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Insilico Design of Novel Kinase Inhibitor and its Docking Studies

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Abstract : Imidazoles have occupied a unique position in heterocyclic chemistry, and its derivatives have attracted considerable interests in recent years for their versatile properties in chemistry and pharmacology. Imidazole in nitrogen-containing heterocy clic ring which possesses biological and pharmaceutical importance. Considering its activies we are trying to synthesis a novel derivatives in this track we trying to spill its kinase inhibitor activity against cancer receptors. From our docking studies it is revealed that P4, P5, P6, P13, P15 have excellent kinase inhibitor activity with greatest minimizing energy values. Among them P13 & P 15 scored highest minimizing energy values with -403.3 and -403.37 respectively.
Key Words : Docking studies, Conjugation reactions, Imidazoles, Kinase Inhibitors,

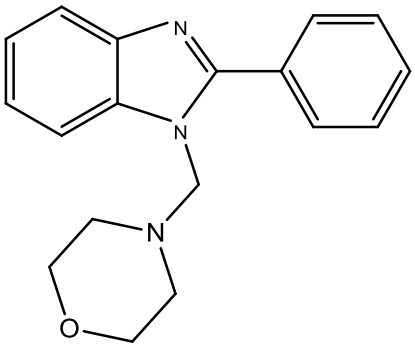
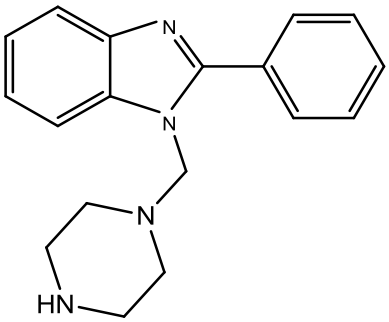
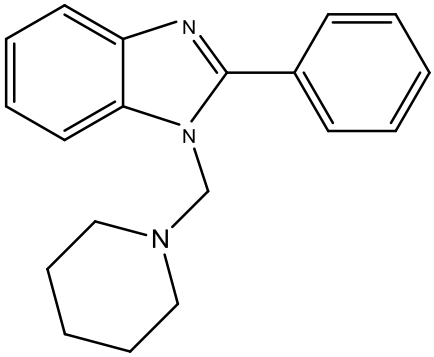
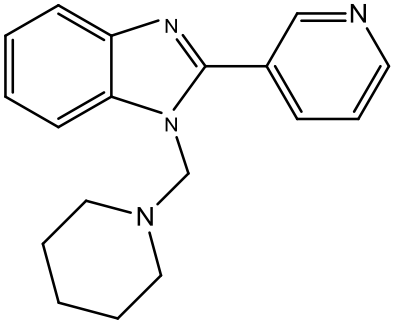
Introduction:

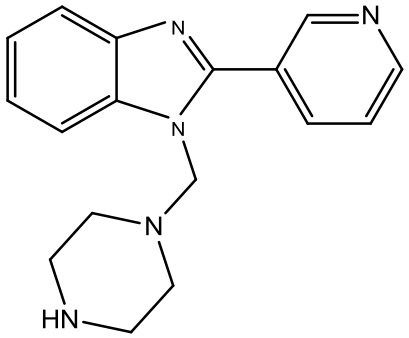
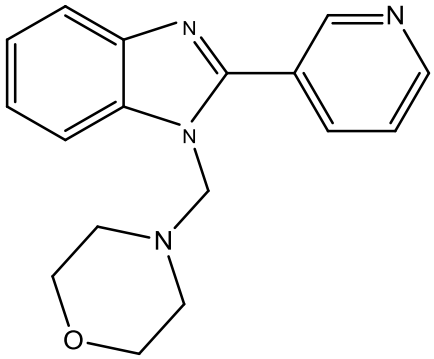
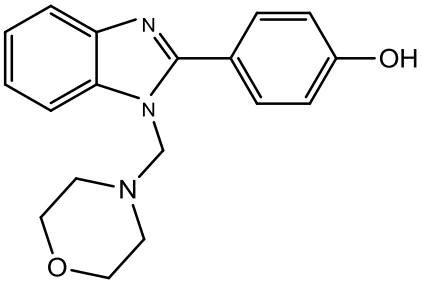
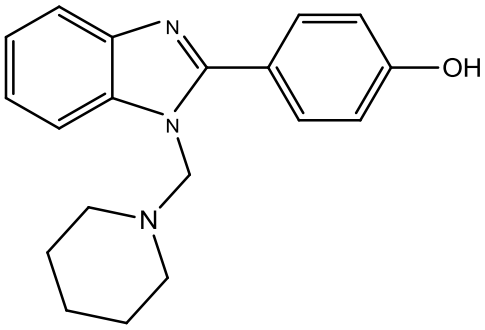
Kinase linked receptors are a super family of receptors which activate enzymes directly and do not require a G-protein. Important example of kinase-linked receptors is the tyrosine kinase receptors which are proving to be highly important targets for novel anticancer drugs. Drug discovery and development strategies have explored numerous approaches to target the inhibition of protein kinase signaling. [1] Drugs are foreign substances as far as the body is concerned and the body has its own method of getting rid of such chemical invaders. Imidazoles are well known heterocyclic compounds which are common and have important feature of a variety of medicinal agents. On the basis of various literature surveys Imidazole derivatives shows various pharmacological activities like antifungal, antibacterial, analgesics, anti inflammatory, anti tubercular,anti cancer, anti viral, anti depressant.[2-7]

