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Quantitative Structure activity Relationship of Aminopyrido [2, 3-d] Pyrimidin -7- yl ureas. as Potent compound against Non-receptor c- Src Tyrosine Kinases.

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Abstract
Non-receptor c-Src Tyrosine kinases have attracted much attention in recent times in the design of new agents to treat proliferative diseases. 3D-QSAR studies on 2-substituted aminopyrido [2, 3-d] Pyrimidin7-yl- ureas as a novel class compound of this series displayed submictomolar to low nano molar potency against non-receptor c-Src classes. 3D-QSAR studies have been performed on a series of Pyrimidin derivatives by using the receptor surface analysis (RSA) method. The RSA analysis have been carried out on 42 analogues of which 37 were used in the training set and the rest five molecules were test sets. The study produced reasonably good predicted models with good cross-validated and conventional r^2 values in both the models.
Keywords:- *cSrc tyrosine Kinases 3D- QASR studies, RSA, TKs,NRTKs.*

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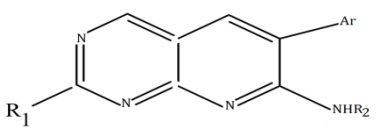
I. Introduction

Signaling for a large number of cellular functions including cell growth differentiation and migration [1, 2] is modulated by a varity of transmembrane growth factor receptor and cytoplasmic protein tyrosine Kinases have been linked to a number of Patho- Physiological states including cancer, cardiovascular and immunoinlammatory diseases. Since distinct TKS are implicated in such diverse conditions as angiogenesis [4,5], restenosis [6,7] atherosclerosis [8] and tumor growth [9]. Selective TK inhibitors should be less, likely to affert normal cells and thus produce fewer side effects, broadly acting non selective inhibitors may be required to overcome redundancies in growth signaling pathways in order to arrest aggressively proliferating cells. The complex nature of signal transduction

i.e. redundancies and crosstalk between signaling pathways, absolute selectivity may not be desirable when the need arises to simultaneously inhibit multiple growth signals. The strategy for uncovering broadly acting non selective small molecule inhibitors of the c-Src TKs; [10] which might serve to over come these redundancies in growth signaling. The main objective of the work is to provide a detailed understanding of the molecular mechanism of the Src family of non receptor tyrosine Kinases (NRTKs). The human form of the c-Src NRTKs, the Prototipical Src family of TK will be used as a model system to study the mechanism of Phosphoryl transfer from ATP to tyrosine. Using a transient state Kinetic analysis as well as standard biochemical an biophysical approaches and to investigate the auto phosphorylation mechanism of c-Src. RSA of 3D-QSAR Study an analogue-based rational drug design method will provide a foundation for further studies that will focus on structure-activity relationship for small molecules inhibitors and mechanistic analysis of other Src family tyrosine Kinases.



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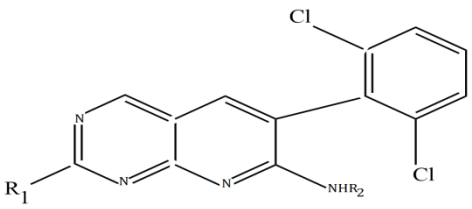

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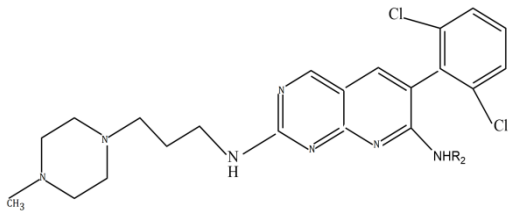

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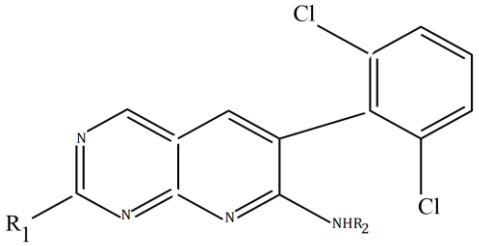

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TABLE 1. Training and test set structure with reported and RSA calculated activities.

