COMPUTER AIDED IDENTIFICATION OF BIPYRAZOLE AND TETRAZOLE DERIVATIVES AS POSSIBLE BTK INHIBITORS

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Bruton'sTyrosine Kinase(BTK)has been regarded as target for the treatment of Rheumatoid Arthritis (RA), multiplesclerosis and B-cell malignancies.Among different Tec family of kinases,BTK is the one associated with pathogenesis in humans. Several BTK inhibitors were evolved consisting of reversible and covalent irreversible ones. Despite the discovery of several inhibitors to treat RA, research is continually growing to develop diverse pharmacophoric groups as BTK inhibitors. Hence, in this paper we report computer-aided virtual screening analysis on diverse pharmacophoric groups of ligands such as bipyrazole systems, pyrazole, arylpyrazoline derivatives, indoles, pyrazolopyridine, indazoles, imidazo[4,5-c]pyridines, tetrazoles, oxadiazoles and benzimidazole derivatives etc to evaluate the efficacy of binding affinity towards BTK. Our analysis suggested that the presence of freely flexible torsions with increase in molecular weight would favour Btkinhibition.Itis thereforeproposed that tetrazole derivatives and bipyrazole ring systems enhanced BTK inhibition and hence these analogs should be widely explored.

Keywords: Docking;Bruton'sTyrosine Kinase; binding affinity; Rheumatoid Arthritis.
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1.Introduction

Bruton'sTyrosine Kinase (BTK) is known to assume significant part in the progression, seperation and reproduction of B-lineage cells.[1] BTK has been an alluring objective for the treatment of Rheumatoid Arthritis (RA), multiplesclerosis and B-cell malignancies.[2]BTK has a place with Tec own circle of relatives of kinases that arethe second onegreatestown circle of relatives of cytoplasmic tyrosine kinases in mammalian cells[3]and BTK is the most effective member of this own circle of relativesthat isrelated to pathogenesis in humans.Deficiency in BTK gene results in a condition called X-linked agammaglobulinemia.[4] Loss of function mutations in the BTK gene prevent the

development of B cells. BTK is expressed in B-cells,[5] mast cells, monocytes/macrophages,[6]neutrophils,[7] dendriticcells, erythroid cells,[8] hematopoietic stemcells and multipotent progenitors.[9]Btk has conjointly been coupled to persistent BCR activation in activated B-cell-like diffuse giantB cellcancer (ABC-DLBCL).10[10]

Despite the discovery of several inhibitors to treat RA, there has been a pressing need to develop novel compounds with alternate mechanism of action for patients who are unresponsive to treatment regimes. Further, a drug with oral bioavailability would be more advantage option for therapy. Furthermore, orally bioavailable drugs would be desirable factor in the therapy involving RAbased on the fact that such drugs are convenient and has the ability to clear rapidly from the body.[11] The successful oral drug tofacitnib has demonstrated biological efficacy for RA.[12,13]

The principle data onBtk was accessible in 1990s, and from that point several Btk inhibitors have been developed.[14]These inhibitors would fall in two significant classes, reversible and covalent irreversible ones.Irreversible Btk inhibitors have specialcapabilitiesassociated with in advance reversible ones, alongside a extended drug–goalhouse time and the decoupling of pharmacokinetic and pharmacodynamic properties.[15]Btk inhibitorswere exceptionally fruitful in creature models of RA, lupus, and lymphoma.[16] In cellular mechanism,Btk is first activated through a method of its upstream kinases through phosphorylation of a key tyrosine residue (Tyr551), which will expand the reactantinterest of Btkby means of method for 10-fold.[17] Following autophosphorylation of some other tyrosine residue (Tyr223), Btktransforms intoabsolutely initiated and phosphorylates its substrates, consisting of PLC-γ2 withinside the BCR pathway.[18]Several gatherings revealed small molecule BTK selective inhibitors for malignant growth treatments as well as therapy of RA,[19] with ibrutinib as of nowendorsed for mantle cell lymphoma and chronic lymphocytic leukemia.[20]

Despite several compounds tested experimentally as Btk inhibitors such as phenylpyridin-2(1H)-one,[21]thieno[3,2-c]pyridin-4-amines,[22]Imidazo[1,5-a]quinoxaline,[23]Purine derivatives,[24]CarbazoleCarboxamides,[25]Pyridazinone Analogs,[26]1,3-Diaminopyrimidine,[27]imidazo[1,5‑a]pyrazine,[28]Diaminopyrimidine,[29]Pyrrolo[2,3-d]pyrimidine,[30]Pyrrolo[2,3-b]pyridine,[31] there is a need to develop analogs with diverse pharmacophoric groups. Hence, in this study, we performed virtual screening analysis on diverse pharmacophores such as bipyrazole derivatives, pyrazole, arylpyrazoline derivatives, indoles, pyrazolopyridine, indazoles, imidazo[4,5-c]pyridines, tetrazoles, oxadiazoles and benzimidazole derivatives respectively.

2. Materials and Methods

A set of 285 compounds reported in literature were used as a complete dataset to assess Btk inhibitory properties. Software AutoDockwas utilized to perform docking analysis.

2.1 *Dataset-1*

About 30 bipyrazoles[32]were selected as inhibitors against Btk knowing the fact that these compounds have been synthesized and reported in literature with no tested inhibitor activity against a biological target.

2. 2 *Dataset-2*

Nearly115compounds with dihydropyrazole sulphonamide moiety,[33] 1,3,5-triarylpyrazoline and 1,5-diarylpyrazole[] triarylpyrazoline[34] and pyrazolinederivatives[35] which were known to inhibit COX-2 activity are selected as dataset against Btk inhibition.

