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A PHARMACOPHORE BASED DRUG DESIGN APPROACH TO OVERCOME IMATINIB RESISTANCE AND GET MORE POTENT BCR-ABL TYROSINE KINASE INHIBITOR

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Keywords:

Structure Activity Relationship (SAR), Pharmacophore, Drug design, Imatinib, Molecular docking, MolSoft, Lazar toxicity, OSIRIS Property Explorer, MetaPrint2D.

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ABSTRACT: BCR-ABL Tyrosine Kinase inhibitor is an ideal pharmacological target for Chronic Myeloid Leukemia (CML). After the effective use of Imatinib as a therapeutic agent for Chronic Myeloid Leukemia, resistance has been observed in much patience with the treatment of Imatinib. The main objective of this study is to develop some new novel BCR-ABL Tyrosine Kinase inhibitor for the treatment of Chronic Myeloid Leukemia by Structure Activity Relationship (SAR) and Pharmacophore based drug design approach with Imatinib as a prototype drug. Moreover to overcome the resistance with Imatinib and get some new innovative BCR-ABL Tyrosine Kinase inhibitor with increased potency. In this study, we have designed some new BCR-ABL Tyrosine Kinase inhibitor and reported them as potentially new BCR-ABL Tyrosine Kinase inhibitor by using molecular docking analysis and various free internet based Insilco tools. The drug properties like toxicity, metabolic site, Binding energy, Inhibition constant, Ligand efficiency and many other parameters are predicted through *In-silico* tools.

INTRODUCTION: Chronic Myeloid Leukemia (CML) is a clonal myeloproliferation disorder characterized by the expansion of hematopoietic cells [1]. It is strongly linked to genetic mutation that produces an abnormal chromosome in bone marrow stem cells known as Philadelphia chromosome (Ph) and its oncogenic product.

BCR-ABL is present in more than 95% of patients suffering from Chronic Myeloid Leukemia (CML) and it is the causative agent of this disease. BCR-ABL encloses a protein tyrosine kinase activity [2-4]. The Philadelphia chromosome carries a defective mutated gene called BCR-ABL.

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This is present in cases of all Chronic Myeloid Leukemia thought the disease. These BCR-ABL gene acts like a set of instructions for the body cells "What to do". They instruct the body to produce abnormal protein BCR-ABL. This abnormal BCR-ABL protein in turn instructs the bone marrow to produce more White Blood Cells than the required amount including abnormal and immature cells [5].

The Philadelphia chromosome is a somatic mutation that results from the reciprocal translocation between the long arms of chromosome. The t (9, 22) translocation fuses the genetic sequence on chromosome 22 (BCR) with c-abl (Abelson Tyrosine Kinase, ABL1) sequences translocated from the chromosome 9. This t (9, 22) translocation fuses BCR sequences on the upper stream of the second exon of c-ABL. Thus this process in turn generates one of the two BCR-ABL fusion proteins, p185 and p210. Both BCR-ABL proteins are known as chimeric proteins. But p210

is observed in 95% of patients with Chronic Myeloid Leukemia where as p185 is observed in approximately 10% of patience only with Chronic Myeloid Leukemia [4, 6-8]. These two BCR-ABL fusion proteins is constitutively activated and its activity may increase over time as the disease progresses from Chronic Myeloid Leukemia stable phase to blast crisis phase [5, 9]. As the BCR-Abl tyrosine kinase enzyme exists only in cancer cells and not in healthy cells, as a result Imatinib works as a targeted therapy and due to this reason only cancer cells are killed through the drug action. But in some patients especially in the advance phase of Chronic Myeloid Leukemia a resistance is found on treatment with Imatinib a BCR-ABL tyrosine kinase inhibitor. This resistance is usually due to point mutation in the kinase domain of the BCR-ABL enzyme that reduces the sensitivity towards Imatinib [9-12].

In this study, Structure Activity Relationship (SAR) and Pharmacophore based drug design approach has been adopted to overcome the resistance with Imatinib and get some new innovative BCR-ABL Tyrosine Kinase inhibitor with increased potency. Whose activity and efficiency has been proved by some Insilco tools and internet JAVA based servers.

MATERIALS & METHODS: Imatinib is a first generation therapeutic agent of BCR-ABL Tyrosine Kinase. It is generally used for treating Philadelphia chromosome-positive (Ph^+) chronic myelogenous leukemia (CML) and is having following molecular structure **(Fig. 1)**

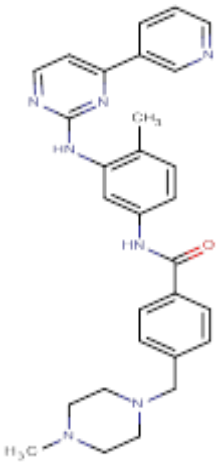


FIG. 1: MOLECULAR STRUCTURE OF IMATINIB

The new ligands have been designed by taking Imatinib as prototype and substituting hydroxyl group, amine group, and chloride group at position -R, $-R_1$, $-R_2$, $-R_3$, $–R_4$ and $–R_5$ in Imatinib skeleton lead to increase its pharmacological and drug likeness activities **(Fig. 2)** But when similar substitution was done at position $–R''$, $-R''_1$, $-R''_2$, $-R''_3$, $-R''_4$ and $–R''_5$ of Imatinib with hydroxyl group, amine group, halide group, alkane and halo alkane group decrease in druglikeness property and pharmacological activity was found **(Fig. 3).** Thus, Imatinib derivatives were designed by making substitution at -R, $-R_1$, $-R_2$, $-R_3$, $–R_4$ and $–R_5$ positions.

Protein preparation: The 3D structure of our protein is available in Protein Data Bank. Human Abl kinase domain in complex with imatinib (PDB ID 2HYY) is selected for performing the docking studies [13, 14]. The selected protein 3D structure is having 4 chains, hence only chain A was isolated from the structure and used for docking.

Molecular Docking Analysis: Autodock is used for the Molecular docking studies of the ligands with the receptor protein. Autodock uses binding free energy evaluation to find the best binding mode. Autodock energy values were calculated by the characterization of intermolecular energy (consist of van der Walls energy, hydrogen bonding energy, desolvation energy, and electrostatic energy), internal energy of ligand, and torsional free energy. The designed ligands were subjected to molecular docking studies and the docked complex is visualized using Python molecule viewer [15] as shown in **(Fig. 10)** Binding energy, ligand efficiency, inhibition constant, hydrogen bond interactions and their bond lengths are calculated as shown in **Table 1.**

Pharmacological properties analysis: Analogues have been designed by taking Imatinib as a prototype. Substitutions have been made by –OH, $-NH_2$ and -Cl at position -R, $-R_1$, $-R_2$, $-R_3$, $–R_4$ and $–R_5$ in such a way that binding energy, molecular properties (Druglikeness score, Hydrogen bond donor, hydrogen bond acceptor etc) and other pharmacological properties (Absorption, Distribution, Metabolism, Excretion, Toxicity etc) are higher than that of the prototype as discussed in **Table (2, 3, 4, 5).**