Structure no.	Ar	R^1	R^2	Activity –(log IC_50) (μM) Platelet aggreg.)	Calculated activity (RSA).
1	2,6 $(cl)_2$Ph	NH_2	t-BuNHCO	0.22	0.658
2	2,6 $(cl)_2$Ph	NH_2	H	0.21	0.678
3	2,6 $(cl)_2$Ph	NH $(CH_2)_3NEt_2$	H	0.75	0 .125
4	2,6 $(Me)_2$Ph	NH_2	H	0.43	0.367
5	2,6 $(Me)_2$Ph	NH_2	t-BuNHCO	0.11	0.959
6	2,6 $(Me)_2$Ph	NH $(CH_2)_3NEt_2$	H	0.45	0.374
7	2,6 $(Me)_2$Ph	NH $(CH_2)_3NEt_2$	t-BuNHCO	0.098	1.009
8	2,6 $(Br)_2$Ph	NH_2	H	1.6	-0.204
9	2,6 $(Br)_2$Ph	NH_2	t-BuNHCO	0.21	0.678
10	2,6 $(Br)_2$Ph	NH $(CH_2)_3NEt_2$	H	0.76	0.119
11	2,6 $(Br)_2$Ph	NH $(CH_2)_3NEt_2$	t-BuNHCO	0.097	1.013
12			H_2 NCO	0.061	1.640
13			Et-NHCO	0.024	1.620
14			4- MePhNHCO	0.036	0.036
15			2- MePhNHCO	0.016	0.016
16			3- MeOPhNHCO	0.029	0.029
17			4- MeOPhNHCO	0.033	0.033
18			1-naphthyINHCO	0.13	0.130
19		NH $(CH_2)_3$(N- methyl Piperazin-1-yl)	t- BuNHCO	0.032	-0.231
20		NH $(CH_2)_3NEt_2$	Me_2NCH	4.0	-0.602
21		NH $(CH_2)_4NEt_2$	(morpholin-1yl) $(CH_2)_3$ NHCS	0.022	1.658
22		NH $(CH_2)_3$(N- methyl Piperazin-1-yl)	$EtCH_2CO$	2.7	-0.431
23		NH $(CH_2)_3$(N- methyl Piperazin-1-yl)	t-$BuCH_2CO$	0.073	-0.924
24		NH $(CH_2)_3$(N- methyl Piperazin-1-yl)	$PhCH_2CO$	3.3	1.495
25		NH $(CH_2)_3$(N- methyl Piperazin-1-yl)	$PhSO_2$	0.022	1.658
26		NH $(CH_2)_3$(N- methyl Piperazin-1-yl)	PhNHCNH	0.86	0.066
27		NH $(CH_2)_3$(N- methyl Piperazin-1-yl)	t-Bu NHCS	0.22	0.658
28		NH $(CH_2)_3$(N- methyl Piperazin-1-yl)	Ph NHCS	0.022	1.658
29		$NH(CH_2)_3NEt_2$	t-Bu NHCO	0.073	1.137
30		$NH(CH_2)_3NEt_2$	t-Bu NHCO	4.1	-0.613
31		$NH(CH_2)_3NEt_2$	Et NHCO	0.094	1.027
32		$NH(CH_2)_3NEt_2$	i-Pr NHCO	0.078	1.108
33		$NH(CH_2)_4NEt_2$	Et NHCO	0.018	1.745
34		$NH(CH_2)_4NEt_2$	t- Bu NHCO	0.0074	2.131
35		$NH(CH_2)_4NEt_2$	Cyclohexyl NHCO	0.012	1.932
36		$NH(CH_2)_4NEt_2$	Ph NHCO	0.0075	2.125
37		$NH(CH_2)_3NMe_2$	t-Bu NHCO	0.12	0.921
38		$NMe(CH_2)_3$ NMe_2	t-Bu NHCO	1.1	0.041
39		$NHCH_2CMe_2$ CH_2 NMe_2	t-Bu NHCO	3.5	-0544
40		$NH(CH_2)_3$(morpholin-l-yl)	t-Bu NHCO	0.10	1.000
41		$NH(CH_2)_3$ (2 methyl	t-Bu NHCO	0.016	1.796

		piperidin-1-yl)			
42		NH $(CH_2)_3$(N- methyl Piperazin-1-yl)	t-Bu NHCO	0.010	2.000