2.3 *Dataset-3*

A set of nearly 140 structures were considered from published sources, however, these compounds are known to exhibit inhibitory

properties against hypertension as reported in literature but no such data was found on Btk inhibition. A series of indole derivatives,[36]pyrazolopyridine, indazolemoieties of compounds[37] as well as imidazo[4,5-c]pyridin-4-onederivatives,[38]5-(Biphenyl-2-yl)-1H-tetrazole derivatives,[39]
oxadiazole compounds [40], 5-sulfamoyl benzimidazole derivatives,[41] carbamoylbenzimidazoles[42] were selected to study the affinity of interactions of these ligands with Btk receptor.

2.4 ***Btk receptor***

The 3 dimensional coordinates of X-ray crystal structure of Btkkinase domain complexed with 6-cyclopropyl-2-2[3-[5-[[5-(4-ethylpiperazin-1-yl)-2-pyridyl]amino]-1-methyl-6-oxo-3-3pyridyl]-2(hydroxymethyl)phenyl]-8-fluoro-isoquinolin-1-one inhibitor (PDB code: 4OTR) was selected as receptor in the study. Before performing docking on inhibitor datasets, the procedureemployed for docking was validated by docking 4OTR bound ligand with default parameters of AutoDock software.

2.5 ***Docking***

Docking analysis or virtual screening routines areperformed to dock various conformational states of ligands to a receptor followed by assessment of the molecules geometrical positioning and complementarity in terms of shape and properties, such as electrostatics.[43] Protein-Ligand docking results in interactions between protein amino acid residues and ligand atoms in terms of non-bonded, non-covalent interactions to form an intermolecular complex.[44] The outcome of such analysis results in affinity prediction (scoring), reported as kcal/mol.[45]

2.6 ***AutoDock Software***

Docking program AutoDock Tools (ADT) version 1.5.6[46]was used to produce grids, work out dock score and assess the conformers. The construction of compounds were drawn victimization ISIS Draw 2-D drawing software systemand subsequently the designs were brought back to life to three-d coordinates followed by energy improvement was performed utilizing on-line server.[47] Most significant energy diminishedstructures are choosen for moorage and the differentpdbq and pdbqt files were ready in AutoDock.

To acquire upgradedunderstandingon the associations between compounds and target protein, AutoDockwas utilized to dock the datasets compounds.AutoDock requires receptor and ligand facilitates in MOL2 or PDB design. Nonpolar hydrogen atoms have beenkilled from the receptor report and their incomplete costshave beenacquainted with the relating carbon atoms. The grid calculations have beeninstallation and maps have been calculated with this systemAutoGrid. The grid maps have beenengagedat theligand bindingwebsite on the web and have been of sizeforty × forty × forty focuses. The grid spacing become 0.375 Å and the default AutoDock boundary settings have been utilizedfor docking. All docking runs have beencompletedthree timesthe utilization of the Lamarckian genetic set of rules and the top-notchexpense becomerecommended in kcal/mol. The wellknown docking protocol for bendy ligand docking comprised of 10 unbiased runs in sync with ligand, the use of apreliminarypopulaceof fifty randomly positioned individuals, a mostquantity of 2.five x a hundred and fiveelectricity assessments, a changecharge of 0.02, a hybridcharge of 0.80, and an elitism expense of 1.[48]

3. Results and Discussion

Docking reenactments with 4OTRand co-solidified ligand shows a dock score of - 9.11 kcal/mol and a RMSD worth of 1.11A° brought about five H-bond communications with Lys430, Asp539, Met477, Ala478 buildups, individually (Fig 1). It has been reported in literature that Met477 as key residue and retaining interactions with this residue favors inhibition of Btk.[49]

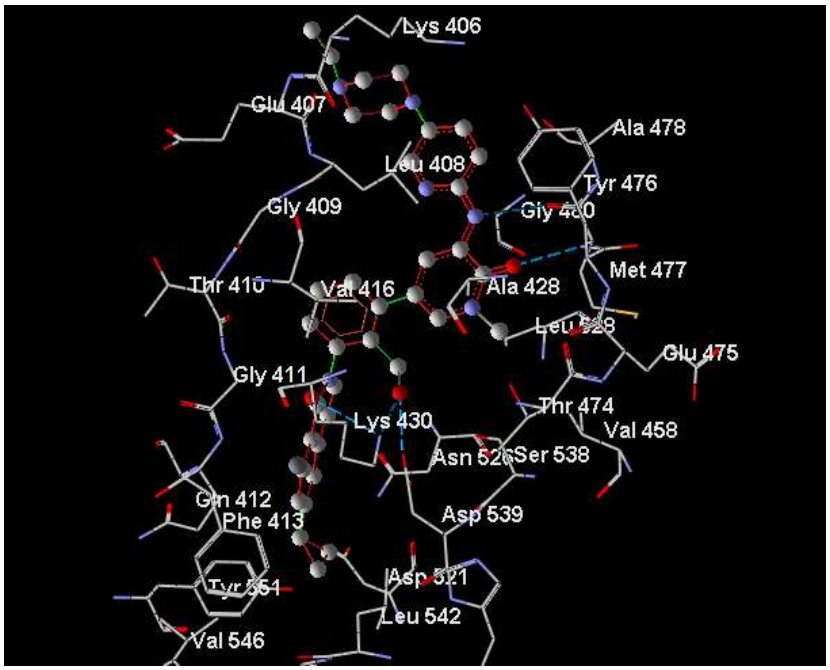


Fig 1: Docked pose of co-crystallized ligand showing H-bond interactions with Lys430, Asp539, Met477, Ala478 residues.Interactions visualized using Molegro Molecular Viewer software v.2.5.

