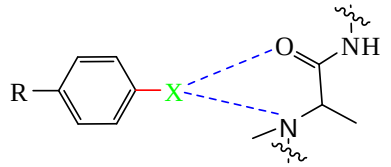
R = Any substituent
X = Cl/Br/I

Figure 4: Formation of symmetrical bifurcated halogen bond between organic compound and amino acid.

The bidentate compounds like 1,10-phenanthroline 5,6-dione [16], 1,2-dimethoxybenzenes [17], 1,10-diazaphenanthroline [18] etc. are best substrate for the development of the regular bifurcated halogen bond. One of the examples of symmetrical bifurcated halogen bond has been already reported between supramolecular synthons of -NO_2 and halogen synthon as NO_2…X (where X could be any halogen atom like F, Cl, Br) [19].

1.2.3 Asymmetric bifurcated halogen bonds

Asymmetrical bifurcated halogen bond is the type of bond in which there is interaction of two nucleophile atoms with a halogen atom in a molecular unit which leads to formation of bond in in such a way that they are not in the symmetrical manner/form (Fig. 5) [20, 21]. Different forms of halogen results in anisotropic electron supply of halogen atoms upon its connection with electron-withdrawing moieties, which can be of any organic or inorganic in nature.

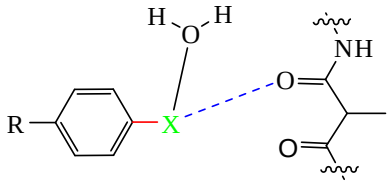


R = Any substituent
X = Cl/Br/I

Figure 5: Formation of asymmetric bifurcated halogen bond between organic compound and amino acid.

1.2.4 Double charge-assisted halogen bridge bond

Double charge-assisted halogen bonds are formed when there is formation of noncovalent contact between halogen atoms and other electron donating species where there is development of charges on both the interacting groups. This results in formation of double charged (+/-) assisted halogen bond as depicted in the figure-6 [22].



R = Any substituent
X = Cl/Br/I

Figure 6: Formation of double charge-assisted halogen bridge bond between organic compound and amino acid in presence of polar substituents.

1.3 SIGNIFICANCE OF HALOGEN BOND

Halogen elements, i.e., fluorine, chlorine, bromine, and iodine, were integrated in designing drugs for delightful motives: (I) to enhance their selectivity with the addition of bromine or iodine, (II) to boom their ADME properties through including chlorine and fluorine, or (III) to lessen undesired reactions along with ring hydroxylation [23].

1.3.1 σ-Hole and halogen bonding

Heavy halogen elements like chlorine, bromine, and iodine, have an anisotropic electron distribution on their equatorial surfaces resulting in outer area alongside their covalent bond referred to as the σ-hole. Its size relies upon on a couple of elements: a heavier halogen or electron-retreating make contributions to a more positive σ-hole. Fluorine presentations in such a location is excellent, but it's far normally considered as σ-hole deficient because of its excessive electronegativity and the molecular interactions. Experimentally, halogen bonds have largely paid to affinity development on specific drugs. Anticoagulant protein family consisting of component X or prothrombin has been enhanced by means of adding a chlorine cooperating with the aromatic establishment of tyrosine [24].

Introduction of halogen is critical for enhancing drug properties to increase the membrane penetrability and half-life in in-vivo research. However, halogenated organic pollutants are raising the concerns on the organic relevance of halocarbons, and that is chiefly the situation for chlorinated and brominated diphenyl and diphenyl ethers, that are uplifting the highest concerns due to the fact their structural and chemical similarity to thyroid hormones rises the effect of their existence in the living being [25].

Halogen bonds also are answerable for reactivity like molecular iodine (I_2) which acts as a catalyst for lots of organic reactions. The catalytic results of I_2 are allocated to the possibility of molecular iodine for formation of halogen bonds, initiating the electrophiles, drastically reducing the initiation of unfastened and free energies. Halogen σ-holes are also accountable for the reactivity of chlorine within the lowering of a trichloromethyl group by sulfur nucleophiles. In such case, the sulfur atom, performing as the halogen bond acceptor, interacts with the chlorine σ-hole, ultimately to the concept of the halogen and the formation of a carbanion [22, 26, 27]. As mentioned, halogen bonds are important in biological molecules and confirmed that halogen bonds were constructively formed with the protein backbone (~65 %), and the maximum designing idea of drugs. Halogen bonds also enables the dissimilarity of peptide-receptor interactions as shown by the halogenation of two natural opioid peptides that bind opioid receptors. The substitution of hydrogen in peptides by a larger halogen atom can produce steric crashes lowering the binding in minor voids and increase the binding, if the halogen (chlorine, bromine, iodine) interrelates with negatively charged atoms of the protein. For example, the replacement of the hydroxyl group in tyrosine by an iodine causes the movement of the aromatic side chain toward an oxygen acceptor, displaying that halogen bonds can overcome weakening effects that no other replacements are able to show [28-30]. Chlorine is the remarkably observed element among the halogen. The free element of chlorine is widely used as a water-purifying agent, and it's far hired in a number of chemical strategies. Table salt, sodium chloride is one of the most familiar chemical substances used every day. Fluorides are mainly applicable for their addition to public water and toothpaste to prevent teeth decay, but organic fluorides are also used as refrigerants and lubricants. Iodine is most accounted as an antiseptic, and bromine is used mainly to prepare bromine derived compounds which might be used in flame retardants and as general pesticides [31].

Some examples of drugs containing halogen atoms forming halogen bonds are discussed below:

1.3.2 Thyroid hormones and analogues

The biological activities of active form of thyroid hormones are associated with their binding to the thyroid receptor α and β (TRα/β) [32]. The triodothyronine (T3) is a thyroxine hormone produced from outer ring deiodination of prohormone tetraiodothyronine (T4) by action selenocysteine proteins iodothyronine

deiodinase type-I (Dio1) and II (Dio2). While deiodinase type-III (Dio3) converts T4 or T3 into inactive form of hormone as 3,3',5'-tiiodothyronine by inter ring deiodination and thus, maintain the thyroxine homeostasis [33].