II. Materials and Methods :

The structures of the 6- arylpyrido [2,3 d] Pyrimidines ureas have been taken for this study are shown in (table 1). They were evaluated for their ability to prevent Phosphorylation of c-Src Tks. Variation about the C-6 aryl and N-7 urea moieties was explored and showed that compounds with the 2, 6 – dichlorophenyl substituent (e.g. compound 1) at C-6 were the most potent inhibitors against c-Src Tks. Three positions of the template, namely C-6 aryl, the N-7 urea and N-2 amino substituents offered potential sites for structural changes to increase potency and solubility [11]. The 3-D molecular structures were generated and optimized with OFF methods of cerius[2]. [12] while AM1 calculations were used for further geometric optimizations following eigen vector method. Electrostatic potential charges were also derived from AM1 calculations. Optimized molecular structures and partial atomic charges were used for the molecular alignment using the shape reference of the most active molecule 32. Forty two molecules were considered in the training set and their over lay plot is shown in Fig 1. Electrostatistically stabilized receptor surface is shown in Fig 2.

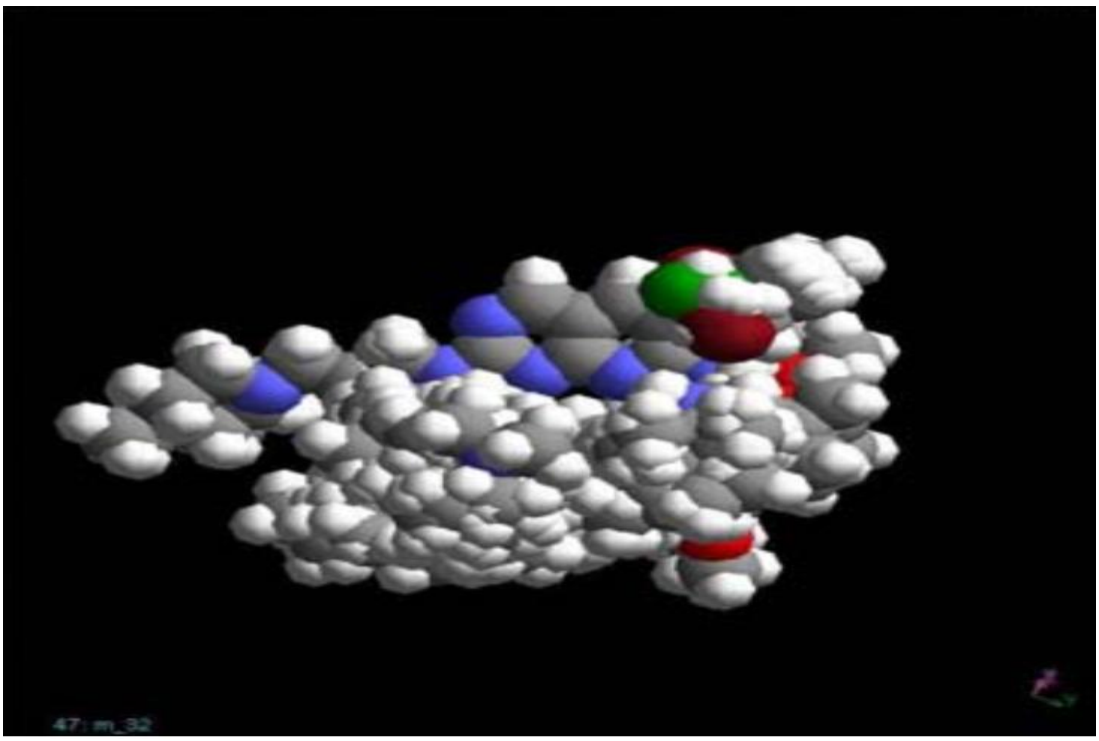

FIGURE -1 overlap diagram showing molecular alignment of all 42 molecules

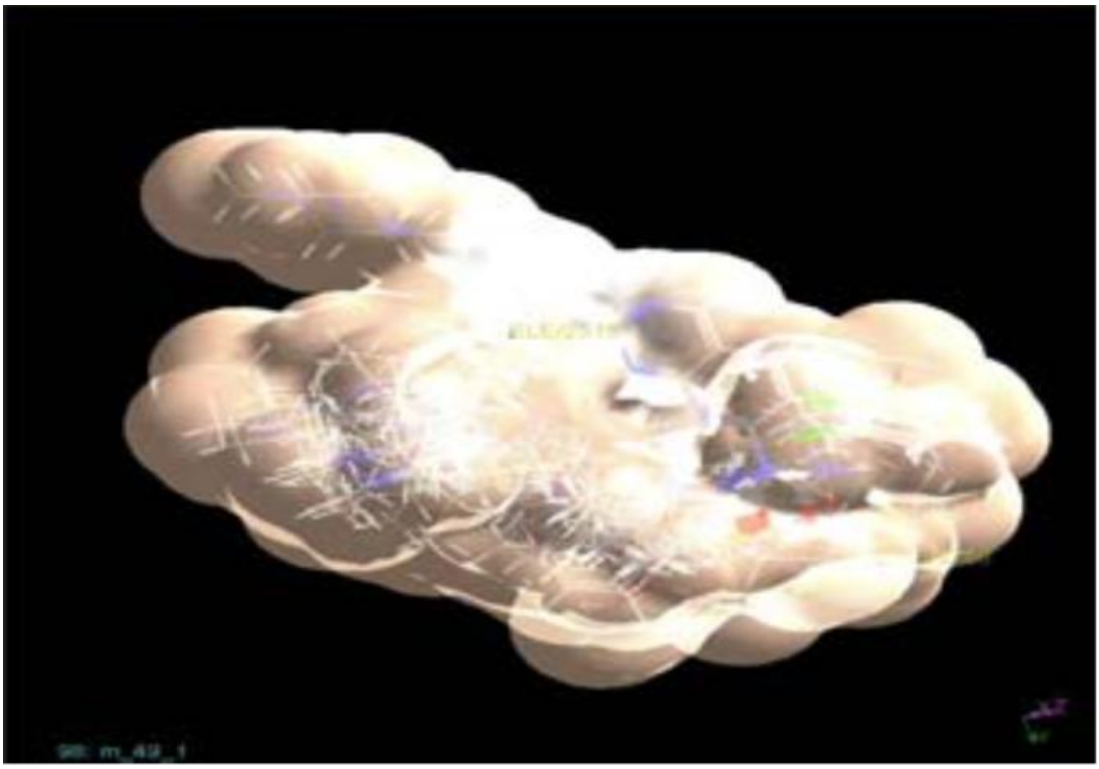

FIGURE -2 Electrostatically stabilized Receptor Surface.