Our docking examination with 285 different arrangement of mixtures came about in practically all inhibitors showed hydrogen holding associations with amino corrosive deposits covering the limiting site. The dock scores are given in Table-1. The limiting site area of Btk was shaped by Gln412, Phe413, Lys430, Glu475, Met 477, Ser538 and Asp539 amino acids. Not many of these critical buildups were found to connect with the reference inhibitor and mixtures under study. As far as H-holding connections, the bound ligand showed comparative h-bonds as seen with screened compounds.

Table 1: Top three best dock scores obtained after screening three dataset compounds towards Btk inhibition.

S. No.	Ligand No.	AutoDock score (kcal/mol)	Molecular Weight	Flexible torsions	H-bond Interacting amino acids
Btk	bound Ligand	9.11	621.724	6	Lys430, Asp539, Met477, Ala478
Dataset-1					
1	26	11.12	748.631	9	Asp521, Asn526, Tyr551

2	25	11.03	843.651	7	Gly411, Arg525
3	8	9.16	588.721	8	Tyr551
Dataset-2					
4	10	8.65	528.462	7	Gly411, Phe413, Lys430
5	9	8.39	514.435	7	Gly411, Lys430, Thr474, Asn526, Ser538
6	17	8.32	655.699	15	Lys430, Phe413, Asn526, Asp539
Dataset-3					
7	133	10.27	615.724	10	-
8	121	10.21	573.13	7	Gln412
9	136	10.06	573.663	10	Asp526, Ser538, Lys430, Thr474

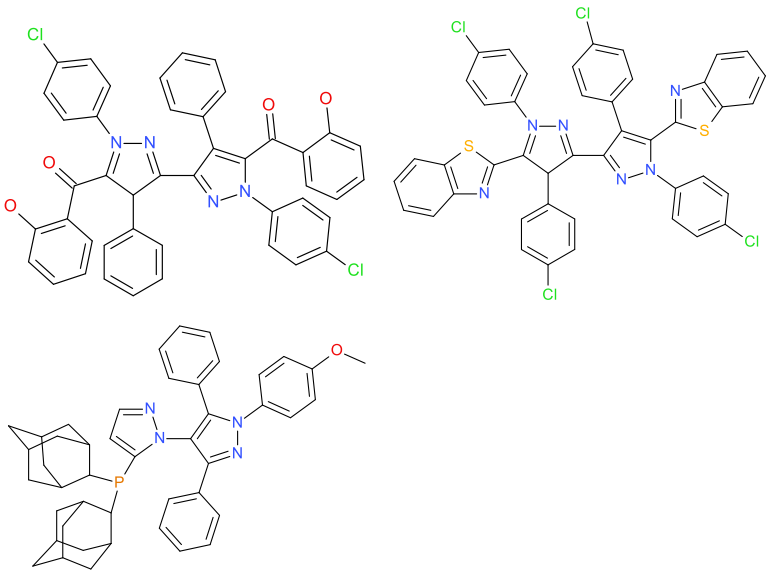
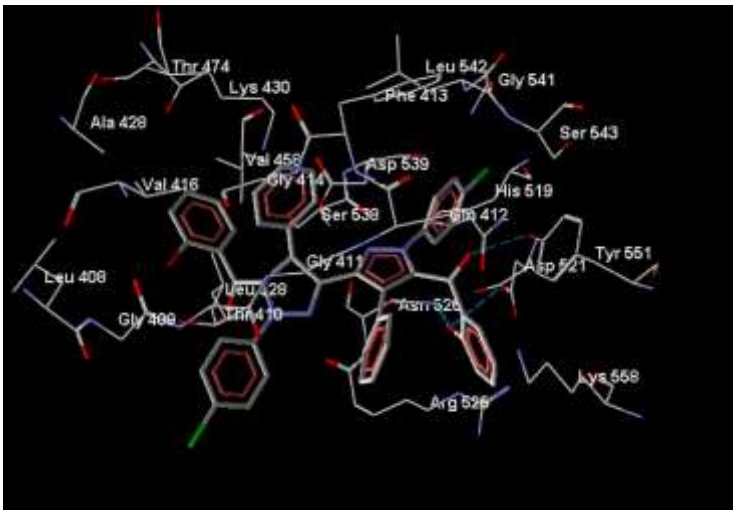
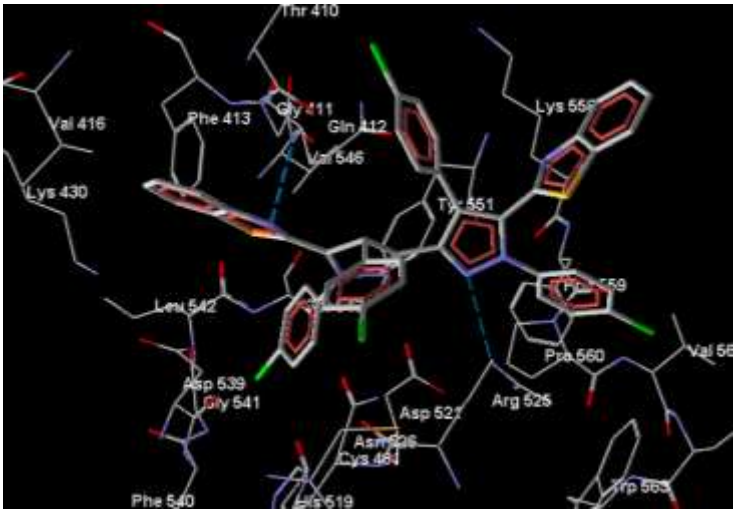