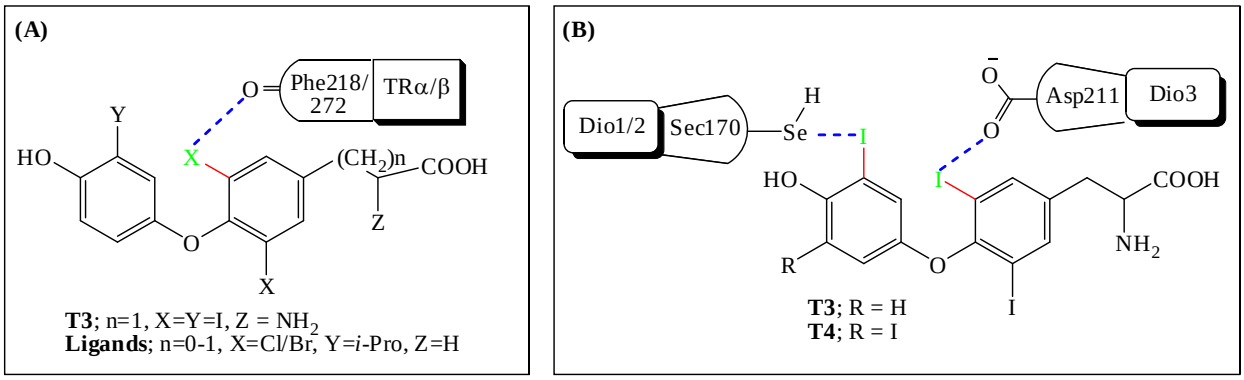


Figure 7: Halogen bonding between thyromimetics-TRα/β (A) and thyroxine-Dios interaction (B).

Earlier, Valadares *et al.* have been reported that halogen atoms present in thyroxin and other ligands important structural features essential for binding to the TRα/β receptors through halogen bonding [34]. The inner ring iodine of T3 form I…O bond with backbone >C=O of Phe218 and Phe272 in TRα and β receptors, respectively (Fig. 7A). Further, the C-O-I (θ_1) and C-I-O (θ_2) bond angles were found to be 121.2°/121.8° and 173.3°/165.9° in T3-TRα/β complexes. While bond lengths were found to be 3.05 Å and 3.23 Å for TRα and β receptors, respectively. The halogen bond (XB) lengths were dependent on type of halogens in different ligands such as I (≤3.50Å), Br (≤3.37Å) and Cl (≤3.27Å) with bond angles θ_1 ~120° and θ_2 ~165°.

In another study, Schweizer *et al.* have been mentioned that formation of I…Se halogen bond between thyroxine and selenocysteine (Sec170) residue of deiodinases as essential step of deiodination mechanism [35]. Recently, Bayse *et al.* have been reported that selectivity of Dio3 for inner ring deiodination is associated with stabilization of Dio3-T4 complex by halogen bonds (I…O) between T4 and side chain of Asp211 in Dio3 (Fig. 7B) [36]. These studies clearly indicated that halogen bonding is essential feature biological activity and metabolism of thyroid hormones and other thyromimetics.

1.3.3 Chloroquine and hydroxychloroquine

Chloroquine and its derivative, hydroxychloroquine, are well known for their antimalarial activity, additionally used to treat rheumatic sicknesses and also tried in the COVID-19 cases [37-39]. These drugs interfere with lysosome-autophagosome fusion, engage with membrane stability and might modify signaling pathways and transcriptional interest, resulting in inhibition of cytokine production and modulation of certain co-stimulatory molecules. At the cellular degree, they inhibit the Toll-like receptors signaling and reduce the CD-154 molecule expression in T cells [40, 41]. The presence of chlorine at the 7th position has been found to be essential feature for inhibition of parasite growth and hematin polymerization by quinolines in malaria [42]. Earlier, Kasende *et al.* have been mentioned the existence of halogen bond (Cl…N) in chloquine- temozolomide dimers [43]. Recently, Noureddine *et al.* with help of in-silico study reported that these chloroquinoline drugs form the halogen bond (Cl…O/S) with Met49 and Cys44 residues of chain A in SARS-CoV main protease (PDB 5R7Y) (Fig. 8) [44]. This halogen-bond possibly involves in enhancement of activity potential of drugs against COVID-19 main protease, however, there is need to explore it by crystallographic or other data.

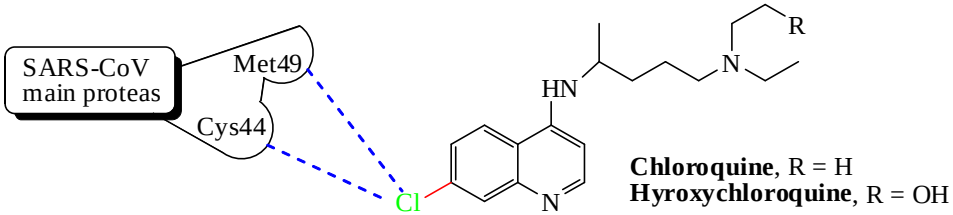


Figure 8: Halogen bonding in chloroquinolines-SARS-CoV main protease complex.

1.3.4 Aripiprazole

Aripiprazole is a partial agonist for 5HT1A and dopamine D2 receptors but antagonist for 5HT2A receptors. It is used to treat psychoses and related bipolar disorders [45]. Earlier studies have been reported that 99% aripiprazole and its metabolite bind to human plasma protein [46, 47]. Recently, Sakurama *et al.* have been identified formation of halogen bond (Cl…S) between *m*-Cl of phenyl ring in aripiprazole and S-atom of

Cys392 in plasma albumin with bond length 3.4-3.6 Å using equilibrium dialysis, spectroscopic and crystallographic techniques (Fig. 9) [48]. This study also included the Cl…S bond formation between diazepam and Cys392 residue of serum albumin. Similarly, diazepam and iodipamide have also been shown halogen bonding with serum albumin [25, 49]. These data clearly indicated that presence of halogen atom in drug molecules significantly contributes to their pharmacokinetic properties.

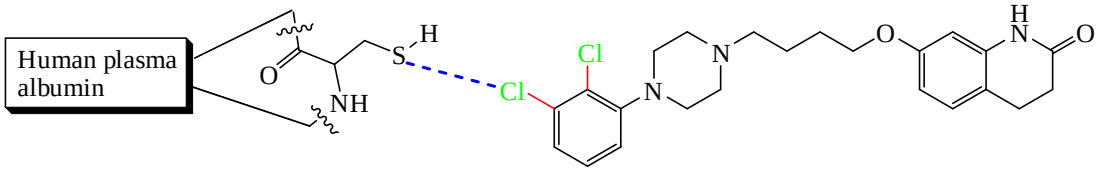


Figure 9: Formation of halogen bond between aripiprazole and human plasma albumin.