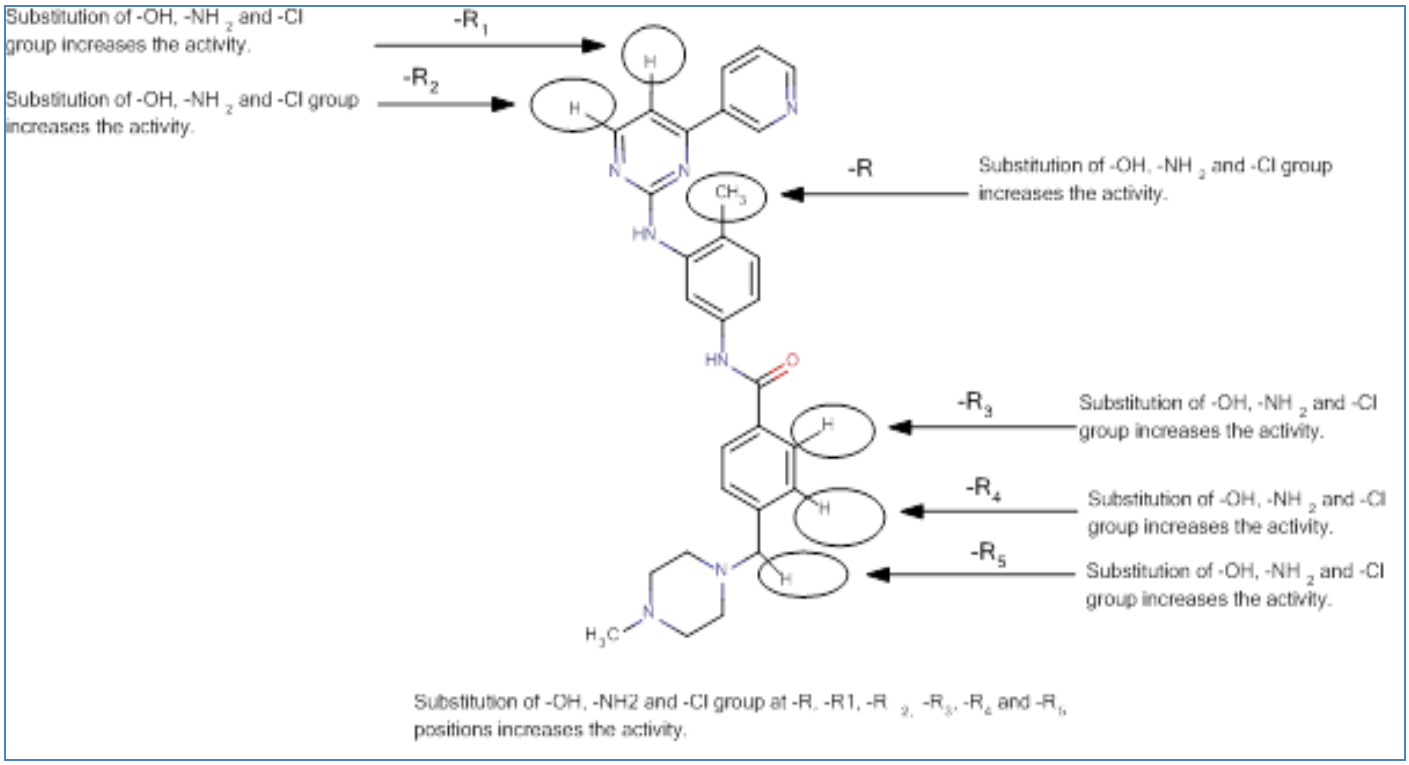


FIG. 2: PICTORIAL REPRESENTATION OF SUBSTITUTION LEADING TO INCREASE IN ACTIVITY

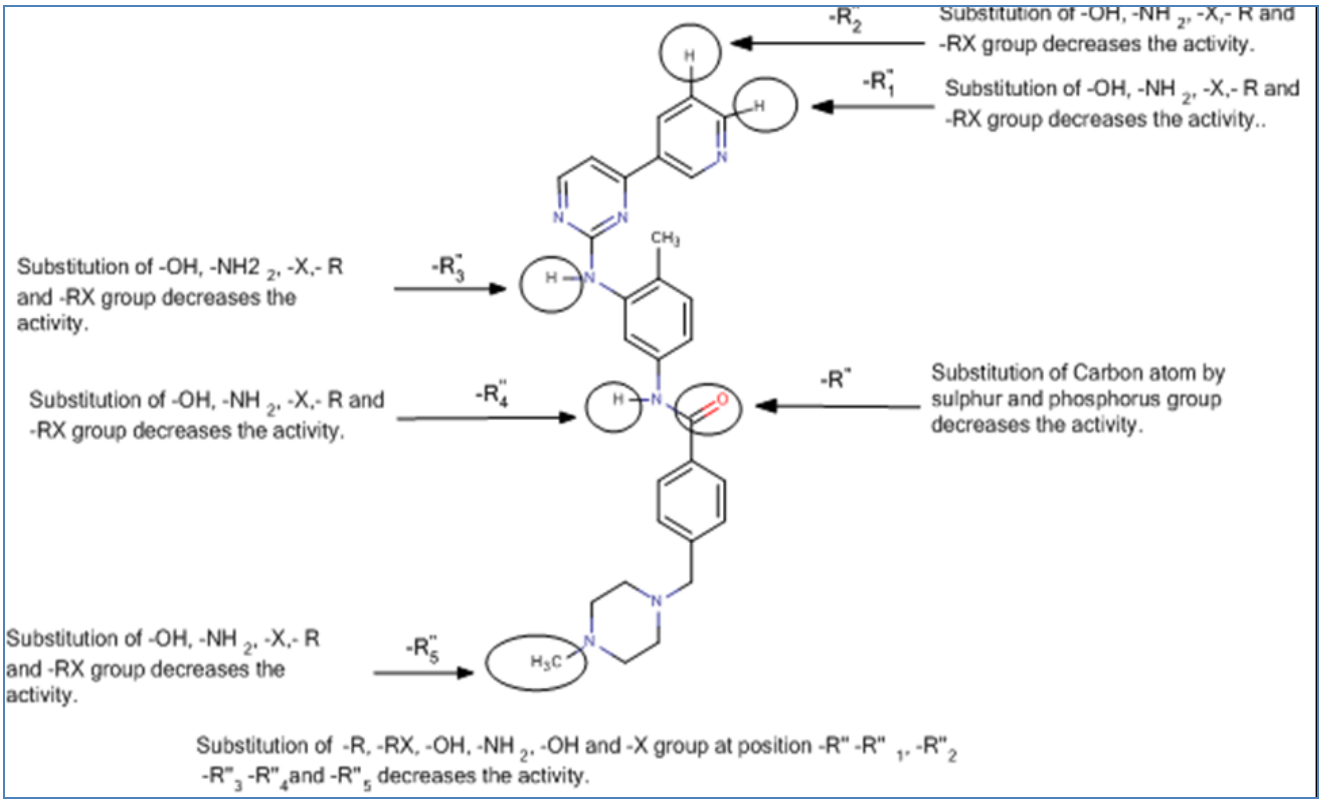


FIG.3 PICTORIAL REPRESENTATION OF SUBSTITUTION LEADING TO DECREASE IN ACTIVITY

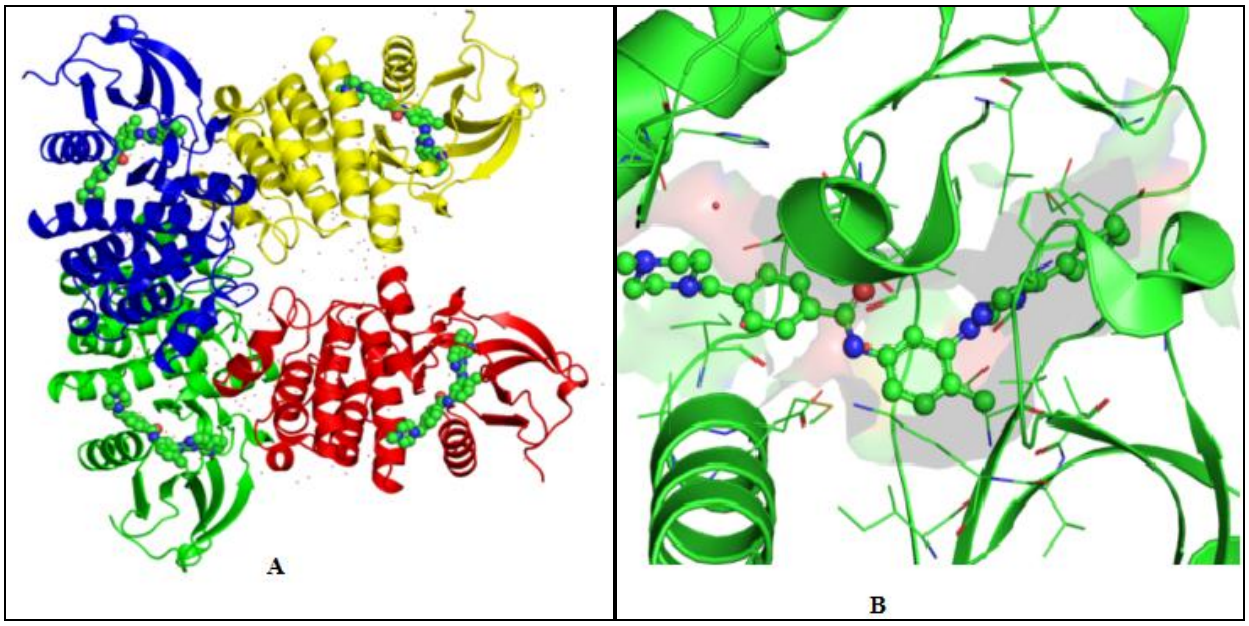


FIG. 3: (A) PICTURE OF 2HYY PDB WITH 4 CHAINS (A, B, C AND D) COMPLEXED WITH STI-571 (IMATINIB). (B) BINDING SITE OF 2HYY PDB CHAIN A WITH STI-571 (IMATINIB), SELECTED FOR DOCKING. Pictures have been taken from server (http://www.ebi.ac.uk/pdbe-srv/view/entry/2hyy/summary.html)

The lazar toxicity of all these designed drugs have been performed using in silico internet based lazar toxicity prediction tool [16]. OSIRIS property Explorer is also used to predict toxicity and other drug like properties [17]. The metabolic sites of these designed drugs have been predicted using MetaPrint2D [18] as shown in **(Fig. 11)** Molecular Property has been predicted using Mol Soft [19]. ADME and toxicity was predicted using admetexp server [20].