Fig 2: 2-dimensional structures of bipyrazole ligands **26**, **25** and **8** representing best compounds from dataset-1


Thr 474
Lys 430
Leu 542
Gly 541
Phe 413
Ala 428
Ser 543
Val 458
Asp 539
Val 416
Gly 414
His 519
Ser 538
Gln 412
Tyr 551
Gly 411
Asp 521
Leu 408
Leu 428
Asn 525
Gly 409
Thr 410
Lys 558
Arg 526


Thr 410
Val 416
Phe 413
Gly 411
Gln 412
Lys 558
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Lys 430
Tyr 551
Leu 542
Pro 560
Asp 539
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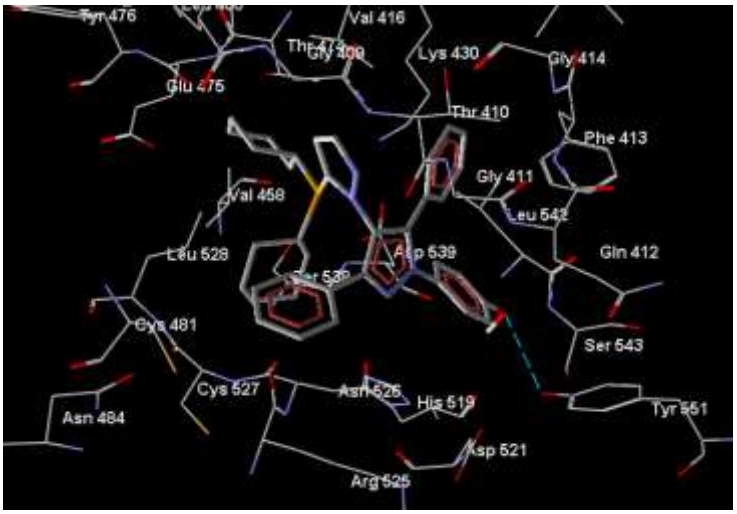
Asp 521
Arg 525
Cys 484
Phe 540
His 519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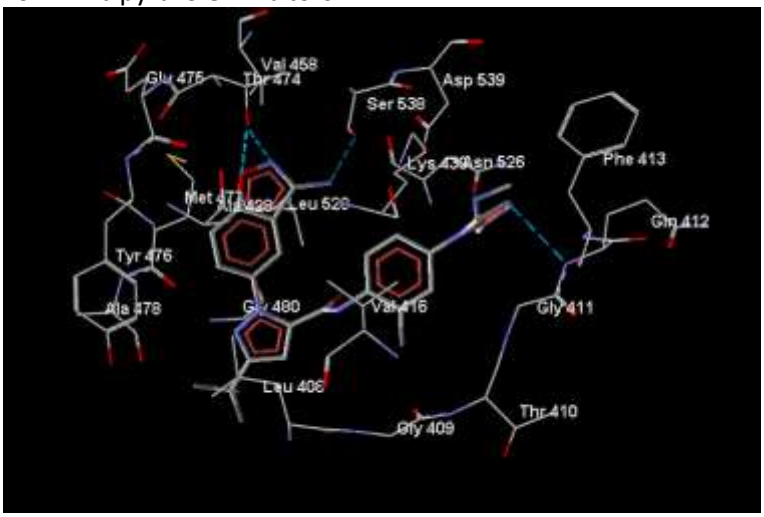
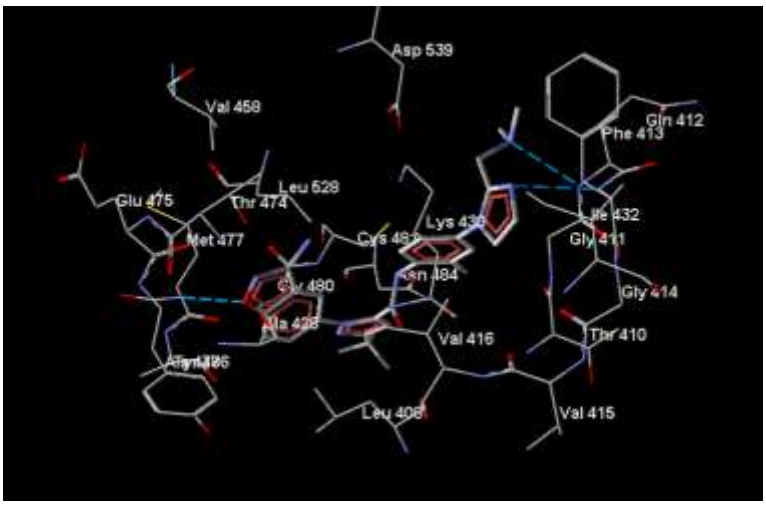
Val 416
Gly 409
Lys 430
Gly 414
Glu 475
Thr 410
Phe 413
Gly 411
Val 458
Leu 542
Leu 528
Asp 539
Gln 412
Cys 481
Ser 543
Cys 527
Asn 525
His 519
Tyr 551
Asn 484
Asp 521
Arg 525

Fig 3: H-bond interactions between top three ligands of dataset-1 and 4OTR active site region.