1.3.5 Avanafil

Avanafil is a phosphodiesterase 5A1 (PDE5A1) inhibitor and used as vasodilator to treat the cardiovascular disorders and erectile dysfunction [50]. Recently, Hsieh et al. have been reported that formation of halogen-bond (Cl…O, bond length 3.0 Å and bond angle 167.6°) between chlorine atom of avanafil and oxygen atom of Ala779 carbonyl backbone of PDE5A1 is essential for potency and PDE5A1 inhibitory activity [51]. As data indicated that sequestering of Cl…O bond by steric hindrance through mutation of chlorine binding pocket residues Ala779 and Ala783 with Val/leu779 and Val/leu783 resulted in remarkable reduction in PDE5A1 inhibitory activity of avanafil. While inhibitory activity of avanafil against wild-type PDE5A1 (un-mutated) was remains unaltered.

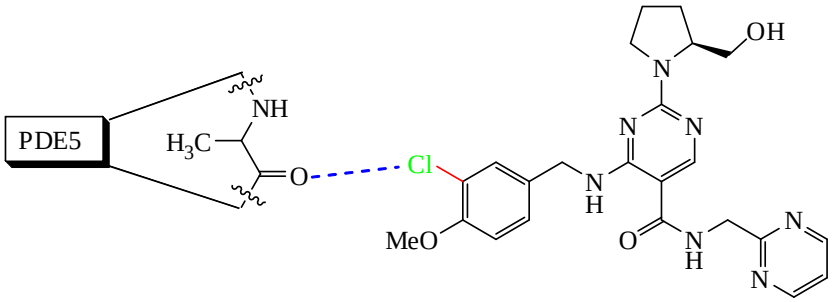


Figure 10: Halogen bond formation between avanafil and PDE5**.**

1.3.6 Hologenated anticancer agents (vorasidenib and halomitoxantrones)

There are long list of halogenated anticancer drugs with diverse mechanism of actions. The presence of halogens not only have significance as good leaving group during covalent binding of drug to neucleophilic sites at target protein but also they have been identified to participate in non-covalent halogen bonding interactions. Earlier, Koseki *et al.* have been reported that clinically used anticancer drug, trifluridine, distorts and destabilizes the double helical DNA conformation by formation of halogen bond [52]. Saleh *et al.* have been reported stabilization of halomitoxantrone ligands-DNA topoisomerase IIα complex via formation of halogen bond (F…O) by compound M1 and M2 with Ile715 (bond length 3.62 Å) and Arg713 (bond length 3.73 Å), respectively [53]. Recently, Konteatis *et al.* have been reported that vorasidenib, ivosidenib analogue and inhibitor of mutant isocitrate dehydrogenase 1/2, forms halogen bond (Cl…O) between chloropyridine and >C=O group of Asp273 side chain during its binding to enzyme [54]. Additionally, there is also existence of F…O bond between -CF_3 group and >C=O groups of Gln277, Val255 and Val255' backbone (Fig. 11). These studies signify the importance of halogen bonds in stabilization of ligand-target complex for anticancer activity of halogenated molecules.

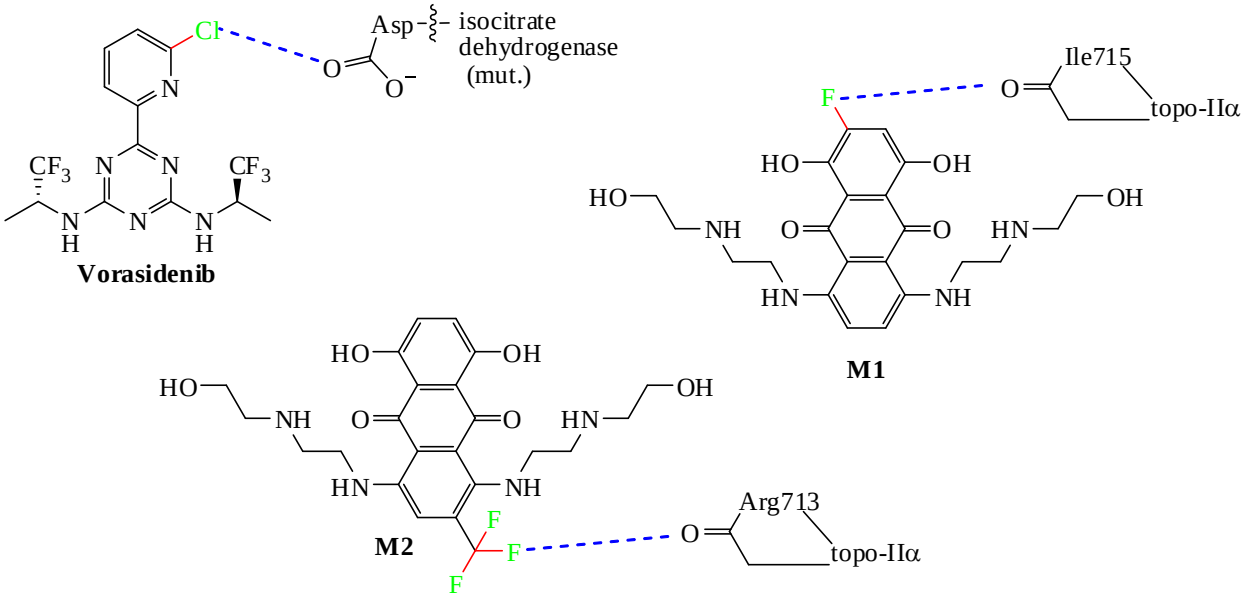


Figure 11: Halogen bonding of anticancer agents (vorasidenib, M1 and M2) with their target sites.

1.3.7 Chloramphenicol

Chloramphenicol is a bacteriostatic antibiotic effective against both Gram-positive and Gram-negative bacteria. Chemically, it is dichloroacetamide derivative of amphenicol family isolated from *S. venezuelae* and now being produced by chemical synthetic methods [55-57]. It has been shown effectiveness against aerobacter, streptococcus, staphylococcus, diplococcus, proteus, bacillus, vibrio etc. Chloramphenicol is an important active constituent in the remedy for typhoid and paratyphoid fevers, dysentery, brucellosis, poisonous dyspepsia, trachoma, and other sicknesses with better absorption and bioavailability [57].

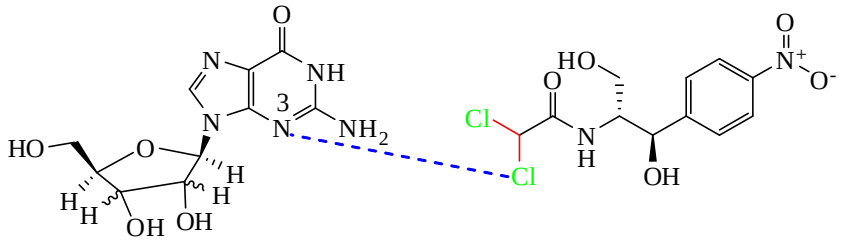


Figure 12: Halogen bond (Cl…N^3) between chloramphenicol and guanosine 2505.