RESULTS AND DISCUSSION:

1. **Ligands with substitution of –OH, -NH_2 and –Cl group at position –R:**

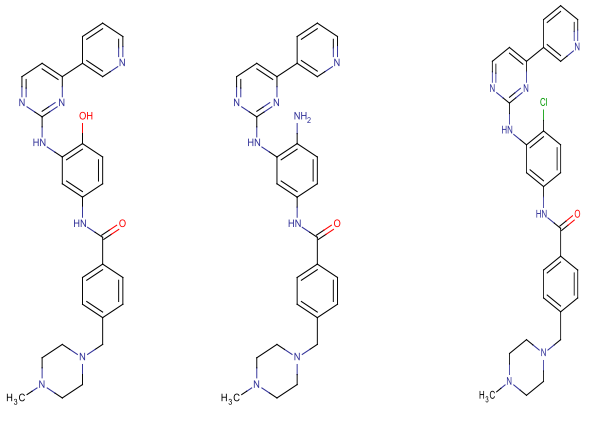


FIG. 4: REPRESENTS THE SUBSTITUTION ON IMATINIB AT POSITION –R.

When methyl group of Imatinib at position –R was substituted with –OH, -NH_2 and –Cl group then our results showed that substituted ligands are having better pharmacological property as compared to Imatinib. But the ligand which is substituted with hydroxyl group (IA-1) is showing best result as compared with amine and chloride substituted ligands (IA-2 and IA-3) as shown in the **Table (1, 2, 3, 4 and 5).** Thus further substitution was carried out at position -R_1, -R_2, -R_3, –R_4 and –R_5 after keeping hydroxyl group substitution static at position –R.

2. **Ligands with substitution of –OH, -NH_2 and –Cl group at position –R_1:**

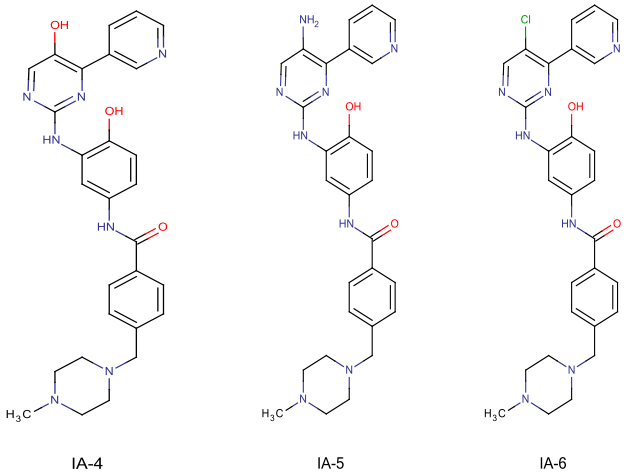


FIG. 5: REPRESENTS THE SUBSTITUTION ON IMATINIB AT POSITION –R_1.

When the substitution of –OH, -NH_2 and –Cl group was done at position -R_1 after keeping hydroxyl group substitution static at position –R , then our results showed that substituted ligands are having more better property as compared to hydroxyl group substituted ligand at position –R. But the ligand which is substituted with hydroxyl group (IA-4) is showing better result as compared to amine and chloride substituted ligands (IA-5 and IA-6) as shown in the Table (1, 2, 3, 4 and 5). Thus further substitution was carried out at position -R_2, -R_3, –R_4 and –R_5 after keeping hydroxyl group substitution static at position –R.

3. Ligands with substitution of –OH, -NH_2 and –Cl group at position –R_2:

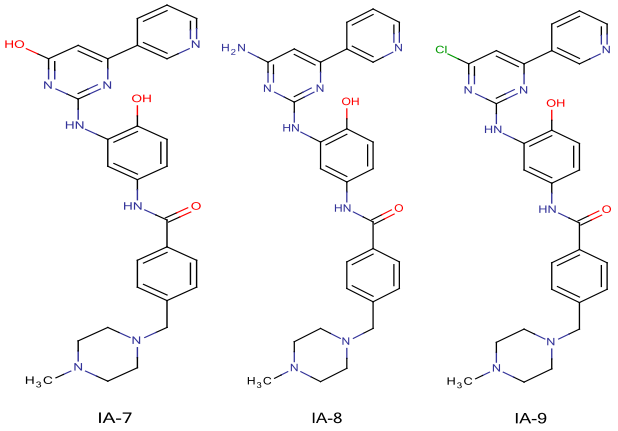


FIG. 6 REPRESENTS THE SUBSTITUTION ON IMATINIB AT POSITION –R_2.

When the substitution of –OH, -NH_2 and –Cl group was done at –R_2 position after keeping hydroxyl group substitution static at position –R then our results showed that substituted ligands are having better property as compared to our prototype (Imatinib) as shown in Table 1, 2, 3, 4 and 5. But according to docking studies designed ligand which is substituted with hydroxyl and amine group (IA-7 and IA-8) is showing approximately similar docking result as shown in Table 1. But both hydroxyl and amine substituted ligands has shown better result as compared to chloride substituted ligand (IA-9). On further examining the drug likeness property as calculated my molsoft server as shown in Table 2, amine substituted ligand (IA-8) was found to possess more druglikeness score as compared to hydroxyl group substituted ligand (IA-7). Thus further substitution was carried out at position -R_3, –R_4 and –R_5 after keeping hydroxyl and amine group substitution static at position –R and–R_2 respectively.

4. Ligands with substitution of –OH, -NH_2 and –Cl group at position –R_3:

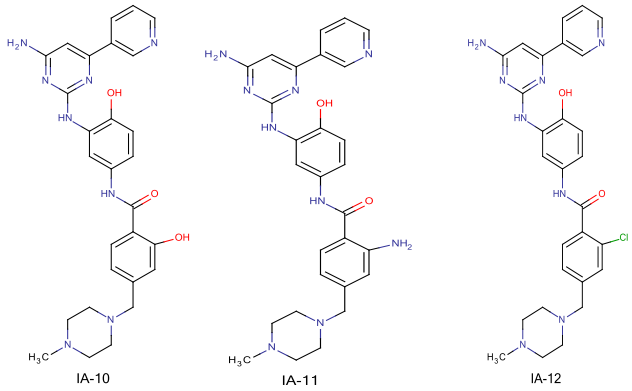


FIG. 7: REPRESENTS THE SUBSTITUTION ON IMATINIB AT POSITION –R_3

When the substitution of –OH, -NH_2 and –Cl group was done at –R_3 after keeping hydroxyl and amine group substitution static at position –R and –R_2 respectively, then our results showed that substituted ligands are having better property as compared to -R, -R_1 and -R_2 substituted ligand. But the ligand which is substituted with amine group (IA-11) is showing better result as compared to hydroxyl and chloride substituted ligands (IA-11 and IA-12) as shown in the **Table (1, 2, 3, 4 and 5).** Thus further substitution was carried out at position –R_4 and –R_5 after keeping hydroxyl and amine group substitution static at position –R and–R_2 respectively.