Dataset-1

The biyrazole systems containing two pyrazole rings at the nucleus stabilizes the complete structure thereby the side chain groups with electron donating and withdrawing properties (Fig 2) displayed favourable H-bond interactions with amino acid residues lining the active site cavity. It can be inferred from Table-2 that the binding affinities of bipyrazoleinhibitors displayed activity more than the 4OTR co-crystallized ligand. Structural inference data from figures 2 and 3 suggest that the activity of ligands **26** and **25** was due to the presence of H-bond donor and acceptor groups. The major interacting residue was reported to be Tyr551 and the geometric shape of the ligand fitted exactly into the active site space of 4OTR.





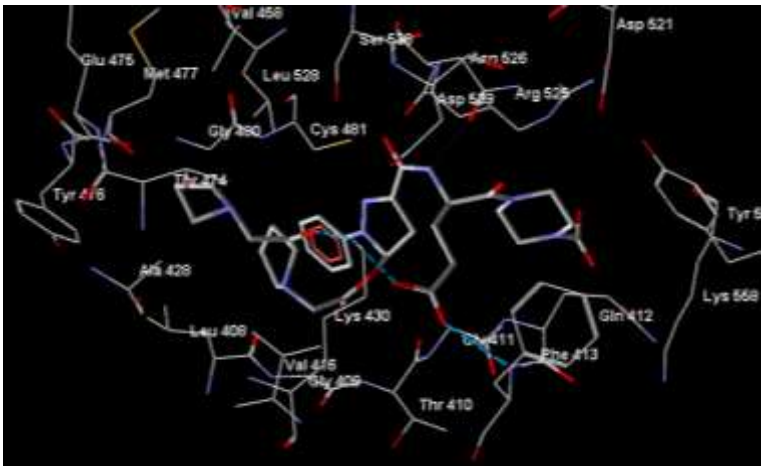
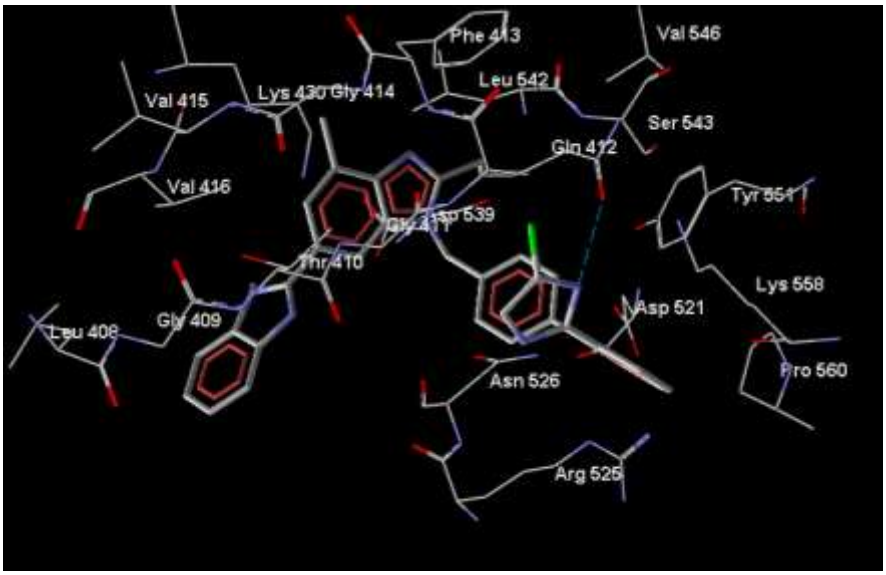


Fig 4: H-bond interactions between top three ligands of dataset-2 and 4OTR active site region.

Dataset-2

The second dataset of 115 pyrazole and pyrazoline derivatives tested for possible 4OTR inhibitory activity resulted in reduced affinity towards the receptor. Although the molecular weights of these compounds are sufficient enough as per Lipinski Rule of 5,[50] ligand **17** with nearly 15 freely rotatable bonds could not generate favourable interactions with the receptor as evidenced by dock score value of 8.32 kcal/mol. Lys430 is the predominant amino acid with which h-bond interactions are made by these set of ligands (Fig 4).