Study by Hansch *et al.* has been shown that halogenated actamido derivatives of chloramphenicol are more active than acetamido derivatives *in vitro* and *in-vivo* [58]. Later, it was reported that presence of halogens in the chlroramphenicol or its derivatives is essential and participate in the halogen-bonding with ribosome [59]. In the chloramphenicol-ribosome (bacterial) complex, Cl-atom and N^3 of residue G2505 are able to form halogen bond with bond distance 3.4 Å and bond angle 133° (Fig. 12). On the basis of position and conformational orientation of dichloroacetamido moiety, Makarov and Makarova also admitted the existence of halogen bond during binding of chloramphenicol to the ribosome and possibility of its involvement in the antibacterial activity [60]. Meaurio *et al.* also reported the significance of dichloroacetamido moiety as its folding induce conformational change that results in intramolecular halogen bonding with pi-bonds of phenyl ring (C-Cl…π bond) [61, 62]. All the above reports indicated that the halogen bond formation plays important role essential for antibacterial activity of chloramphenicol.

1.3.8 Tetracyclines

Chlortetracycline is first halogenated member of tetracycline class of antibiotics isolated from *S. aureofaciens*. It is effective against bacterial infections and has valuable applications in mycoplasma, rickettsiae, and chlamydiae infections [63]. Till now, several halogenated tetracycline derivatives have been reported with different biological activities [64-67]. Demeclocycline and meclocyline are also the members of halogenated tetracyclines being used clinically. So, regularity in presence of halogen atoms in tetracycline structure indicated the significance of halogenations. These antibiotics primarily act via binding to the microbial ribosomes and

inhibition of protein synthesis. Earlier, Fuoco has been reported the structure-activity-relationship of different subclasses of tetracyclines but without any focus on the role of halogen [68].

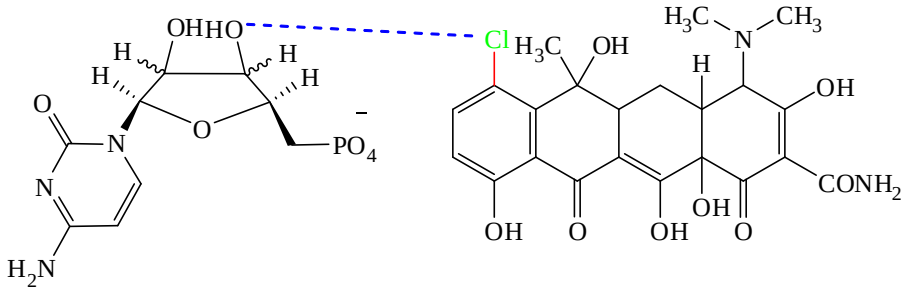


Figure 13: Halogen-bond (Cl…O) between tetracycline and cytidine.

The earlier review study by Erdelyi, on existence of halogen bonding as weaker molecular interaction in different solutions, suggested that halogen bonding is significantly important in the halogen containing antibiotics also such as chlortetracycline [69]. Further, Dong *et al.* have been mentioned that higher ability of electron attraction by C-7 chlorine atom in chlortetracycline helps in its binding with detoxifying enzymes and make it more toxic to *Eisenia fetida* than tetracycline (lacking halogen) [70]. Later, Kolar and Tabarrini reported that chlorine of chlortetracycline forms interaction with ribose oxygen of cytidine (bond length 3.7 Å and bond angle 151°) in a designed RNA aptamer (PDB 3egz) (Fig. 13) [71]. Thus, from above studies it may be concluded that halogen atoms present in halogenated tetracyclines are important for their interactions with target sites via formation of halogen-bonds.

1.3.9 Chlorzoxazone

Chlorzoxazone is a centrally-acting agent for painful musculoskeletal situations. Chlorzoxazone primarily acts on its target sites as spinal cord and subcortical regions of the brain where it inhibits multi synaptic reflex involved in generation of musculoskeletal spasms. The inhibition of synaptic reflex results in reduction in painful spasm, skeletal muscle relaxation and elevated mobility of the involved muscular tissues [72]. Earlier studies have been suggested that chlorzoxazone and related compounds (riluzole, SKA121, EBIO etc.) act through binding to the small conductance potassium (SK2) ion channels for their muscle relaxant activity (Fig. 14) [73]. However, their exact binding target site is not well explored.

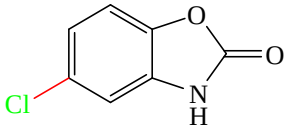


Figure 14: Chemical structure of chlorzoxazone.

Chlorzoxazone has also been shown blocking of release of histamine, slow-reacting substance of anaphylaxis, type 1 hypersensitivity reaction intermediates as well as mast cells degranulation. Additionally, it interferes and diminishes the release of leukotrienes to prevent the inflammation. Further, by inhibiting neuromuscular K^+ and Ca^{2+} ion influx it induces neuronal inhibition and muscle relaxation. Kerdawy *et al.* have been reported, using DFT calculation with different halobenzene probes, that -Cl atom of chlorzoxazone has higher propensity of halogen-bond formation with other molecular species (including protein target sites) [74].

1.3.10 Diclofenac

Diclofenac is a 2,6-dichloroaniline derivative of phenylacetic acid and used mainly as non-steroidal anti-inflammatory drug (NSAID). NSAIDs are class of drugs which primarily act by cyclooxygenase enzymes (COX-1/2) which are involved in biosynthesis of prostaglandins (PGs) and thromboxane A2 (TXA2) [75]. PGs make a contribution to inflammation and pain signaling. Diclofenac, like other NSAIDs, is regularly used as first line therapy for acute and chronic pain and microbial infections. Diclofenac become the product of coherent drug design based on the structures of phenylbutazone, mefenamic acid, and indomethacin. It is often used in combination with misoprostol to prevent NSAID-induced gastrointestinal ulcer [76]. The presence of two chlorine groups at the ortho positions of the phenyl ring, locks the ring in rigid torsion which appears to be related to increased potency [77].

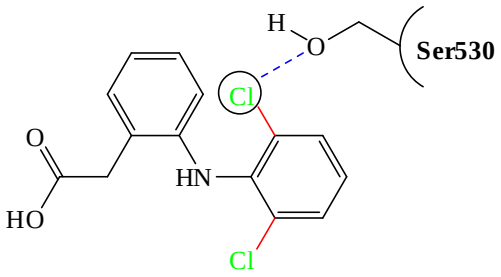


Figure 15: Formation of halogen bond (Cl…O) in COX-2-diclofenac complex.