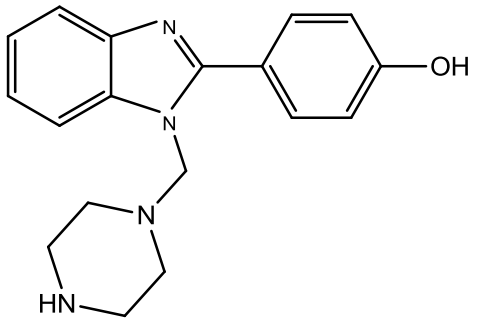
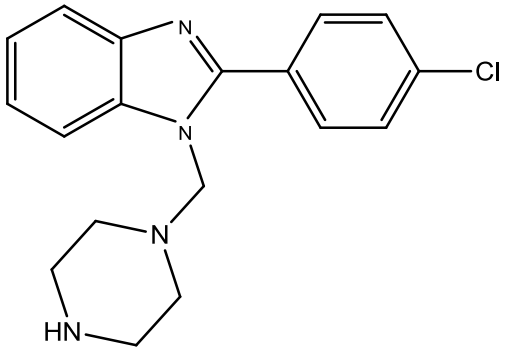
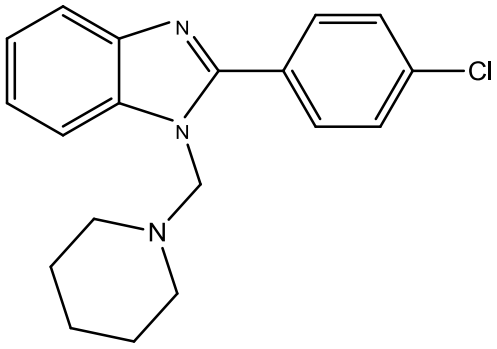
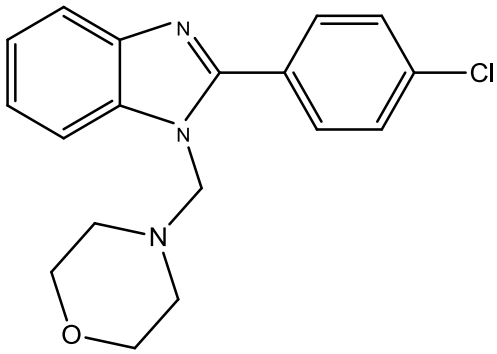
In this article we even presented the possible metabolism and metabolites of the ligands.