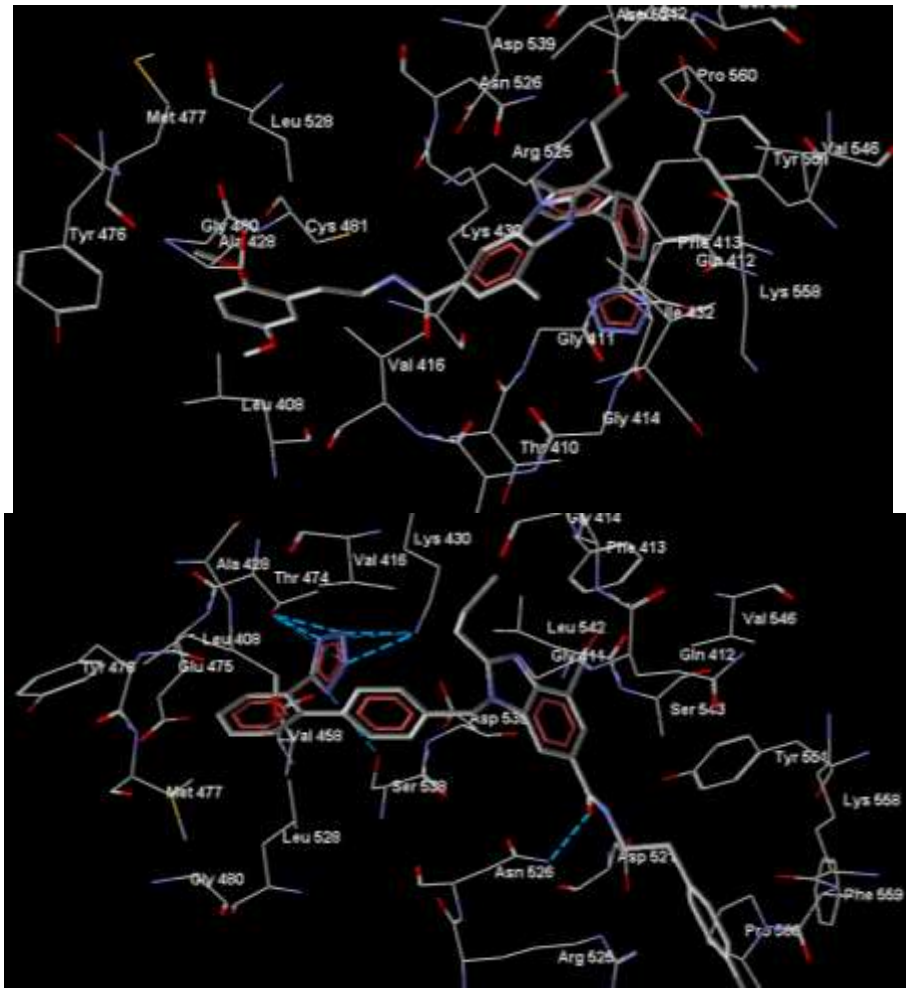


Fig 5: H-bond interactions between top three ligands of dataset-3 and 4OTR active site region.

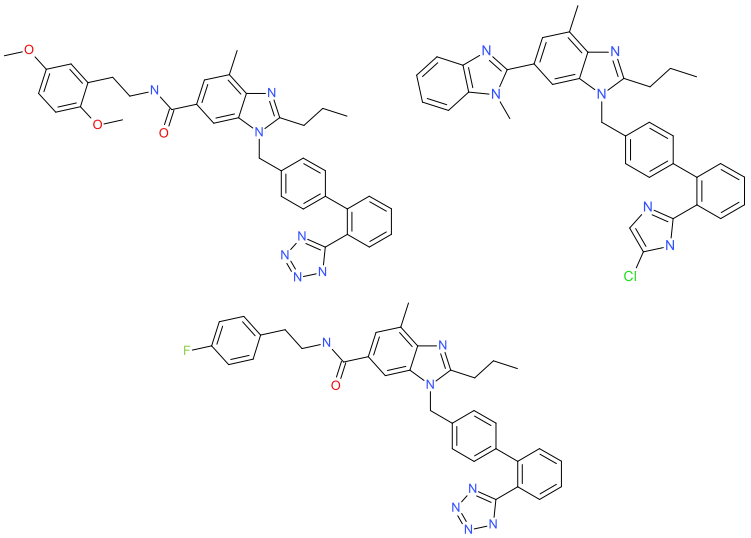


Fig 6: 2-dimensional structures of top 3 compounds from dataset-3, viz. **133**, **121** and **136** ligands

Dataset-3

This dataset has diverse structural features encompassing a variety of scaffolds such as indoles, pyrazolopyridine, indazoles, imidazo[4,5-c]pyridines, tetrazoles, oxadiazoles and benzimidazole derivatives. Interestingly, from table-2, it was observed that the molecular weights of top 3 compounds in this class were nearly similar to the bound ligand of 4OTR with reasonable flexible torsions in the ligands. Moreover, ligand **133** was devoid of any h-bond interactions with active site residues, whereas ligand **136** embedded with tetrazole moiety (figures 5 and6) displayed about six h-bond interactions with Lys430 and Thr474 respectively.

Further, a PubChem Structure search[51] for comparable compounds showed that thosehave beennow no longerexamined experimentally for the inhibition of Btk and for this reason we recommend that those compounds may be novel Btk inhibitors.

4. Conclusion

From this analysis, a variety of model compounds were evaluated for their potential to inhibit Btk. It was found that compounds containing freely flexible torsions of increasing molecular weight are likely to be effective Btk inhibitors. This is based on the fact that the active site region of 4OTR would accommodate high molecular weight ligands as evidenced in this analysis and hence favourable interactions were noted. This increase in binding affinity was observed for compounds with donor and acceptor groups on the side chain regions of ligand.Hence, designing compounds such as terazole derivatives and bipyrazole ring systems would represent positive contribution towards enhancing inhibition of Btk.

References

1. Satterthwaite, A. B. Witte, O. N. Immunol. Rev. 2000, 175, 120
2. Brunne, R. C.; Muëller, B.; Wirth, T. Histol. Histopathol.2005, 20, 945
3. Gomez-Rodriguez J, Readinger JA, Viorritto IC, Mueller KL, Houghtling RA, Schwartzberg PL. Tec kinases, actin, and cell adhesion. Immunol Rev 2007;218:45–64
4. Puri, K. D., Di Paolo, J.; Gold, M. R. Int. Rev. Immunol. 2013, 32, 397.
5. Tsukada, S.; Saffran, D. C.; Rawlings, D. J.; Parolini, O.; Allen, R. C.; Klisak, I.; Sparkes, R. S.; Kubagawa, H.; Mohandas, T.; Quan, S.; et al., Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. Cell 1993, 72 (2), 279-290
6. de Weers, M.; Verschuren, M. C.; Kraakman, M. E.; Mensink, R. G.; Schuurman, R. K.; van Dongen, J. J.; Hendriks, R. W., The Bruton's tyrosine kinase gene is expressed throughout B cell differentiation, from early precursor B cell stages preceding immunoglobulin gene rearrangement up to mature B cell stages. Eur. J. Immunol. 1993, 23 (12), 3109-3114.
7. Lachance, G.; Levasseur, S.; Naccache, P. H., Chemotactic factor-induced recruitment and activation of Tec family kinases in human neutrophils.Implication of