In a SAR study for COX-2 inhibition, Blobaum and Marnett have been reported that halogen atoms in different arylacetic acid derivatives (diclofenac, lumiracoxib, and their derivatives) are essential for COX-2 inhibitory activity [78]. In the aniline ring, a combination of F-Cl, Cl-Cl, or Cl-CH_3 is allowed at 2,6-positions to maintain potency. These halogen atoms participate in the halogen-bonding with oxygen-atom of side chain -OH group of Ser530 in the binding sub-pocket covered by other hydrophobic residues Val349, Ala527, Ser530 and Leu531 (Fig. 15). Earlier, Parisini *et al.* have also mentioned the formation of halogen bond in the existing four different COX-2-dichlofenac complexes with bond distances and bond angles of 3.18-3.56 Å and 140.7-147.5°, respectively [79]. Similarly, Jelsch *et al.* have shown the formation of halogen bonds not only between COX-2 aceclofenac but also between two molecules aceclofenac in its crystal [80].

1.3.11 DDT (dichlorodiphenyltrichloroethane)

DDT is a polyhalogenated pesticide that was banned in the United States in 1972 because of the ability of dangerous results on human fitness. In the second half of World War II, it was used to control malaria and typhus among civilians and troops. After dangerous environmental influences of DDT have been recognized, it was banned in agricultural use globally. It kills insects *via* opening sodium ion channels in insect's neurons, imposing the neurons to fire spontaneously. This ends in spasms and eventual loss of life. Insects with certain mutations of their sodium channel gene may be resilient against DDT and different comparable pesticides [81]. Truong *et al.* have been have been reported that DDT and its derivatives binds to ryanodine receptor type-1 and modify it conformation to alter the Ca^{2+} ion dynamics in sarcoplasmic reticulum for impairment of normal functioning of muscles [82]

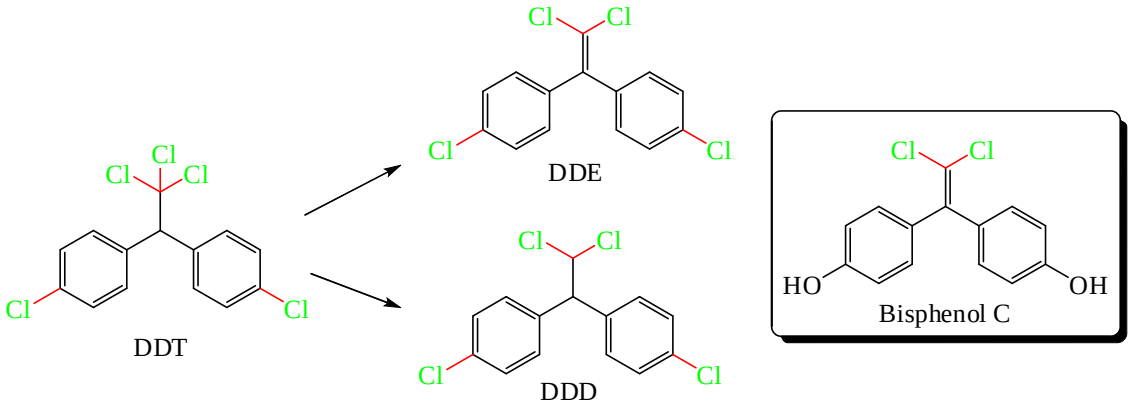


Figure 16: Comparative structures of DDT, its metabolites and bisphenol C.

DDT has not only been reported as a marker of higher cancer risk but also a predictor of breast cancer and endocrine disruptor. It is preferably deposited in adipose tissues and its exposure increase the risk of utero and ER(+)/(-) breast cancers [83]. The higher plasma level or exposure to organochlorine compounds, including DDT, has been found as one of the factor for higher mortality in breast cancer [84]. This higher risk of health cancer development is probably associated with it DDT induced higher production of IL-1β and interference in p38 MAPK pathway which are involved in inflammatory diseases and development of cancer [85]. Earlier, Matsushima has been mentioned that DDT and its metabolite (DDE, DDD) have structural similarity with bisphenol C has ability to form halogen bond with biological systems to induce toxic effect (Fig. 16) [86]. Iramain *et al.* reported halogen bond formation in the DDT solution with evidences based on theoretical calculations and vibrational spectroscopic experimental data [87]. However, there was no availability of direct biological experimental data on DDT but still above facts indicated that role of halogen bonding associated with DDT toxicity to endocrine or other biological system.

II. CONCLUSION

Generally, halogen bonds formed between proteins and their ligands and it has been widely employed in drug design because of their role in improving ligand binding affinities. Halogen bonds were observed in the proteins with different functional characteristics, including hydrolases, transferases, oxidoreductases, lyases, isomerases, ligases, and transporters, which nearly constitute 20% of pharmacokinetic process. In a protein-ligand biosystem, the halogen bond can shift the enzyme's substrate selectivity by adjusting the substrate binding conformation. It can be used as a powerful tool, similarly to hydrogen bond and electrostatic interactions in enzyme design for better biological activities.

ACKNOWLEDGEMENTS

Authors are thankful to Senior Dean, School of Pharmaceutical Sciences (LPU) for providing work facilities and valuable suggestions, respectively.