5. Ligands with substitution of –OH, -NH_2 and –Cl group at position –R_4:

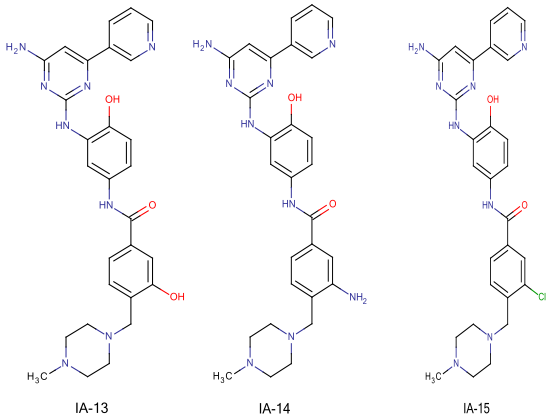


FIG. 8: REPRESENTS THE SUBSTITUTION ON IMATINIB AT POSITION –R_4

When the substitution of –OH, -NH_2 and –Cl group was done at –R_4 after keeping hydroxyl and amine group substitution static at position –R and –R_2 respectively, then our results showed that substituted ligands at position –R_4 are having better property as compared to -R, -R_1, -R_2 and –R_3 substituted ligands. But out of all designed ligands, chloride substituted ligand (IA-15) at position–R_4 has given the best result as shown in Table (1, 2, 3, 4 and 5). Thus further substitution was carried out at position –R_5 after keeping hydroxyl and amine group substitution static at position –R and–R_2 respectively to get more active and potent molecule.

6. Ligands with substitution of –OH, -NH_2 and –Cl group at position –R_5:

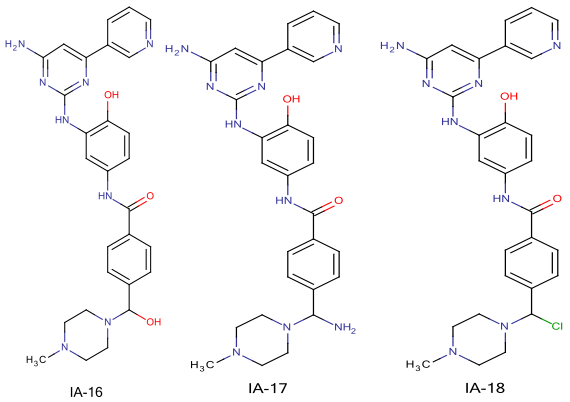


FIG. 9: REPRESENTS THE SUBSTITUTION ON IMATINIB AT POSITION –R_5.

When the substitution of –OH, -NH_2 and –Cl group was done at position –R_5 after keeping hydroxyl and amine group substitution static at position –R and –R_2 respectively, then our results showed that ligands substituted at position –R_5 are having more better property as compared to -R, -R_1, -R_2, -R_3 and –R_4 substituted ligands. But out of all designed ligands, hydroxyl substituted ligand (IA-16) has given the best result as compared to different substitutated ligands at position –R, -R_1, -R_2, -R_3, –R_4 and –R_5 with different functional group.

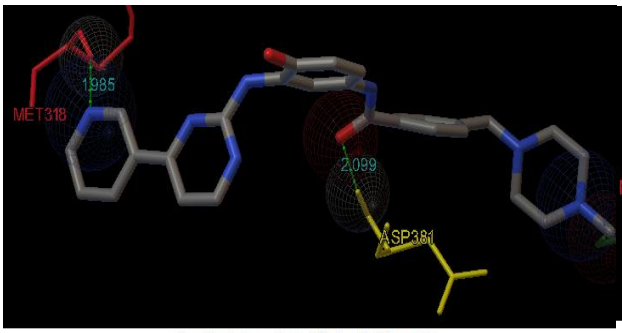
Docking Analysis: The molecular docking study of the designed ligands with Human Abl kinase domain in complex with Imatinib (PDB ID 2HYY) shows that all the ligands substituted with –OH, -NH_2 and –Cl group at position -R, -R_1, -R_2, -R_3, –R_4 and –R_5 are showing better docking score than that of prototype Imatinib. Thus results predict that the designed ligands have the better binding affinity with BCR-Abl tyrosine kinase than Imatinib **(Table 1).**

This prediction leads us to believe that the designed ligands will possibly help us to overcome resistance with Imatinib and get more potent therapeutic agent for the treatment of Philadelphia chromosome-positive (Ph^+) chronic myelogenous leukemia (CML)

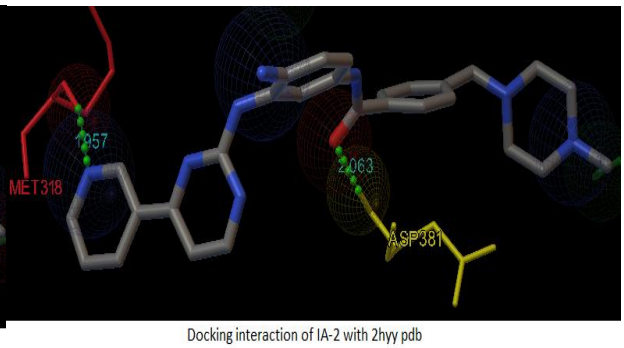
TABLE 1: DOCKING RESULT OF THE DESIGNED LIGANDS AND IMATINIB WITH 2HYY PDB.

Sl. No.	Name of the Ligand	Binding energy (K. Cal/Mol)	Ligand efficiency	Inhibition constant (298.15 K) Ki	H-Bond interactions	Bond length (A°)
1	IA-1	-15.6	-0.41	7.76 pM	MET318:HN ASP381:HN	1.985 1.985
2	IA-2	-15.12	-0.41	8.23pM	MET318:HN ASP381:HN	1.957 2.053
3	IA-3	-11.98	-0.32	1.66nM	-	-
4	IA-4	-15.21	-0.40	7.1 pM	MET318:HN ASP381:HN	1.703 2.169
5	IA-5	-11.5	-0.30	3.7nM	ASP381:HN	2.109
6	IA-6	-13.5	-0.35	240.44pM	-	-
7	IA-7	-11.89	-0.31	1.93nM	ASP381:HN	1.979
8	IA-8	-11.81	-0.31	2.19nM	ASP381:HN	2.132
9	IA-9	-11.0	-0.29	8.68nM	GLU286:OE2	2.935
10	IA-10	-15.2	-0.39	7.25pM	MET318:HN	2.098
11	IA-11	-15.89	-0.41	2.24pM	MET318:HN ASP381:HN	1.95 1.97
12	IA-12	-15.46	-0.4	4.63pM	MET318:HN ASP381:HN	2.014 2.0
13	IA-13	-15.62	-0.4	3.57pM	MET318:HN ASP381:HN	2.312 1.924
14	IA-14	-15.31	-0.39	5.95pM	MET318:HN	2.114

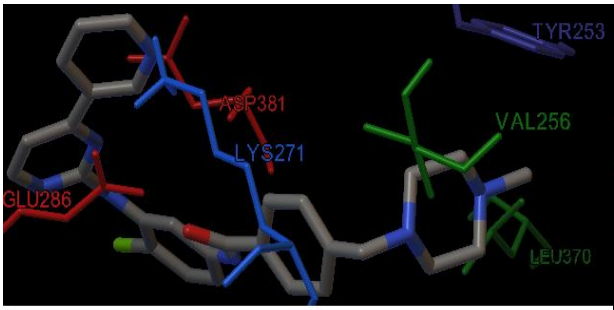
15	IA-15	-15.8	-0.41	2.62pM	ASP381:HN MET318:HN	1.906 2.137
16	IA-16	-16.25	-0.42	1.22pM	ASP381:HN MET318:HN	1.947 2.112
17	IA-17	-15.9	-0.41	2.2pM	ASP381:HN MET318:HN	1.939 2.033
18	IA-18	-15.74	-0.4	2.89pM	ASP381:HN MET318:HN	2.193 2.124
19	Imatinib	-11.85	-0.32	2.06nM	ASP381:HN -	2.19 -