phosphatidynositol3-kinases. J. Biol. Chem. 2002, 277 (24), 21537-21541
8. Whyatt, D.; Lindeboom, F.; Karis, A.; Ferreira, R.; Milot, E.; Hendriks, R.; de Bruijn, M.; Langeveld, A.; Gribnau, J.; Grosveld, F.; Philipsen, S., An intrinsic but cell-nonautonomous defect in GATA-1-overexpressing mouse erythroid cells. Nature 2000, 406 (6795), 519- 524
9. Phillips, R. L.; Ernst, R. E.; Brunk, B.; Ivanova, N.; Mahan, M. A.; Deanehan, J. K.; Moore, K. A.; Overton, G. C.; Lemischka, I. R., The genetic program of hematopoietic stem cells. Science 2000, 288 (5471), 1635-1640
10. Rickert, R. C. New insights into pre-BCR and BCR signalling with relevance to B cell malignancies. Nat. Rev. Immunol. 2013, 13, 578−591
11. Yan Lou, Xiaochun Han, Andreas Kuglstatter, Rama K. Kondru et al. Structure-Based Drug Design of RN486, a Potent and Selective Bruton's Tyrosine Kinase (BTK) Inhibitor, for the Treatment of Rheumatoid Arthritis. J. Med. Chem. dx.doi.org/10.1021/jm500305p
12. Fleischmann, R. Novel small-molecular therapeutics for rheumatoid arthritis. Curr.Opin.Rheumatol. 2012, 24, 335−341
13. Garber, K. Pfizer's JAK inhibitor sails through phase 3 in rheumatoid arthritis. Nature Biotechnol.2011, 29, 467−468
14. Pan, Z. Bruton's tyrosine kinase as a drug discovery target. Drug News Perspect.2008, 21, 357
15. Copeland, R. A.; Pompliano, D. L.; Meek, T. D. Drug-target residence time and its implications for lead optimization. Nat. Rev. Drug Discovery 2006, 5, 730−739
16. Chang, B. Y.; Huang, M. M.; Francesco, M.; Chen, J.; Sokolove, J.; Magadala, P.; Robinson, W. H.; Buggy, J. J. The Bruton tyrosine kinase inhibitor PCI-32765 ameliorates autoimmune arthritis by inhibition of multiple effector cells. Arthritis Res. Ther.2011, 13, R115
17. Dinh, M.; Grunberger, D.; Ho, H.; Tsing, S. Y.; Shaw, D.; Lee, S.; Barnett, J.; Hill, R. J.; Swinney, D. C.; Bradshaw, J. M. Activation mechanism and steady state kinetics of Bruton's tyrosine kinase. J. Biol. Chem. 2007, 282, 8768−8776
18. Wahl, M. I.; Fluckiger, A.-C.; Kato, R. M.; Park, H.; Witte, O. N.; Rawlings, D. J. Phosphorylation of two regulatory tyrosine residues in the activation of Bruton's tyrosine kinase via alternative receptors. Proc. Natl. Acad. Sci. U.S.A. 1997, 94, 11526−11533
19. Hendriks, R. W.; Yuvaraj, S. Targeting Bruton's tyrosine kinase in B cell malignancies. Nat. Rev. Cancer 2014, 14 (4), 219−232
20. Cameron, F.; Sanford, M. Ibrutinib: First Global Approval. Drugs 2014, 74 (2), 263−271
21. Zhao X, Xin M, Huang W et al. Design, synthesis and evaluation of novel 5-phenylpyridin-2(1H)-one derivatives as potent reversible Bruton's tyrosine kinase inhibitors Bioorg Med Chem. 2015 Jan 15;23(2):348-64
22. Zhao X, Xin M, Wang Y et al. Discovery of thieno[3,2-c]pyridin-