REFERENCES

[1]. Desiraju GR, Ho PS, Kloo L, Legon AC, Marquardt R, Metrangolo P, et al. Definition of the Halogen Bond (IUPAC Recommendations 2013). Pure Appl Chem 2013; 85: 1711-1713.
[2]. Anon. Categorizing Halogen Bonding and Other Noncovalent Interactions Involving Halogen Atoms. Chemistry International--Newsmagazine for IUPAC 2010; 32: 20-21.
[3]. Lu Y, Wang Y, Zhu W. Nonbonding Interactions of Organic Halogens in Biological Systems: Implications for Drug Discovery and Biomolecular Design. Phys Chem Chem Phys 2010; 12: 4543-4551.
[4]. Auffinger P, Hays FA, Ho PS, Westhof E. Halogen Bonds in Biological Molecules. Proc Natl Acad Sci USA 2004; 101: 16789-16794.
[5]. Kalgutkar AS, Kiefer JR, Kozak KR, Kurumbail RG, Marnett LJ, Pawlitz JL et al. A Novel Mechanism of Cyclooxygenase-2 Inhibition Involving Interactions with Ser-530 and Tyr-385. J Biol 2003; 278: 45763-45769.
[6]. Clark T, Hennemann M, Murray JS, Politzer P. Halogen bonding: the σ-hole. J Mol Model 2007;13;291-296
[7]. Murray JS, Lane P, Politzer P. Expansion of the sigma-hole concept. J Mol Model. 2009;15(6):723-9.
[8]. Pascoe DJ, Ling KB, Cockroft SL. The origin of chalcogen-bonding interactions. J Am Chem Soc 22017;139:15160-15167.
[9]. Rezac J, Riley KE, Hobza P. Benchmark calculations of noncovalent interactions of halogenated molecules. J Chem Theor Comput 2012;8:4285-4292.
[10]. Oliveira V, Kraka E, Cremer D. The intrinsic strength of the halogen bond: electrostatic and covalent contributions described by coupled cluster theory. Phys Chem Chem Phys. 2016;18(48):33031-33046.
[11]. Robertson CC, Wright JS, Carrington EJ, Perutz RN, Hunter CA, Brammer L. Hydrogen bonding vs. halogen bonding: the solvent decides. Chem Sci. 2017;8(8):5392-5398.
[12]. Costa, PJ The halogen bond: Nature and applications. Phys. Sci. Rev., 2017; 2(11):20170136.
[13]. Wegeberg C, Donald WA, McKenzie CJ. Noncovalent Halogen Bonding as a Mechanism for Gas-Phase Clustering. J Am Soc Mass Spectrom. 2017;28(10):2209-2216.
[14]. Sirimulla S, Bailey JB, Vegesna R, Narayan M. Halogen interactions in protein-ligand complexes: implications of halogen bonding for rational drug design. J Chem Inf Model. 2013;53(11):2781-91.
[15]. Kolaric A, Germe T, Hrast M, Stevenson CEM, Lawson DM, Burton NP, Voros J, Maxwell A, Minovski N, Anderluh M. Potent DNA gyrase inhibitors bind asymmetrically to their target using symmetrical bifurcated halogen bonds. Nat Commun. 2021;12(1):150.
[16]. Ding X-H, Chang Y-Z, Ou C-J, Lin J-Y, Xie L-H, Huang W. Halogen bonding in the co-crystallization of potentially ditopic diiodotetrafluorobenzene: a powerful tool for constructing multicomponent supramolecular assemblies, Natl Sci Rev 2020;7(12):1906-1932.
[17]. Novak M, Foroutan-Nejad C, Marek R. Asymmetric bifurcated halogen bonds. Phys Chem Chem Phys. 2015;17(9):6440-50.
[18]. Bartashevich E, Troitskaya E, Pendas AM, Tsirelson V. Understanding the bifurcated halogen bonding N···Hal···N in bidentate diazaheterocyclic compounds. Comput Theor Chem 2015; 1053:229-237.
[19]. Ramana CV, Chatterjee S, Durugkar KA, Gonnade RG. "Click" synthesis of isomeric compounds for assessing the efficiency of the bifurcated Br···NO2 synthon. CrystEngComm 2009; 11:143-150.
[20]. Efimenko ZM, Eliseeva AA,Ivanov DM, Galmes B, Frontera A, Bokach NA,Kukushkin VY. Bifurcated μ2-I•••(N,O) Halogen Bonding: The Case of (Nitrosoguanidinate)NiII Cocrystals with Iodine(I)-Based σ-Hole Donors. Cryst Growth Des 2021;21(1):588–596.
[21]. Hage KE, Pandyarajan V, Phillips NB, Smith BJ, Menting JG, Whittaker J, Lawrence MC, Meuwly M, Weiss MA. Extending Halogen-based Medicinal Chemistry to Proteins: Iodo-insulin as a case study. J Biol Chem. 2016;291(53):27023-27041.
[22]. Domagała M, Lutynska A, Palusiak M. Extremely Strong Halogen Bond. The Case of a Double-Charge-Assisted Halogen Bridge. J Phys Chem A 2018;122(24):5484-5492.
[23]. Xu Z, Yang Z, Liu Y, Lu Y, Chen K, Zhu W. Halogen bond: its role beyond drug-target binding affinity for drug discovery and development. J Chem Inf Model. 2014;54(1):69-78.
[24]. Jaskolski, M.; Nangia, A.; Saha, B.K. CrystEngComm. 2005, 7, 355–358.
[25]. Cavallo, G.; Metrangolo, P.; Milani, R.; Pilati, T.; Priimagi, A.; Resnati, G.; Terraneo, G. The halogen bond. Chemical reviews. 2016, 116(4), 2478-601.
[26]. Saha BK, Nangia A, Jaskolski M. Crystal Engineering with Hydrogen Bonds and Halogen Bonds. CrystEngComm 2005; 7: 355-358.
[27]. Gong Z, Li J, Lu T, Zhang X. Intermolecular Sulfur Oxygen Interactions: Theoretical and Statistical Investigations. J Chem Inf Model 2015; 55: 2138-2153.
[28]. Gong, Z.; Li, J.; Lu, T.; Zhang, X. Intermolecular Sulfur Oxygen Interactions: Theoretical and Statistical Investigations. J. Chem. Inf. Model. 2015, 55, 2138−2153
[29]. Laskowski, R.A.; Thornton, J.M.; Wallace, A.C. LIGPLOT: A Program to Generate Schematic Diagrams of Protein-Ligand Interactions. Protein Eng., Des. Sel. 1995, 8, 127−134.
[30]. Metrangolo, P.; Parisini, E.; Pilati, T.; Resnati, G.; Terraneo, G. Halogen Bonding in Halocarbon-Protein Complexes: A Structural Survey. Chem. Soc. Rev. 2011, 40, 2267−2278

[31]. Windham GC, Pinney SM, Voss RW, Sjödin A, Biro FM, Greenspan LC, Stewart S, Hiatt RA, Kushi LH. Brominated Flame Retardants and Other Persistent Organohalogenated Compounds in Relation to Timing of Puberty in a Longitudinal Study of Girls. Environ Health Perspect. 2015;123(10):1046-52.

[32]. Sandler B, Webb P, Apriletti JW, Huber BR, Togashi M, Cunha Lima ST, Juric S, Nilsson S, Wagner R, Fletterick RJ, Baxter JD. Thyroxine-thyroid hormone receptor interactions. J Biol Chem. 2004;279(53):55801-8.

[33]. Miura M, Tanaka K, Komatsu Y, Suda M, Yasoda A, Sakuma Y, Ozasa A, Nakao K. Thyroid hormones promote chondrocyte differentiation in mouse ATDC5 cells and stimulate endochondral ossification in fetal mouse tibias through iodothyronine deiodinases in the growth plate. J Bone Miner Res. 2002;17(3):443-54.