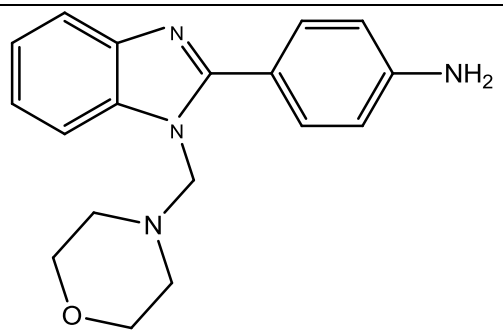
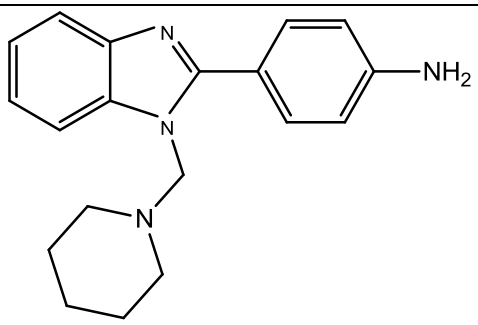
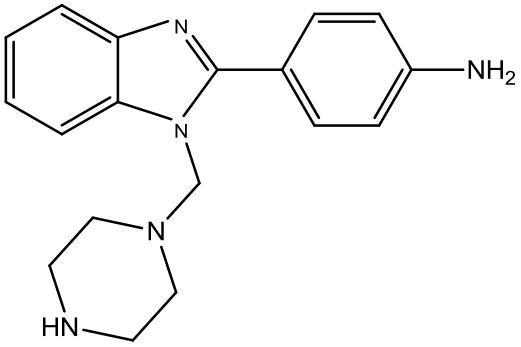
Materials And Methods

We designed around 15 ligands as shown in the table 1

S.NO	Molecular Formula	Ligand and its IUPAC Name
P1	$C_{18}H_{19}N_3O$	 4-((2-phenyl-1*H*-benzo[*d*]imidazol-1-yl)methyl)morpholine
P2	$C_{18}H_{20}N_4$	 2-phenyl-1-(piperazin-1-ylmethyl)-1*H*-benzo[*d*]imidazole
P3	$C_{19}H_{21}N_3$	 2-phenyl-1-(piperidin-1-ylmethyl)-1*H*-benzo[*d*]imidazole
P4	$C_{18}H_{20}N_4$	 1-(piperidin-1-ylmethyl)-2-(pyridin-3-yl)-1*H*-benzo[*d*]imidazole

P5	$C_{18}H_{19}N_5$	 1-(piperazin-1-ylmethyl)-2-(pyridin-3-yl)-1*H*-benzo[*d*]imidazole
P6	$C_{17}H_{18}N_4O$	 4-((2-(pyridin-3-yl)-1*H*-benzo[*d*]imidazol-1-yl)methyl)morpholine
P7	$C_{18}H_{19}N_3O_2$	 4-(1-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)phenol
P8	$C_{19}H_{21}N_3O$	 4-(1-(piperidin-1-ylmethyl)-1*H*-benzo[*d*]imidazol-2-yl)phenol

P9	$C_{18}H_{20}N_4O$	 4-(1-(piperazin-1-ylmethyl)-1*H*-benzo[*d*]imidazol-2-yl)phenol
P10	$C_{18}H_{19}N_4Cl$	 2-(4-chlorophenyl)-1-(piperazin-1-ylmethyl)-1*H*-benzo[*d*]imidazole
P11	$C_{19}H_{20}N_4Cl$	 2-(4-chlorophenyl)-1-(piperidin-1-ylmethyl)-1*H*-benzo[*d*]imidazole
P12	$C_{18}H_{18}N_3OCl$	 4-((2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)methyl)morpholine

P13	$C_{18}H_{20}N_4O$	 4-(1-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)aniline
P14	$C_{19}H_{22}N_4$	 4-(1-(piperidin-1-ylmethyl)-1*H*-benzo[*d*]imidazol-2-yl)aniline
P15	$C_{18}H_{21}N_5$	 4-(1-(piperazin-1-ylmethyl)-1*H*-benzo[*d*]imidazol-2-yl)aniline

Molinspiration[8]offers broad range of cheminformatics software tools supporting molecule manipulation and processing, including SMILES and SDfile conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR[9], molecular modelling and drug design[10], high quality molecule depiction, molecular database tools supporting substructure and similarity searches. It also supports fragment-based virtual screening, bioactivity prediction and data visualization. Mol inspiration tools are written in Java therefore can be used practically on any computer platform.

MetaPrint2D-React[11] which can make predictions concerning a wider range of reactions, and is able to predict the types of transformation that can take place at ease site of metabolism, and the likely metabolite formed.