4-amines as novel Bruton's tyrosine kinase (BTK) inhibitors. Bioorg Med Chem. 2015 Sep 1;23(17):6059-68
23. Kyung-Hee Kim, Andreas Maderna, Mark E. Schnute et al. Imidazo[1,5-a]quinoxalines as irreversible BTK inhibitors for the treatment of rheumatoid arthritis. Bioorganic & Medicinal Chemistry Letters 21 (2011) 6258–6263
24. Qing Shi, Andrew Tebben, Alaric J. Dyckman et al. Purine derivatives as potent Bruton's tyrosine kinase (BTK) inhibitors for autoimmune diseases Bioorganic & Medicinal Chemistry Letters 24 (2014) 2206–2211
25. Liu Q, Batt DG, Lippy JS et al. Design and synthesis of carbazolecarboxamides as promising inhibitors of Bruton's tyrosine kinase (BTK) and Janus kinase 2 (JAK2). Bioorg Med ChemLett. 2015 Oct 1;25(19):4265-9
26. Young WB, Barbosa J, Blomgren P et al. Discovery of highly potent and selective Bruton's tyrosine kinase inhibitors: Pyridazinoneanalogs with improved metabolic stability. Bioorg Med ChemLett. 2016 Jan 15;26(2):575-9
27. Huang Z, Zhang Q, Yan L et al. Approaching the active conformation of 1,3-diaminopyrimidine based covalent inhibitors of Bruton's tyrosine kinase for treatment of Rheumatoid arthritis. Bioorg Med ChemLett. 2016 Apr 15;26(8):1954-7
28. Liu J, Guiadeen D, Krikorian A et al. Discovery of 8-Amino-imidazo[1,5-a]pyrazines as Reversible BTK Inhibitors for the Treatment of Rheumatoid Arthritis. ACS Med ChemLett. 2015 Dec 19;7(2):198-203
29. Li X, Zuo Y, Tang G et al. Discovery of a series of 2,5-diaminopyrimidine covalent irreversible inhibitors of Bruton's tyrosine kinase with in vivo antitumor activity. J Med Chem. 2014 Jun 26;57(12):5112-28
30. Zhao X, Huang W, Wang Y et al. Discovery of novel Bruton's tyrosine kinase (BTK) inhibitors bearing a pyrrolo[2,3-d]pyrimidine scaffold. Bioorg Med Chem. 2015 Feb 15;23(4):891-901
31. Zhao X, Huang W, Wang Y et al. Pyrrolo[2,3-b]pyridine derivatives as potent Bruton's tyrosine kinase inhibitors. Bioorg Med Chem. 2015 Aug 1;23(15):4344-53
32. Bakr F. Abdel-Wahab and Kamal M. Dawood.Synthesis and applications of bipyrazolesystems.ARKIVOC 2012 (i) 491-545] [Samir Bondock, Abd El-GaberTarhoni, and Ahmed A. Fadda.Utility of cyanoacetic acid hydrazide in heterocyclic synthesis. ARKIVOC 2006 (ix) 113-156
33. Zhong Chen et al. Design, synthesis, biological evaluation and molecular modeling of dihydropyrazolesulfonamide derivatives as potential COX-1/COX-2 inhibitors. Bioorganic & Medicinal Chemistry Letters 25 (2015) 1947–1951
34. Abdellatif, K.R.A. et al. Synthesis, cyclooxygenase inhibition, anti-inflammatory evaluation and ulcerogenic liability of novel triarylpyrazoline derivatives as selective COX-2 inhibitors, Bioorganic & Medicinal Chemistry Letters 2015; 25(24):5787-91

35. Yu, M., Yang, H., Wu, K., Ji, Y., Ju, L. and Lu, X., 2014. Novel pyrazoline derivatives as bi-inhibitor of COX-2 and B-Raf in treating cervical carcinoma. Bioorganic & medicinal chemistry, 22(15), pp.4109-4118
36. YannLamotte, Paul Martres, Nicolas Faucher et al. Synthesis and biological activities of novel indole derivatives as potent and selective PPARγ modulators. Bioorganic & Medicinal Chemistry Letters 20 (2010) 1399–1404
37. Lamotte Y, Faucher N, Sançon J et al. Discovery of novel indazole derivatives as dual angiotensin II antagonists and partial PPARγagonists.Bioorg Med ChemLett. 2014 Feb 15;24(4):1098-103
38. Agustin Casimiro-Garcia, Ronald J. Heemstra, Christopher F. Bigge et al. Design, synthesis, and evaluation of imidazo[4,5-c]pyridin-4-one derivatives with dual activity at angiotensin II type 1 receptor and peroxisome proliferator-activated receptor-γ Bioorganic & Medicinal Chemistry Letters 23 (2013) 767–772
39. Choi MJ, Kwon GH, Han NS et al. Development of 3D-QSAR CoMSIA models for 5-(biphenyl-2-yl)-1H-tetrazole derivatives as angiotensin II receptor type 1 (AT1) antagonists. Bioorg Med ChemLett. 2013 Aug 15;23(16):4540-6
40. Yong-yanNie, Ya-jing Da, HaoZheng et al. Synthesis and biological evaluation of novel potent angiotensin II receptor antagonists with anti-hypertension effect. Bioorganic & Medicinal Chemistry 20 (2012) 2747–2761
41. NavneetKaur, AmardeepKaur, YogitaBansal et al. Design, synthesis, and evaluation of 5-sulfamoyl benzimidazole derivatives as novel angiotensin II receptor antagonists. Bioorganic & Medicinal Chemistry 16 (2008) 10210–10215
42. Jun Zhang, Jin-Liang Wang, Zhi-Ming Zhou et al. Design, synthesis and biological activity of 6-substituted carbamoylbenzimidazoles as new nonpeptidic angiotensin II AT1 receptor antagonists. Bioorganic & Medicinal Chemistry 20 (2012) 4208–4216
43. Kroemer RT. Molecular modelling probes: docking and scoring. Biochemical Society Transactions 31, 2003, 980-984
44. Kuntz ID. 1992. Structure-based strategies for drug design and discovery. Science 257, 1078–1082
45. Drews J. Drug discovery: a historical perspective. Science 287, 2000, 1960–1964
46. http://mgltools.scripps.edu/
47. http://crdd.osdd.net:8081/webcdk/2D-3D.js
48. Morris, G.M., Goodsell, D.S., Halliday, S., Huey, R., Hart, W.E., Belew, R.K. and Olson, A.J., J. Comput. Chem., 19 (1998) 1639
49. Zhao X, Huang W, Wang Y et al. Discovery of novel Bruton's tyrosine kinase (BTK) inhibitors bearing a pyrrolo[2,3-d]pyrimidine scaffold. Bioorg Med Chem. 2015 Feb 15;23(4):891-901
50. CA Lipinski, F Lombardo, BW Dominy and P J Feeney, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, Adv Drug Del Rev 46 3-26 (2001)

51. Wang Y, Suzek T, Zhang J, Wang J, He S, Cheng T, et al. PubChemBioAssay: 2014 update. Nucleic acids research. 2014;42(Database issue):D1075–82