[34]. Valadares NF, Salum LB, Polikarpov I, Andricopulo AD, Garratt RC. Role of halogen bonds in thyroid hormone receptor selectivity: pharmacophore-based 3D-QSSR studies. J Chem Inf Model. 2009;49(11):2606-16.

[35]. Schweizer U, Schlicker C, Braun D, Köhrle J, Steegborn C. Crystal structure of mammalian selenocysteine-dependent iodothyronine deiodinase suggests a peroxiredoxin-like catalytic mechanism. Proc Natl Acad Sci U S A. 2014;111(29):10526-31

[36]. Bayse CA, Marsan ES, Garcia JR, Tran-Thompson AT. Thyroxine binding to type III iodothyronine deiodinase. Sci Rep. 2020;10(1):15401

[37]. Cabral RTS, Klumb EM, Couto MINN, Carneiro S. Evaluation of toxic retinopathy caused by antimalarial medications with spectral domain optical coherence tomography. Arq Bras Oftalmol. 2019;82(1):12-17

[38]. Jorge A, Ung C, Young LH, Melles RB, Choi HK. Hydroxychloroquine retinopathy - implications of research advances for rheumatology care. Nat Rev Rheumatol. 2018;14(12):693-703

[39]. Khuroo MS. Chloroquine and hydroxychloroquine in coronavirus disease 2019 (COVID-19). Facts, fiction and the hype: a critical appraisal. Int J Antimicrob Agents. 2020;56(3):106101

[40]. Mauthe M, Orhon I, Rocchi C, Zhou X, Luhr M, Hijlkema KJ, Coppes RP, Engedal N, Mari M, Reggiori F. Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion. Autophagy. 2018;14(8):1435-1455

[41]. Roldan QE, Biasiotto G, Magro P, Zanella I. The possible mechanisms of action of 4-aminoquinolines (chloroquine/hydroxychloroquine) against Sars-Cov-2 infection (COVID-19): A role for iron homeostasis? Pharmacol Res. 2020;158:104904

[42]. Vippagunta SR, Dorn A, Matile H, Bhattacharjee AK, Karle JM, Ellis WY, Ridley RG, Vennerstrom JL. Structural specificity of chloroquine-hematin binding related to inhibition of hematin polymerization and parasite growth. J Med Chem. 1999;42(22):4630-9

[43]. Kasende OE, Nziko VPN, Scheiner S. H-bonding and stacking interactions between chloroquine and temozolomide. Int. J. Quantum Chem. 2016; 116:1196-1204

[44]. Noureddine O, Issaoui N, Medimagh M, Al-Dossary O, Marouani H. Quantum chemical studies on molecular structure, AIM, ELF, RDG and antiviral activities of hybrid hydroxychloroquine in the treatment of COVID-19: Molecular docking and DFT calculations. J King Saud Univ Sci. 2021;33(2):101334

[45]. Coustals N, Menard M-L, Cohen D. Aripiprazole in Children and Adolescents. J. Child Adolesc. Psychopharmacol. 2021; 31:4-32

[46]. Bristol-Myers Squibb Company. Abilify (aripiprazole) tablets. In:Physicians' Desk Reference. 58th ed. Montvale, NJ: Thomson PDR,2004:1034-1038

[47]. Citrome E, Josiassen R, Bark N, Salazar DE, Mallikaarjun S. Pharmacokinetics of Aripiprazole andConcomitant Lithium and Valproate. J Clin Pharmacol 2005;45:89-93

[48]. Sakurama K, Kawai A, Chuang VTG, Kanamori Y, Osa M, Taguchi K, et al. Analysis of the Binding of Aripiprazole to Human Serum Albumin: The Importance of a Chloro-Group in the Chemical Structure. ACS Omega 2018;3(10):13790-13797

[49]. Ghuman J, Zunszain PA, Petitpas I, Bhattacharya AA, Otagiri M, Curry S. Structural basis of the drug-binding specificity of human serum albumin. J Mol Biol. 2005;353(1):38-52

[50]. Burke RM, Evans JD. Avanafil for treatment of erectile dysfunction: review of its potential. Vasc Health Risk Manag. 2012;8:517-523

[51]. Hsieh CM, Chen CY, Chern JW, Chan NL. Structure of Human Phosphodiesterase 5A1 Complexed with Avanafil Reveals Molecular Basis of Isoform Selectivity and Guidelines for Targeting α-Helix Backbone Oxygen by Halogen Bonding. J Med Chem 2020;63(15):8485-8494

[52]. Koseki J, Tsunekuni K, Konno M, Nishida N, Kawamoto K, Doki Y, et al. Thermodynamic and molecular orbital analysis of the effects caused by incorporation of novel anti-tumor agent Trifluridine to DNA. Abstract 2706: AACR 107th Annual Meeting, 2016.

[53]. Saleh MA, Solayman M, Hoque MM, Khan MA, Sarwar MG, Halim MA. Inhibition of DNA Topoisomerase Type IIα (TOP2A) by Mitoxantrone and Its Halogenated Derivatives: A Combined Density Functional and Molecular Docking Study. Biomed Res Int. 2016;2016:6817502.

[54]. Konteatis Z, Artin E, Nicolay B, Straley K, Padyana AK, Jin L, et al. Vorasidenib (AG-881): A First-in-Class, Brain-Penetrant Dual Inhibitor of Mutant IDH1 and 2 for Treatment of Glioma. ACS Med Chem Lett. 2020;11(2):101-107.

[55]. Sills MR, Boenning D. Chloramphenicol. Pediatr Rev 1999;20(10):357-358.

[56]. Aronoff DM. Mildred Rebstock: Profile of the Medicinal Chemist Who Synthesized Chloramphenicol. Antimicrob Agents Chemother 2019;63(6):e00648-19.

[57]. Can, J.; Mclnnes, A.G.; Paramasigamani, K.; Simonsen, J.N.; Vining, L.C.; Walter, J.A.; Wright, L.C. Biosynthesis of chloramphenicol. Studies on the origin of the dichloroacetyl moiety. Can. J. Microbiol. 1978, 24, 136-142.

[58]. Hansch C, Nakamoto K, Gorin M, Denisevich P, Garrett ER, Heman-Ackah SM, et al. Structure-activity relation of chloramphenicols. J Med Chem 1973;16(8):917-922.

[59]. Kolar MH, Tabarrini, O. Halogen bonding in nucleic acid complexes. J Med Chem 2017; 60(21):8681-8690.

[60]. Makarov GI, Makarova TM. A noncanonical binding site of chloramphenicol revealed via molecular dynamics simulations. Biochim Biophys Acta Gen Subj. 2018;1862(12):2940-2947.