Hex 8.0.0 protein docking using spherical polar Fourier Correlations [12]. *Hex* is an interactive molecular graphics program for calculating and displaying feasible docking modes of pairs of protein and DNA molecules. *Hex* can also calculate protein-ligand docking, assuming the ligand is rigid, and it can superpose pairs of molecules using only knowledge of their 3D shapes. It is the first protein docking program to be able to use modern graphics processor units (GPUs) to accelerate the calculations.

Results and Discussion:

Activity prediction

Using mol inspiration software we tried to predict the possible biological activity of the quoted ligands. The results are shown in the given table.

Table-2: Molinspirsation Bioactivity score

Ligand	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
P1	-0.09	-0.26	0.12	-0.44	-0.46	-0.02
P2	0.03	-0.11	0.17	-0.48	-0.38	0.04
P3	0.01	-0.15	0.09	-0.4	-0.41	0.04
P4	0.06	-0.08	0.25	-0.43	-0.37	0.13
P5	0.09	-0.04	0.33	-0.51	-0.34	0.12
P6	-0.04	-0.19	0.28	-0.48	-0.41	0.06
P7	-0.03	-0.21	0.17	-0.26	-0.4	0.04
P8	0.07	-0.1	0.14	-0.22	-0.35	0.1
P9	0.09	-0.07	0.21	-0.29	-0.33	0.09
P10	0.04	-0.12	0.15	-0.47	-0.39	0
P11	0.02	-0.15	0.08	-0.39	-0.41	0
P12	-0.08	-0.26	0.11	-0.43	-0.46	-0.06
P13	-0.03	-0.2	0.24	-0.48	-0.33	0.07
P14	0.06	-0.09	0.21	-0.44	-0.29	0.13
P15	0.09	-0.06	0.28	-0.51	-0.26	0.12

The inference from the above table is that among all the 15 ligands P4, P5, P6, P13, P15 have excellent kinase inhibitor activity.

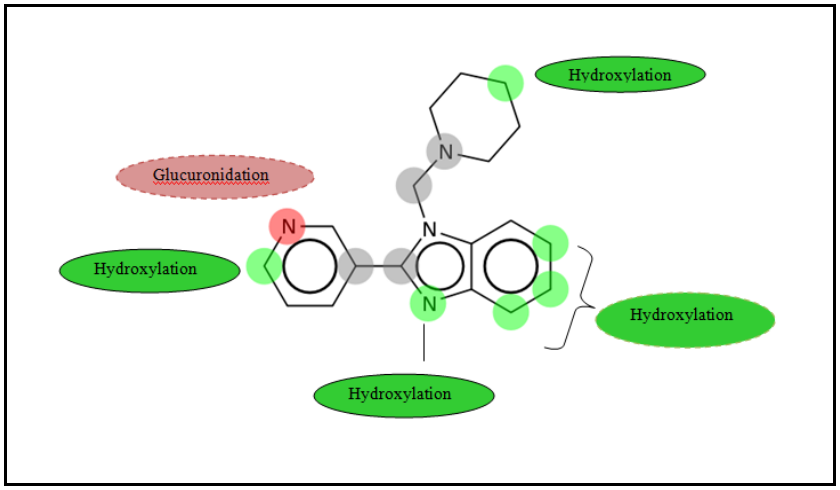
Prediction of metabolism using Metaprint2D- React:

A series of metabolic reactions classed as phase II reactions are occur in liver, most of these reactions area conjugation reactions, where by polar molecule is attached to a suitable polar handle that is already present on the drug. The resulting conjugate has greatly increased polarity, thus increasing its excretion rate in urine or bile even further.