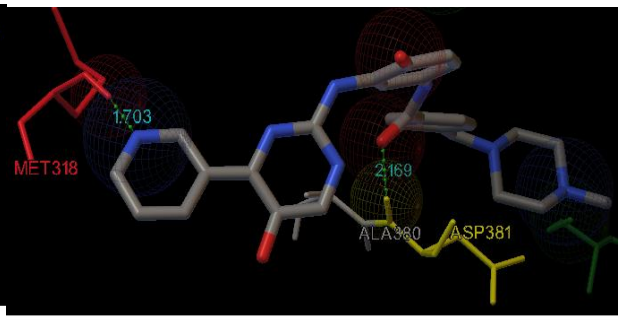
Docking interaction of IA-1 with 2hyy pdb



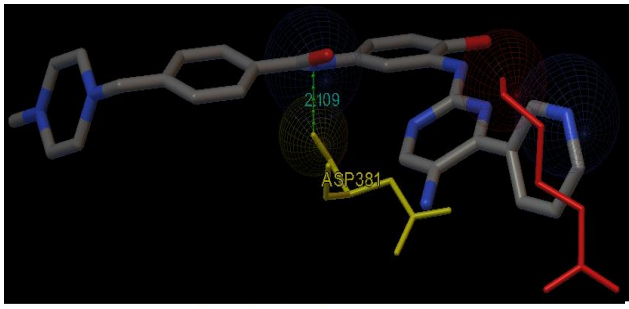
Docking interaction of IA-2 with 2hyy pdb



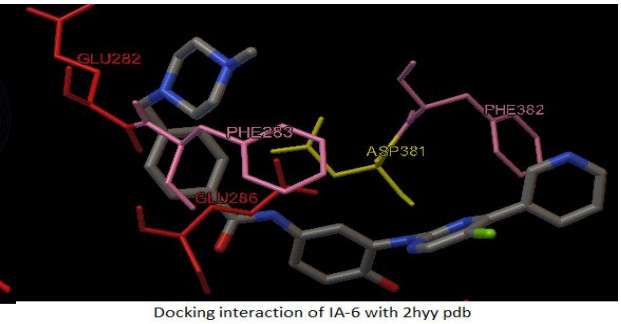
Docking interaction of IA-3 with 2hyy pdb



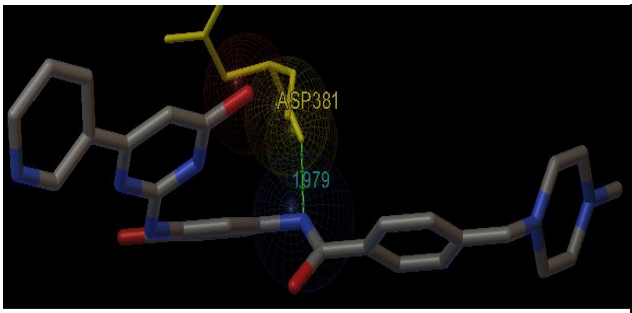
Docking interaction of IA-4 with 2hyy pdb



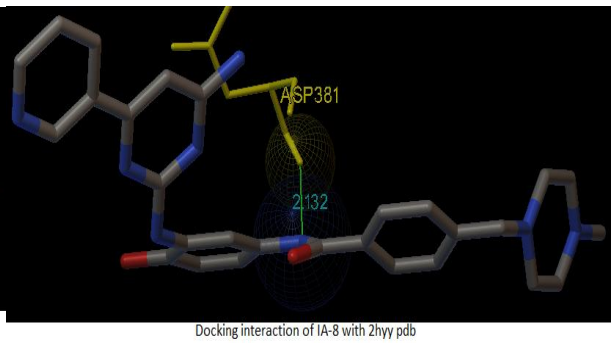
Docking interaction of IA-5 with 2hyy pdb



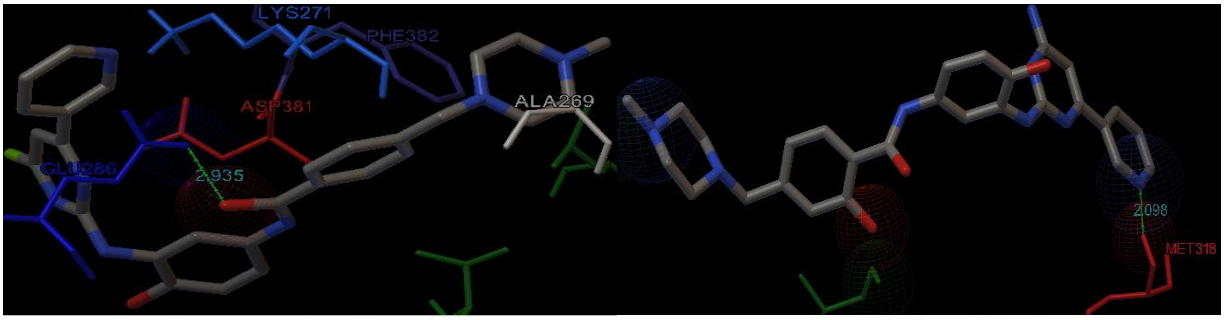
Docking interaction of IA-6 with 2hyy pdb



Docking interaction of IA-7 with 2hyy pdb

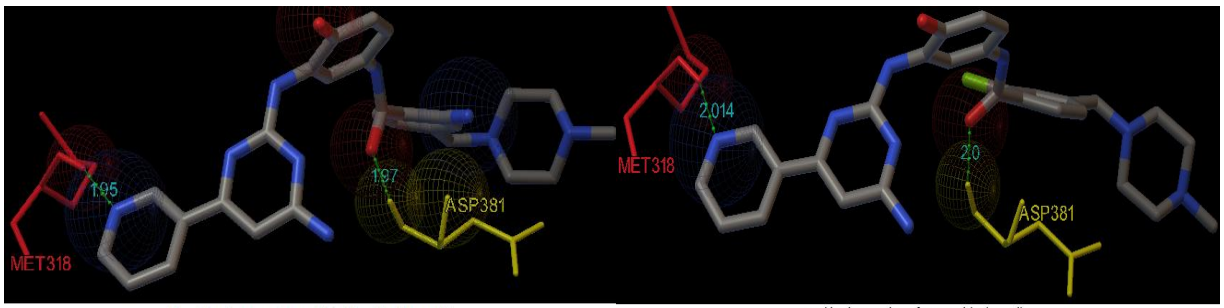


Docking interaction of IA-8 with 2hyy pdb



Docking interaction of IA-9 with 2hyy pdb

Docking interaction of IA-10 with 2hyy pdb

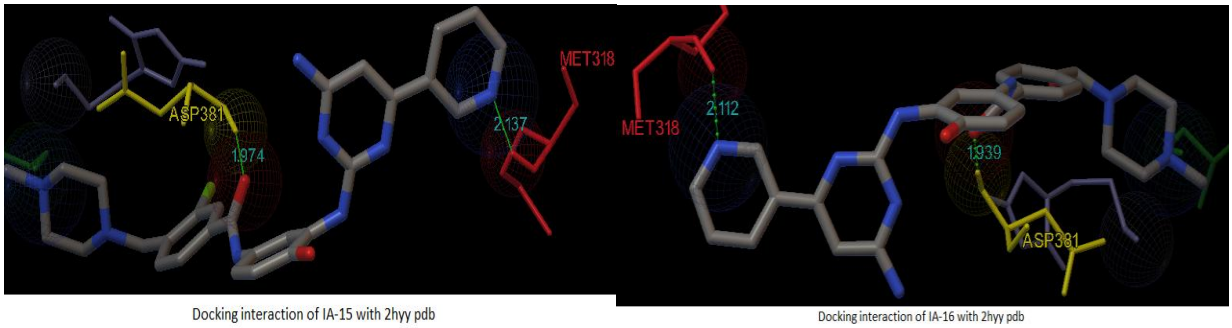


Docking interaction of IA-11 with 2hyy pdb

Docking interaction of IA-12 with 2hyy pdb

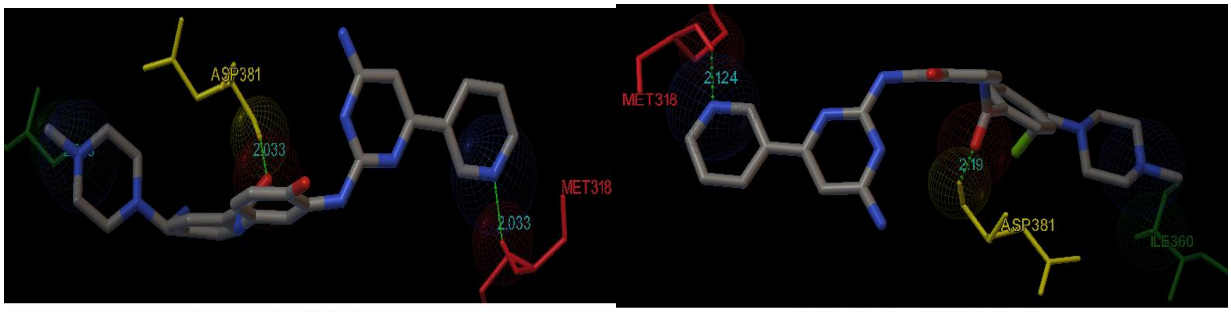
Docking interaction of IA-13 with 2hyy pdb