[61]. Meaurio E, Sanchez-Rexach E, Munoz J, Sarasua J-R. Molecular Conformation of Crystalline and Amorphous Chloramphenicol. In: Proceedings of the 4thWorld Congress on Mechanical, Chemical, and Material Engineering (MCM'18); Madrid, Spain August 16-18, 2018, Paper No. ICCPE 126 (DOI: 10.11159/iccpe18.126).

[62]. Meaurio E, Sanchez-Rexach E, Munoz J, Sarasua J-R. The conformation of chloramphenicol in the ordered and disordered phases. Spectrochim Acta A Mol Biomol Spectrosc 2019; 211:383-392.

[63]. Scholar E. Chlortetracycline. In: Enna SJ, Bylund DB, editors. xPharm: The Comprehensive Pharmacology Reference. Amsterdam: Elsevier; 2007. p. 1-5.

[64]. Beereboom JJ, Rennhard HH, Stephens CR Jr. Halogenated tetracycline derivatives and processes for their preparation. Patent US3043875A; 1962.

[65]. Rezanka T, Spizek J. Halogen-Containing Antibiotics From Streptomycetes. In: Atta-ur-Rahman editor. Studies in Natural Products Chemistry. Volume 29, Part J, Amsterdam: Elsevier; 2003. p. 309-353.

[66]. Markley JL, Fang L, Gasparrini AJ, Symister CT, Kumar H, Tolia NH, et al. Semisynthetic Analogues of Anhydrotetracycline as Inhibitors of Tetracycline Destructase Enzymes. ACS Infect Dis 2019;5(4):618-633.
[67]. Koehne E, Kreidenweiss A, Adegbite BR, Manego RZ, McCall MBB, Mombo-Ngoma G, et al. In vitro activity of eravacycline, a novel synthetic halogenated tetracycline, against the malaria parasite Plasmodium falciparum. J Glob Antimicrob Resist. 2021;24:93-97.
[68]. Fuoco D. Classification Framework and Chemical Biology of Tetracycline-Structure-Based Drugs. Antibiotics (Basel) 2012;1(1):1-13.
[69]. Erdelyi M. Halogen bonding in solution. Chem Soc Rev 2012;41:3547-3557.
[70]. Dong L, Gao J, Xie X, Zhou Q. DNA damage and biochemical toxicity of antibiotics in soil on the earthworm Eisenia fetida. Chemosphere 2012;89(1):44-51.
[71]. Kolar MH, Tabarrini O. Halogen Bonding in Nucleic Acid Complexes. J Med Chem 2017;60(21):8681-8690.
[72]. Zuzan O, Leuwer M. Neuromuscular blocking agents and skeletal muscle relaxants. In: Aronson JK editor. Side effects of drugs annual, Amsterdam: Elsevier; 2009. p. 247-57.
[73]. Cho LT, Alexandrou AJ, Torella R, Knafels J, Hobbs J, Taylor T, et al. An Intracellular Allosteric Modulator Binding Pocket in SK2 Ion Channels Is Shared by Multiple Chemotypes. Structure 2018;26(4):533-544.e3.
[74]. Kerdawy AE, Wick CR, Hennemann M, Clark T. Predicting the Sites and Energies of Noncovalent Intermolecular Interactions Using Local Properties. J Chem Inf Model 2012;52:1061-71.
[75]. Morita I. Distinct functions of COX-1 and COX-2. Prostaglandins Other Lipid Mediat. 2002;68-69:165-75.
[76]. 27. Gan, T.J. Diclofenac: an update on its mechanism of action and safety profile. Curr Med Res Opin. 2010, 26(7), 1715-31.
[77]. Sallmann, A.R. The history of diclofenac. Am. J. Med. 1986, 80(4), 29-33.
[78]. Blobaum AR, Marnett AJ. (2007), "Molecular Determinants for the Selective Inhibition of Cyclooxygenase-2 by Lumiracoxib. J Biol Chem Vol. 282, Pp. 16379-16390.
[79]. Parisini E., Metrangolo P., Pilati T., Resnati G., Terraneo G. (2011), "Halogen bonding in halocarbon-protein complexes: a structural survey" Chem. Soc. Rev. Vol. 40, Pp. 2267-2278.
[80]. Jelsch, C, Devi R.N., Noll B.C., Guillot B., Samuel I., Aubert E. (2020), "Aceclofenac and interactions analysis in the crystal and COX protein active site" J. Mol. Struct., Vol. 1205, Pp. 127600.
[81]. Turusov V, Rakitsky V, Tomatis L. (2002), "Dichlorodiphenyltrichloroethane (DDT): ubiquity, persistence, and risks" Environ Health Perspect. Vol. 110, No. 2, Pp. 125-128.
[82]. Truong KM, Cherednichenko G, Pessah IN. (2019), "Interactions of Dichlorodiphenyltrichloroethane (DDT) and Dichlorodiphenyldichloroethylene (DDE) With Skeletal Muscle Ryanodine Receptor Type 1" Toxicol Sci. Vol. 170, No. 2, Pp. 509-524.
[83]. Cohn BA, La Merrill M, Krigbaum NY, Yeh G, Park, JS, Zimmermann L, et al. (2015), "DDT Exposure in Utero and Breast Cancer" J Clin Endocrinol Metab. Vol. 100, No. 8, Pp. 2865-2872.
[84]. Parada H Jr, Sun X, Tse CK, Engel LS, Olshan AF, Troester MA. (2019) Plasma levels of dichlorodiphenyldichloroethene (DDE) and dichlorodiphenyltrichloroethane (DDT) and survival following breast cancer in the Carolina Breast Cancer Study. Environ Int. Vol. 125, Pp. 161-171.
[85]. Martin TJ, Maise J, Gabure S, Whalen MM. (2019), "Exposures to the environmental contaminants pentachlorophenol and dichlorodiphenyltrichloroethane increase production of the proinflammatory cytokine, interleukin-1β, in human immune cells' J Appl Toxicol. Vol. 39, No. 8, Pp. 1132-1142.
[86]. Matsushima A. A (2018), "Novel Action of Endocrine-Disrupting Chemicals on Wildlife; DDT and Its Derivatives Have Remained in the Environment" Int J Mol Sci., Vol. 19, No. 5, Pp. 1377.
[87]. Iramain MA, Castillo MV, Davies L, Manzur ME, Brandan SA (2020), "Structural and SQMFF study of potent insecticide 4′,4′-DDT combining the FT-IR and FT-Raman spectra with DFT calculations" J. Mol. Struct., Vol. 1199, Pp. 12696.