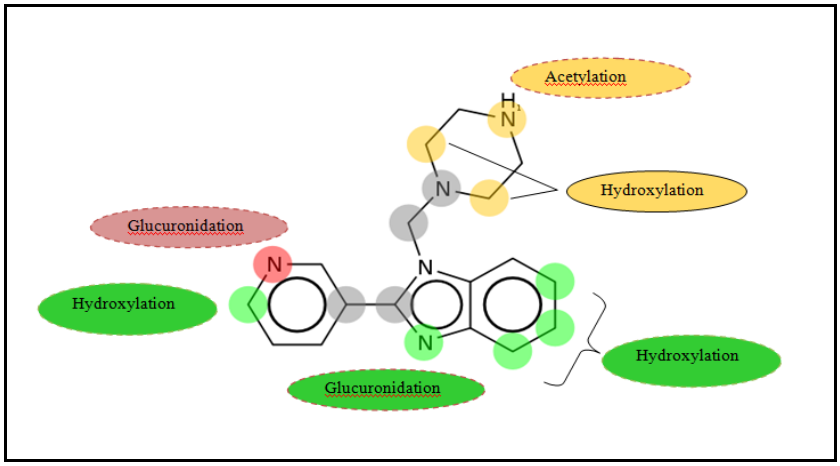
Red	0.66 < = NOR <=1.00
Orange	0.33 < = NOR < 0.66
Green	0.15 < = NOR < 0.33
White	0.00 < = NOR < 0.15
Grey	Llittle/Moderate

The colour highlighting an atom indicates its normalised occurrence ratio (NOR). A high NOR indicates a more frequently reported site of metabolism in the metabolite database.

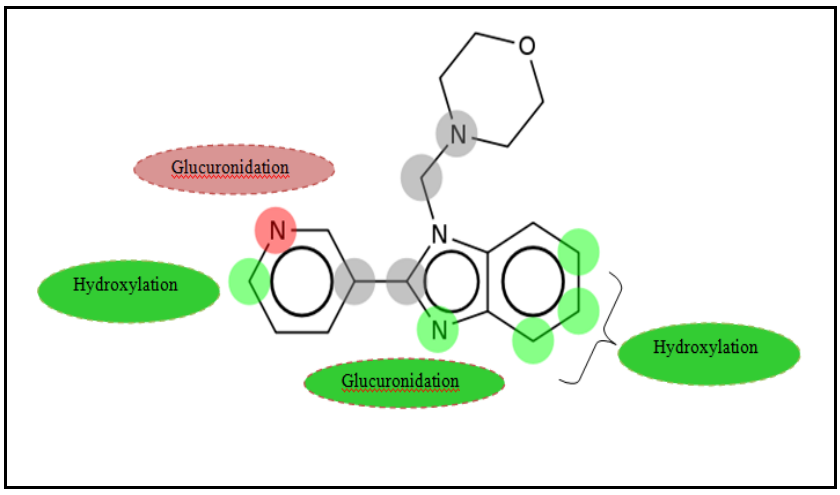
Likelihood of metabolism occurring at a particular site in the P4 molecule



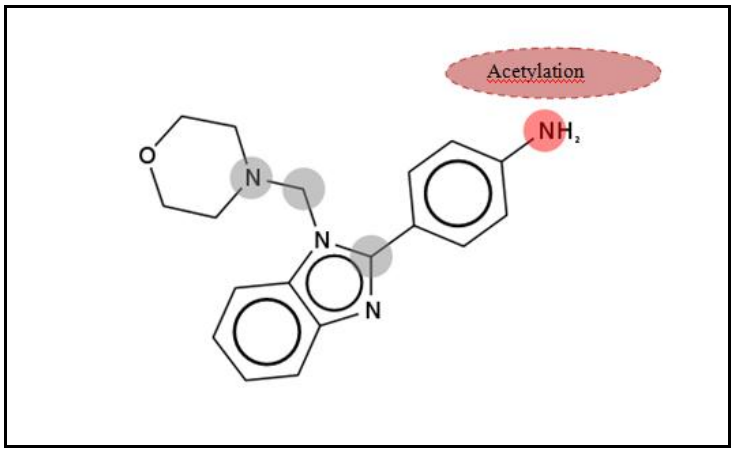
Likelihood of metabolism occurring at a particular site in the P5 molecule