Docking interaction of IA-14 with 2hyy pdb



Docking interaction of IA-15 with 2hyy pdb

Docking interaction of IA-16 with 2hyy pdb



Docking interaction of IA-17 with 2hyy pdb

Docking interaction of IA-18 with 2hyy pdb

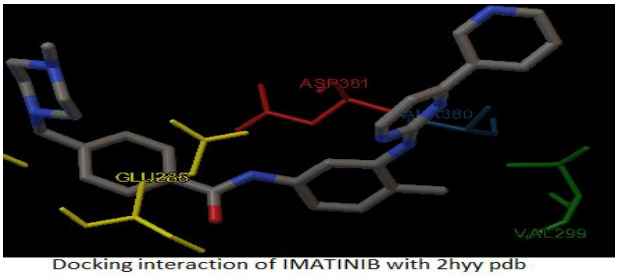


FIG. 10: BINDING SITE OF ALL DESIGNED LIGANDS (IA-1 TO IA-18) RESPECTIVELY AND PROTOTYPE (IMATINIB) WITH 2HYY PDB

TABLE 2: DRUG LIKENESS PROPERTIES OF DESIGNED LIGAND MOLECULE AND PROTOTYPE IMATINIB

Sl.no:	Name of the Ligand	Drug Likeness Model Score	Molecular weight	Acceptor HB	Donor HB
1	IA-1	2.32	495.24	7	3
2	IA-2	1.99	494.25	6	4
3	IA-3	1.99	494.25	6	4
4	IA-4	2.47	511.23	8	4
5	IA-5	2.59	510.25	7	5
6	IA-6	2.48	529.20	7	3
7	IA-7	2.28	511.23	8	4
8	IA-8	2.38	510.25	7	5
9	IA-9	2.19	529.20	7	3
10	IA-10	2.63	526.24	8	6
11	IA-11	2.60	525.26	7	7
12	IA-12	2.61	544.21	7	5
13	IA-13	2.32	526.24	8	6
14	IA-14	2.30	525.26	7	7
15	IA-15	2.32	544.21	7	5
16	IA-16	2.50	526.24	8	6
17	IA-17	2.31	525.26	8	7
18	IA-18	2.30	544.21	7	5
19	Imatinib	1.73	493.26	6	2

Permissible ranges: Mol wt.: (130–725); Donor hb: (0.0–6.0); Accept hb: (2.0–20.0)

TABLE 3: OSIRIS PROPERTY EXPLORER SCORE

SI. No.	Name of the Ligand	cLogP	Solubility	Drug score	Comments
1	IA-1	3.73	-3.74	0.36	Non mutagenic
2	IA-2	3.31	4.12	0.12	Mutagenic
3	IA-3	4.64	-4.78	0.27	Non mutagenic
4	IA-4	3.43	-3.45	0.37	Mutagenic
5	IA-5	3.01	-3.82	0.37	Mutagenic
6	IA-6	4.35	-4.48	0.29	Mutagenic
7	IA-7	3.91	-3.97	0.33	Non mutagenic
8	IA-8	3.49	-4.34	0.33	Non mutagenic
9	IA-9	4.43	-4.24	0.17	Mutagenic
10	IA-10	3.19	-4.05	0.34	Mutagenic
11	IA-11	2.77	-4.42	0.21	Slight mutagenic
12	IA-12	4.1	-5.08	0.26	Mutagenic
13	IA-13	3.19	-4.05	0.34	Mutagenic
14	IA-14	2.77	-4.42	0.21	Slight mutagenic
15	IA-15	4.1	-5.08	0.26	Mutagenic
16	IA-16	2.99	-4.03	0.35	Mutagenic
17	IA-17	2.46	-4.1	0.35	Mutagenic
18	IA-18	4.43	-4.78	0.25	Mutagenic
19	Imatinib	4.35	-4.38	0.19	Mutagenic

TABLE 4: ADMETSAR PREDICTION

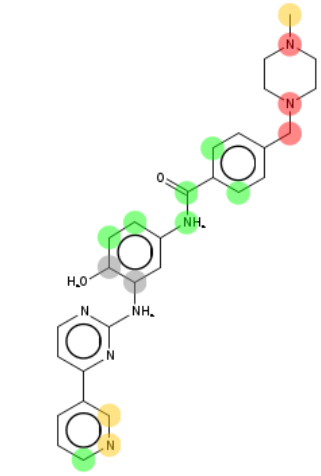
SI. No.	Name of the Ligand	Blood Brain Barrier	Human Intestinal Absorption	$CaCo_2$ permeability	AMES Test	Carcinogens	Rat-Acute Toxicity (LD50. mol/kg)
1	IA-1	0.8187	0.9876	0.5558	Non Ames toxic	Non Carcinogen	2.7593
2	IA-2	0.7454	0.9785	0.5478	Non Ames toxic	Non Carcinogen	2.7005
3	IA-3	0.7519	0.9912	0.5609	Non Ames toxic	Non Carcinogen	2.6777
4	IA-4	0.9027	0.9886	0.5591	Non Ames toxic	Non Carcinogen	2.6759
5	IA-5	0.7711	0.9892	0.5686	Non Ames toxic	Non Carcinogen	2.7686
6	IA-6	0.8496	0.9897	0.5729	Non Ames toxic	Non Carcinogen	2.7479
7	IA-7	0.9239	0.9860	0.5601	Non Ames toxic	Non Carcinogen	2.6388
8	IA-8	0.6220	0.9957	0.5795	Non Ames toxic	Non Carcinogen	2.7321
9	IA-9	0.8496	0.9897	0.5729	Non Ames toxic	Non Carcinogen	2.7479
10	IA-10	0.7989	0.9927	0.6106	Non Ames toxic	Non Carcinogen	2.7231
11	IA-11	0.6914	0.9904	0.6155	Non Ames toxic	Non Carcinogen	2.7839
12	IA-12	0.6610	0.9965	0.5997	Non Ames toxic	Non Carcinogen	2.7374
13	IA-13	0.8307	0.9970	0.5855	Non Ames toxic	Non Carcinogen	2.6395
14	IA-14	0.6741	0.9974	0.5762	Non Ames toxic	Non Carcinogen	2.7379
15	IA-15	0.6610	0.9965	0.5997	Non Ames toxic	Non Carcinogen	2.7374
16	IA-16	0.8106	1.0000	0.5734	Non Ames toxic	Non Carcinogen	2.7423
17	IA-17	0.6921	0.9973	0.5628	Non Ames toxic	Non Carcinogen	2.7963
18	IA-18	0.6109	1.0000	0.5553	Non Ames toxic	Non Carcinogen	2.7716
19	Imatinib	0.7624	0.9865	0.5076	Non Ames toxic	Non Carcinogen	2.6013