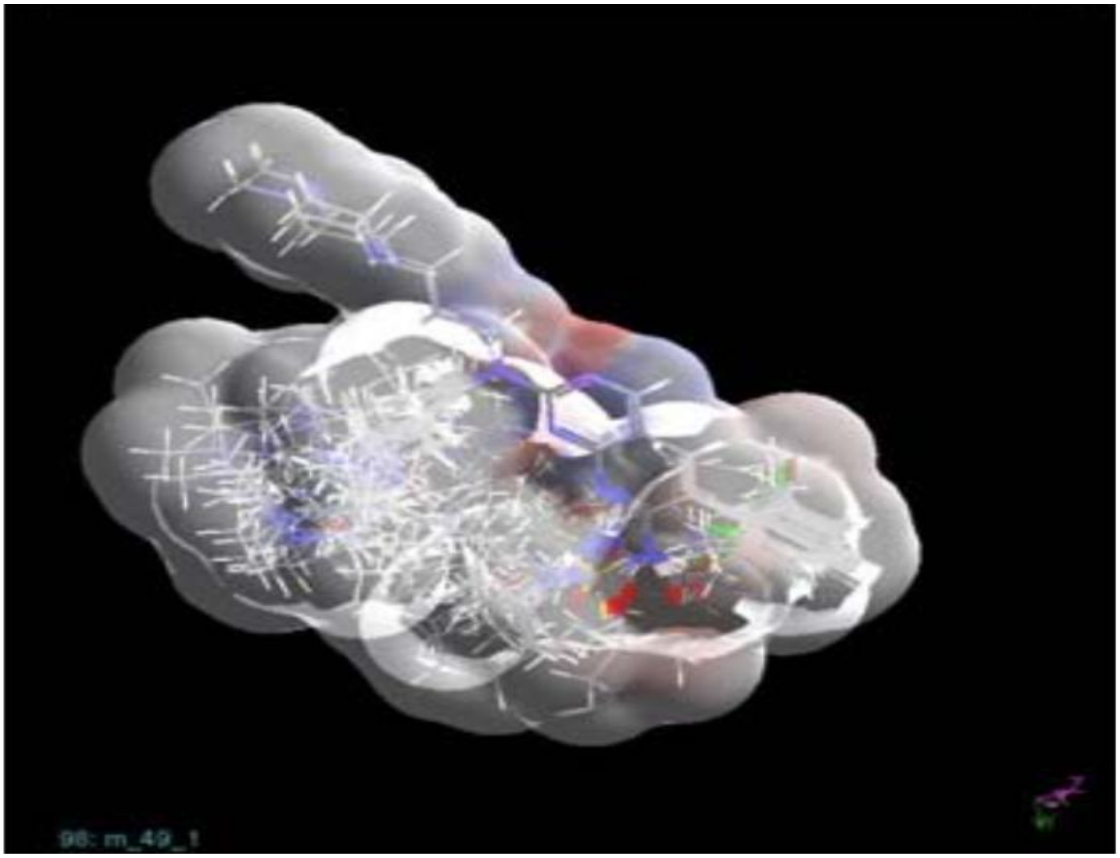

Figure -3 Hydrophobic properties Receptor Surface

Receptor Surface Analysis (RSA):

All the molecules were aligned with respect to 42 molecules based on Fragment 1. The optimized and aligned molecules were loaded for RSA. All the aligned molecules were added to the QSAR study table. Before

adding the molecules in the preferences of molecules menu charges option was checked in the table under the activity column-log IC_{50} of the molecules were entered. Prototype receptor model was generated using durg discovery RSA, generate receptor model deck of cerius[2]. The receptor surface was generated for the aligned molecules with weights proportional to the biological activity. The steric and electrostatic interaction energies for all loaded molecules were calculated. In preferences, use existing charges and activity data from study table options were checked before calculations, molecules were evaluated for each receptor model. In the descriptor, add receptor option was selected and the two default descriptors were added to the QSAR study table. In topological descriptors the shadow indices descriptor was added to the QSAR study table. The interaction energies of each molecules with different probes positioned along the grid points of the receptor surface were added to the study table and were considered as independent variables in the QSAR study. The negative logarithm of the biological activity was chosen as the dependent variable in the generation of QSAR equations. Regression analysis was carried out using the Genetic partial last squares (G/PLS) method consisting nearly 20,000 cross over generations. The G/PLS was configured using the number of component as 8; length of equation was 8 terms and scaled options. The activity is set as the Y- variable and the descriptor are taken as the X- variable (independent variable). The training set molecules were selected from the study table and regression was carried out to obtain the QSAR equation.

III. Results and Discussions:

The QSAR model with 37 molecules yielded a conventional correlation coefficient r^2 of 0.909 statistics of the model are given in table-II. The predictive ability of the RSA model was evaluated by predicting the biological activities of the test set molecules. Structures 2, 9, 25, 27, 28 were taken as a test set. Training and test sets are given in table 1. The receptor models with specific hydrophobic. Properties mapped are shown in Fig. 4. When the electrostatic potential is mapped, each surface vertex is colored accounting to the potential value at the vertex positions. Red areas have electrostatic potential, blue areas have positive potential and white areas have neutral potential.

Table –II

r^2	0.909
$r^{\wedge 2}$	0.809
PRESS	0.909

When the charge property is mapped, the surface colour is based on the average of the charges of the template atoms close to the receptor surface. Red areas are positively charged, blue are negatively charged and white areas are natural. When the hydrogen bonding property is mapped, the colour indicates the tendency for specific areas of the surface to act hydrogen bind donors (purple) or acceptor (light blue). Areas of the model with no hydrogen bonding activity are coloured white. When the property of hydrophobicity is mapped the surface colour is brown showing the hydrophobic regions in the model. Areas that are not hydrophobic relative to the scale on the panel are white. The QSAR equations is

Activity 1= .98314 - 3.00898* "VDW/3171" +7.97919* "ELE/3783" + 3.83075* "ELE/3445" -2.8716* "VDW/2704"+ 6.72815* "ELE/3483" -2.67628*

The QSAR equation derived was statistically validated. It has a correlation coefficient r^2 as 0.909, significant cross validated correlation coefficient XVX^2 of 0.809 Predicted sum of square (PRESS)* 0.953.