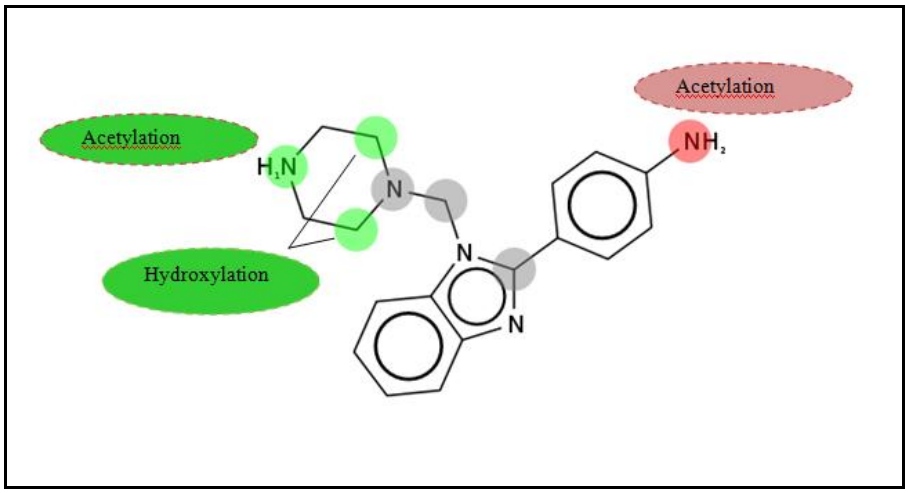
Likelihood of metabolism occurring at a particular site in the P6 molecule



Likelihood of metabolism occurring at a particular site in the P13 molecule



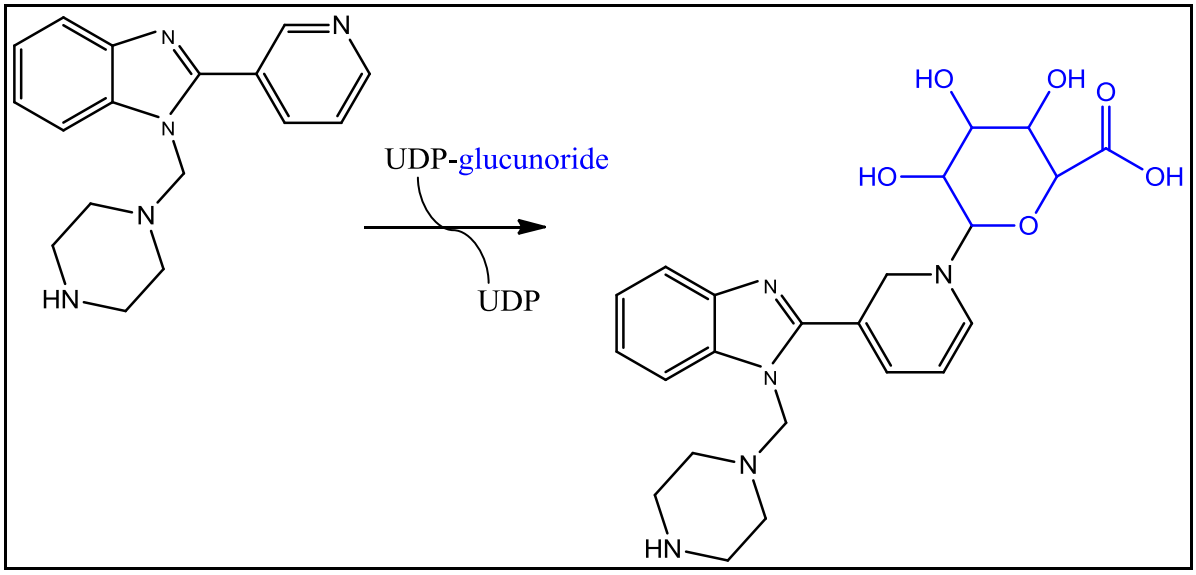
Likelihood of metabolism occurring at a particular site in the P15 molecule



Most phase II reactions are conjugation reactions catalysed by transferase enzymes. Glucuronic acid conjugation is the most common reaction of these reactions. Phenols, alcohols, hydroxyl amines and carboxylic acids form O-glucuronides by conjugation with UDP-glucuronate such that a highly polar glucuronic acid molecule is attached to the drug. The resulting conjugate is excreted in the urine or may also be excreted in the bile.

The quoted ligands are no longer exception for this glucuronide conjugation. Here it is N-Glucuronide conjugation.

The possible metabolite from P15 after conjugation is represented below:



Docking Studies:

After coming to know the possible activity like kinase inhibition, we selected suitable targets/ receptors from protein data bank.