TABLE 5: LAZAR TOXICITY PREDICTION

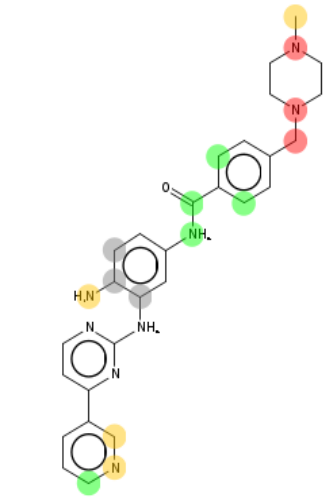
SI.no	Name of the Ligand	DSSTox Carcinogenic Potency DBS MultiCellCall	DSSTox Carcinogenic Potency DBS Rat	DSSTox Carcinogenic Potency DBS Mouse	DSSTox Carcinogenic Potency DBS Mutagenicity
1	IA-1	Non-carcinogen	Non-carcinogen	Non-carcinogen	Mutagenic
2	IA-2	Non-carcinogen	Non-carcinogen	Non-carcinogen	Mutagenic
3	IA-3	Non-carcinogen	Non-carcinogen	Non-carcinogen	Mutagenic
4	IA-4	Non-carcinogen	Non-carcinogen	Non-carcinogen	Mutagenic
5	IA-5	Non-carcinogen	Non-carcinogen	Non-carcinogen	Mutagenic
6	IA-6	Non-carcinogen	Non-carcinogen	Non-carcinogen	Mutagenic
7	IA-7	Non-carcinogen	Non-carcinogen	Non-carcinogen	Mutagenic
8	IA-8	Non-carcinogen	Non-carcinogen	Non-carcinogen	Mutagenic
9	IA-9	Non-carcinogen	Non-carcinogen	Non-carcinogen	Mutagenic
10	IA-10	Non-carcinogen	Non-carcinogen	Non-carcinogen	Non mutagenic
11	IA-11	Non-carcinogen	Non-carcinogen	Non-carcinogen	Mutagenic
12	IA-12	Non-carcinogen	Non-carcinogen	Carcinogen	Mutagenic
13	IA-13	Non-carcinogen	Non-carcinogen	Non-carcinogen	Non mutagenic
14	IA-14	Non-carcinogen	Non-carcinogen	Carcinogen	Mutagenic
15	IA-15	Non-carcinogen	Non-carcinogen	Carcinogen	Mutagenic
16	IA-16	Non-carcinogen	Non-carcinogen	Non-carcinogen	Mutagenic
17	IA-17	Non-carcinogen	Non-carcinogen	Non-carcinogen	Mutagenic
18	IA-18	Non-carcinogen	Non-carcinogen	Non-carcinogen	Mutagenic
19	Imatinib	Non-carcinogen	Non-carcinogen	Non-carcinogen	Mutagenic

Phase I Metabolic site prediction of Imatinib and its analogues: MetaPrint2D server is used to predict Phase I Metabolic site of prototype and its derivatives. By setting the strictness of the fingerprint matching in "DEFAULT" and selecting model "ALL (Metabolite 2010.2)": As shown in **(Fig. 11)**

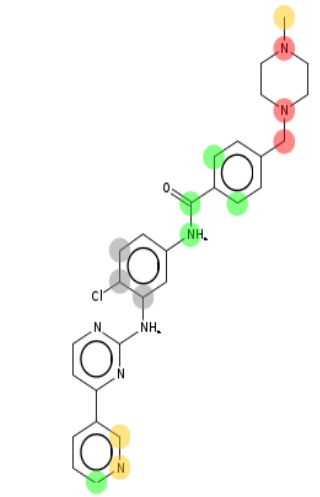
Results Color Scheme:
Red 0.66 <= NOR <= 1.00
Orange 0.33 <= NOR < 0.66
Green 0.15 <= NOR < 0.33
White 0.00 <= NOR < 0.15
Grey Little/no data



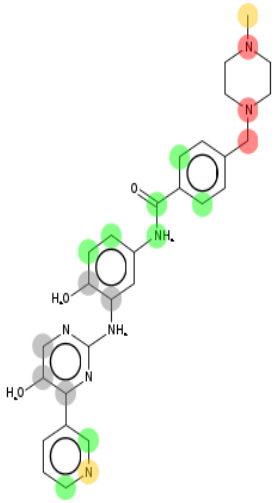
Phase 1 metabolic site of IA-1.