The receptor surface modeling improves our lead compound design and selection. By defining a union volume over one or more aligned compounds and it can account for both solvent accessible receptor regions and regions of the receptor that have not been probed by the collection of active compounds.

Interaction can be measured separately between each compound and a receptor surface model include electrostatic energy, van der walls energy, and intra-molecular strain energy. These interactions can be mapped on to the receptor surface model for qualitative inspection.

Compounds within the receptor surface model can be edited to minimize repulsive interactions and to maximize attractive interactions calculated interaction and strain energies can also be used as descriptors in the construction of structure – activity relationship using QSAR. The shape properties can be similarly measured, manipulated and analyzed.

IV. Conclusion:

RSA of 3D QSAR study, an analogue-based rational drug design method has been used in the optimization of 2-substituted Amine Pyrido [2, 3-d] Pyrimidin - 7-yl-ureas. The method produces a reasonably good model based on which biological activities for the new molecules can be carried out.

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References

[1]. Afsah, S.A.; Ahmad, J Qsar Studies of Some Benzyl-1 (Benzene Sulphonamido) Methyl Phenyl Alkanoic Acid Derivatives as Thromboxane A2 Receptor Antagonists, Malaysian J. Chem 2010, 12, 1, 033-039.
[2]. Levitzki A; Gazit.A.Tyrosine Kinase Inhibition : An Approach to Drug Development Science. 1995, 267, 1782-1788.
[3]. Traxler. P.M. Protein Tyosine Kinase Inhibitors in Cancer Tratement Expert Opin. Ther. Pat 1997, 7, 571-588.
[4]. Saltiel. A.R. Signal Transduction Pathways as Drug Targets, Sci. Am. Sci. Med. 1996, 2, 58-67.
[5]. Shawver L.K. Lipson K.E. Fong A.T. Mc Mohan, G : Plowman G.D. Strawn ,L.M. Receptor Tyrosine Kinases as Target for inhibition of Angiogenesis Drug Discovery Today. 1997, 2, 50-63.
[6]. Folkman. J. Angiogenesis in cancer vascular Rheumatoid and other Diseases Nat. Med. 1995, 1, 27-31.
[7]. Mttsson E : Clowes A.W. Current Concept in Restenosis following Ballon Angioplasty, Trends Cardiovasc. Med 1995, 5, 200-204.
[8]. Shaw ,L.A,: Rudin, M : Cook N.S. Pharmacological inhibition of Restenosis : Learning from Experience Trends Pharm. Sci 1995, 16, 401-404.
[9]. Raines, E.W : Ross, R. Multiple Growth Factors are Associated with Lesions of Atherosclerosis : Specificity or Redunacy ? Bio Eassays, 1996, 18, 271—282.
[10]. Bridges , A.J The Epidermal Growth Factor Receptor family of Tyrosine Kinases and Cancer : can an Atypical examplar be a sound Therapeutic Target? Curr Med. Chem. 1996, 3, 167-194.
[11]. Dahring T. K. : Lu, G.H. : Hamby J. M. : Batley, B.L.: Kraker , A. J. : Panek, R.L. Inhibition of growth Factor- Mediated Tyrosine Phosphorylation in Vascular smooth Muscle by PD 089828, a New Synthetic Protein Tyrosine Kinase, Inhibitor. J. Pharmacol. Exp. Ther. 1997, 281, 1446-1456.
[12]. Hamby. J.M.: Connoly C.J.C.: Schroeder, M.C.: Winters, R.T.: Showalter, H.D.H, et. al Structure Activity Relationships for a Novel series of Pyrido [2, 3-d] Pyrimidine Tyrosine Kinase Inhibitor, J. Med Chem. 1997, 40, 2296-23-3.
[13]. Woolfrey, J.R. : Watson,G.S. The use of Computational Methods in the Discovery and Design of Kinase Inhibitors Curr. Pharma. Design, 2002, 8. 1527-1545.

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