5KZ0 – Human Anaplastic Lymphoma Kinase Receptor
5HCX – Epidermal Growth Factor Receptor
5B7V - Human fibroblast growth Receptor
5DN2 – Vascular Endothelial Growth Factor Receptor

Table 3: Energy values in kcal/mol, obtained from Hex

Ligand	5KZ0		5HCX		5B7V		5DN2	
	E min	E max	E min	E max	E min	E max	E min	E max
P4	-378.88	441.92	-373.65	401.18	-376.49	319.71	-312.11	280.98
P5	-375.81	440.62	-372.66	399.6	-372.6	290.9	-309.44	281.84
P6	-345.95	360.24	-356.63	410.8	-104.66	132.73	-324.2	259.49
P13	-375.03	410.19	-371.18	381.21	-403.3	358.42	-39.24	61.47
P15	-375.03	393.14	-371.85	382.31	-403.37	359.14	-39.26	61.47

From the table it is noticing that P13 & P15 have greatest minimum energy for 5B7V receptor.

Conclusion

Out of 15 ligands, according to bioactivity score from mol inspiration we had chosen 5 best scoring ligands. Phase II reactions of these compounds are checked by Meta print 2D React software, revealing that like many conventional drugs these compounds are also conjugating with glucuronides for their excretion. Before this these compounds have possible kinase inhibitor activity, this point is strengthened by their highest minimum energy values. Out of all P13, P15 compounds have best minimizing energies like -403.3 and -403.37 respectively. There is a possibility to extend this work on cell lines to target the cancer through kinase inhibition.

References

1. https://en.wikipedia.org/wiki/Protein_kinase_inhibitor

2. R. V. Shingalapur, K. M. Hosamani, R.S. Keri, European Journal of Medicinal Chemistry, 2009, 44, 4244–4248.
3. D. Sharma, B. Narasimhan, P. Kumar, V. Judge, R. Narang, E. De Clercq, J. Balzarini, European Journal of Medicinal Chemistry., 2009, 44, 2347–2353.
4. D. Zampieri, M. G. Mamolo, L. Vio, E. Banfi, G. Scialino, M. Fermeglia, M. Ferrone and S. Pricl, Bioorganic & Medicinal Chemistry., 2007, 15, 7444–7458.
5. D. Olender, J. Zwawiak, V. Lukianchuk, R. Lesyk, A.Kropacz , A. Fojutowski, L Zaprutko, European Journal of Medicinal Chemistry., 2009, 44, 645-652.
6. A. Puratchikodya and M. Doble, Bioorganic & Medicinal Chemistry, 2007, 15, 1083–1090. K. C.S. Achar, K. M. Hosamani, H. R. Seetharamareddy, European Journal of Medicinal Chemistry, 2010, 45, 2048–2054.
7. P. Gupta, S. Hameed, R. Jain, European Journal of Medicinal Chemistry, 2004, 39,805–814.
8. Zhao Y H , Abraham MH, Le J, Hersey A, Luscombe C N, Beck G, Sherborne B. Rate-limited steps of human oral absorption and QSAR studies.Pharm. Res. 2001:19; 1446-1457.
9. Prashant A. Patil, Sandeep S. Pathare, Kishore P. Bhusari. QSAR and docking study of p-hydroxyphenylbenzohydrazide derivatives as ACE inhibiters- antihypertensive agents International Journal of PharmTech Research, 2016:9(5); 306-314.
10. Anjali Thakur, Pusp Raj S.Gupta, Prateek Pathak, Ankit Kumar. Design, Synthesis, SAR, Docking and antibacterial evaluation: Aliphatic amide bridged 4-aminoquinoline clubbed 1,2,4- triazole derivatives. International Journal of ChemTech Research, 2016, 9(3), 575-588.
11. Sivudu G et al. In Silico Design, Synthesis, Characterization and Biological Evaluation of Furan Based Hydrazone. Indo American Journal of Pharm Research.2015:5(08); 2722-2746.
12. Joe D, Zheng O, Jeffery T, Andrew B, Yaron T,and Jie L. CASTp: Nucl. Acids Res. 2006: 34; 116-118.

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