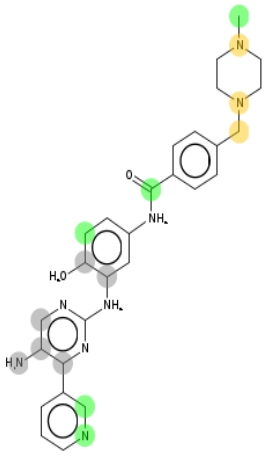
Phase 1 metabolic site of IA-2



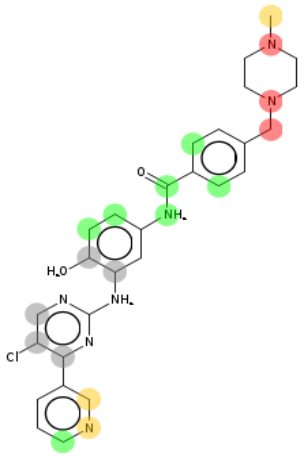
Phase 1 metabolic site of IA-3



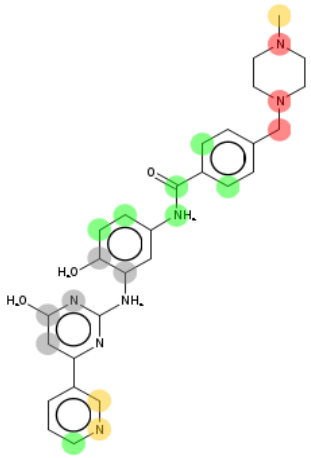
Phase 1 metabolic site of IA-4



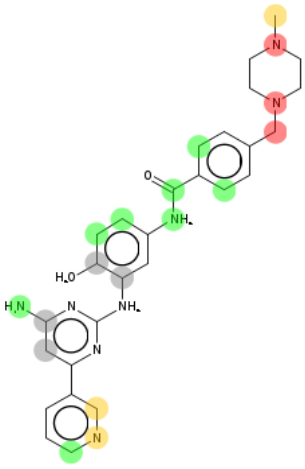
Phase 1 metabolic site of IA-5



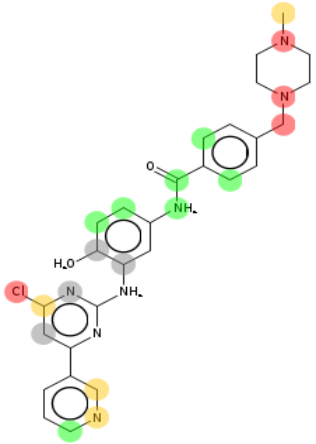
Phase 1 metabolic site of IA-6



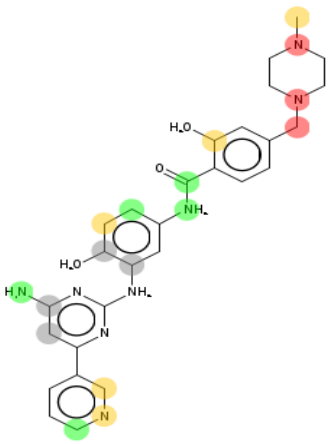
Phase 1 metabolic site of IA-7



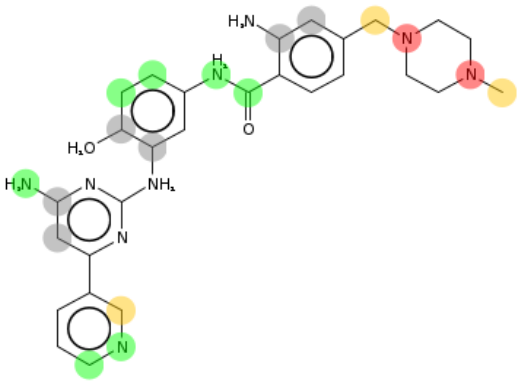
Phase 1 metabolic site of IA-8



Phase 1 metabolic site of IA-9



Phase 1 metabolic site of IA-10



Phase 1 metabolic site of IA-11

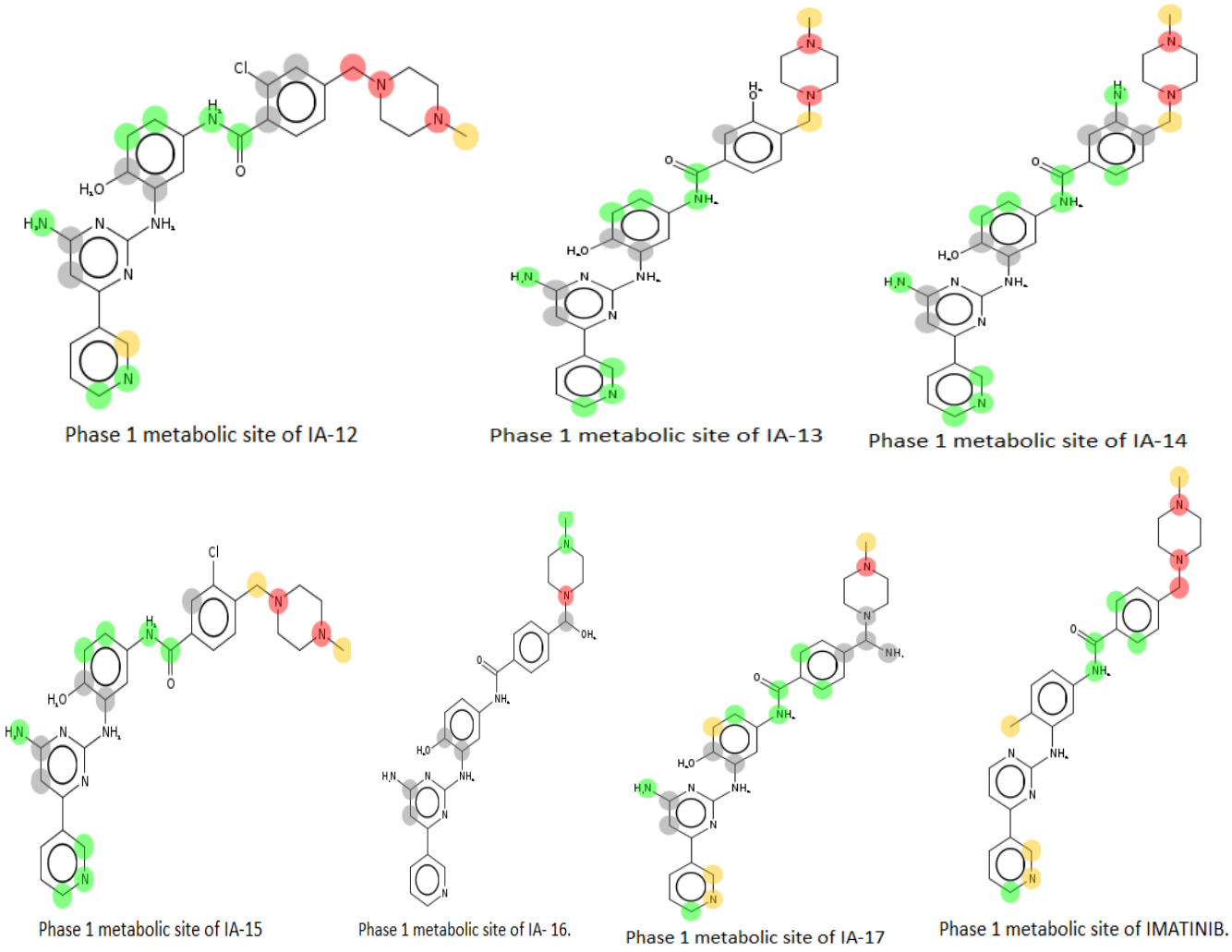


FIG. 11: PHASE 1 METABOLIC SITE PREDICTION OF ALL DESIGNED LIGANDS (IA-1 TO IA-18) RESPECTIVELY AND PROTOTYPE (IMATINIB)

CONCLUSION: Imatinib has been successful drug as a frontline therapy for Philadelphia chromosome-positive (Ph^+) chronic myelogenous leukemia (CML). Our approach was to design the molecules which is similar to that of Imatinib and which binds with more competence to the binding site of similar to Imatinib.

So in this study we found that substitution of hydroxyl group, amine group, and chloride group at -R, $-R_1$, $-R_2$, $-R_3$, $–R_4$ and $–R_5$ position in Imatinib skeleton lead to increase its pharmacological and druglikeness activities. But substitution of hydroxyl group at position –R, $-R_1$ and $–R_5$, amine group at position $–R_2$ and $–R_3$ and chloride group at position $–R_4$ was found to increase its drug binding affinity and pharmacological activities.

Thus, designed ligand with hydroxyl group substitution at position –R and $–R_5$ and amine group substitution at position $–R_2$ (IA-16) was found to be most potent substituted ligand as substitution at position $–R_5$ has increased the binding energy as calculated by autodock 4. But when similar substitution was done at position $–R''$, $-R''_1$, $-R''_2$, $-R''_3$, $-R''_4$ and $–R''_5$ of Imatinib with hydroxyl group, amine group, halide group, alkenes and halo alkenes group decrease in drug likeness property and pharmacological activity was found.

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REFERENCES:

1. Kantarjian, H.M., Giles, F., Gattermann, N., Bhalla, K., Alimena, G., Palandri, F., et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome–positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. Blood. 2007; 110: 3540-6.
2. Druker, B.J., Tamura, S., Buchdunger, E., Ohno, S., Segal, G.M., Fanning, S., et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nature medicine. 1996; 2: 561-6.
3. Stanglmaier, M., Warmuth, M., Kleinlein, I., Reis, S., Hallek, M. The interaction of the Bcr-Abl tyrosine kinase with the Src kinase Hck is mediated by multiple binding domains. Leukemia. 2003; 17: 283-9.
4. Lugo, T.G., Pendergast, A.-M., Muller, A.J., Witte, O.N. Tyrosine kinase activity and transformation potency of bcr-abl oncogene products. Science. 1990; 247: 1079-82.
5. Druker, B.J., Sawyers, C.L., Kantarjian, H., Resta, D.J., Reese, S.F., Ford, J.M., et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. New England Journal of Medicine. 2001; 344: 1038-42.
6. Deininger, M.W., Vieira, S., Mendiola, R., Schultheis, B., Goldman, J.M., Melo, J.V. BCR-ABL tyrosine kinase activity regulates the expression of multiple genes implicated in the pathogenesis of chronic myeloid leukemia. Cancer research. 2000; 60: 2049-55.
7. Sattler, M., Verma, S., Shrikhande, G., Byrne, C.H., Pride, Y.B., Winkler, T., et al. The BCR/ABL tyrosine kinase induces production of reactive oxygen species in hematopoietic cells. Journal of Biological Chemistry. 2000; 275: 24273-8.
8. Anderson, S.M., Mladenovic, J. The BCR-ABL oncogene requires both kinase activity and src-homology 2 domain to induce cytokine secretion. Blood. 1996; 87: 238-44.
9. Weisberg, E., Manley, P.W., Cowan-Jacob, S.W., Hochhaus, A., Griffin, J.D. Second generation inhibitors of BCR-ABL for the treatment of imatinib-resistant chronic myeloid leukaemia. Nature Reviews Cancer. 2007; 7: 345-56.
10. Patel, D., Suthar, M.P., Patel, V., Singh, R. BCR ABL kinase inhibitors for cancer therapy. Int J Pharm Sci Drug Res. 2010; 2: 80-90.
11. Nagar, B. c-Abl tyrosine kinase and inhibition by the cancer drug imatinib (Gleevec/STI-571). The Journal of nutrition. 2007; 137: 1518S-23S.
12. Cowan-Jacob, S.W., Fendrich, G., Floersheimer, A., Furet, P., Liebetanz, J., Rummel, G., et al. Structural biology contributions to the discovery of drugs to treat chronic myelogenous leukaemia. Acta Crystallographica Section D: Biological Crystallography. 2006; 63: 80-93.
13. Zhong, H., Tran, L.M., Stang, J.L. Induced-fit docking studies of the active and inactive states of protein tyrosine kinases. Journal of Molecular Graphics and Modelling. 2009; 28: 336-46.
14. Lü, S., Luo, Q., Hao, X., Li, X., Ji, L., Zheng, W., et al. Synthesis and docking study of 2-phenylaminopyrimidine Abl tyrosine kinase inhibitors. Bioorganic & medicinal chemistry letters. 2011; 21: 6964-8.
15. Sanner, M.F. Python: a programming language for software integration and development. J Mol Graph Model. 1999; 17: 57-61.
16. http://lazar.in-silico.de/predict.
17. http://www.cheminformatics.ch/propertyExplorer/.
18. http://www-metaprint2d.ch.cam.ac.uk/.
19. http://www.molsoft.com/mprop/.
20. http://www.admetexp.org/.

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