ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Molecular Docking Studies On Antiviral Activity Of Novel Pyrazole Contain Hydrazineyl Pyrimidine Derivatives.

Rashmi T, Naveen K Mathew *, Pramila T, Swaroopa HM, and Muvendan C.

Department Of Pharmaceutical Chemistry, Bharathi College Of Pharmacy, Bharathinagar-571422, Maddur Taluk, Mandya District, Karnataka, India.

ABSRACT

This molecular docking study used target receptor associated with antiviral activity. The binding energies of mentioned analogs, further clarify the design of potential drug candidates against Pokeweed Antiviral Protein (PDB ID: 1J1S). Among the docked ligands, novel pyrazole contain hydrazineyl pyrimidine derivatives 1b, 1c, 1e reported lowest binding energy of -9 Kcal/mol. Binding energy of all the compounds ranged from -9 (compound 1a) to -8.4 (compound 1o). Compounds 1a, 1b, 1c, 1e, 1f, 1n possess two hydrogen bonds each with ARG: 178 and GLY: 208 amino acids. The confirmation with lowest binding energy was displayed as the best binding energy.

Keywords: Molecular docking, Antiviral activity, Pokeweed antiviral protein, Novel pyrazole contain hydrazineyl pyrimidine compounds.

https://doi.org/10.33887/rjpbcs/2022.13.4.4

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Molecular docking is a kind of computational modeling, which facilitates the prediction of preferred binding orientation of one molecule (eg. ligand) to another (eg. Receptor), when both interact each other in order to form a stable complex [1].

Scientists around the globe are actively searching for potent antiviral drugs to treat and cure all kind of diseases caused by various viral infections. The main strategies to develop such antivirals have been focused on small virus-specific molecules that hinder a precise mechanism in the viral cycle, over time, and on neutralizing antibodies, i.e. Vaccines or monoclonal antibodies. Those strategies have been successful so far; however, they are not without limitations. Indeed, the small virus-specific molecules lead to mutated forms of the viruses, over time, that are resistant to treatments, and the development of neutralizing antibodies is a lengthy and costly process. In order to develop virus-specific vaccines or monoclonal antibodies, an average of five to ten years is required [2].

Pokeweed antiviral proteins (PAPs) 1 are members of the type I ribosome inactivating proteins (RIPs). Many plants produce different RIPs, which can catalytically inactivate ribosome and thereby inhibit protein synthesis [3-4]. As is wellknown, most of the RIPs consist of one or two peptide chains, and are, respectively, classified as type I or type II RIPs. The type I RIPs are similar in sequence, and even more in structure, to the active chain of the type II RIPs, such as the ricin in A-chain. All RIPs are RNA N-glycosidases. They are characterized by their ability to cleave the N-glycosidic bond of a specific exposed adenine base on the sarcin-ricin-loop (SRL) of the large rRNA subunit [5].This loop is responsible for the binding of the elongation factor to the ribosome [6]. Depurination of the SRL impairs the binding interaction between SRL and elongation factor, resulting in irreversible inhibition of protein synthesis. Many RIPs are discovered by their ability to inhibit the growth of microbes, such as viruses, bacteria, and fungi. PAPs are also discovered by their ability to inhibit the proliferation of viruses. Now, we know that at various developing stages the different tissues of the plant, P. Americana (pokeweed), synthesize different PAPs. PAP-I was found from spring leaves[7-9], PAP-II from summer leaves, PAP-S from seeds , and PAP-R from roots [10].Other isozymes are also found in cell culture (PAP-C), or resulted from genomic clones (a-PAP) [11].Most recently two is forms, PAP-S1 and S2, from seeds were identified [12].
Study on antiviral activity of novel pyrazole contains hydrazinyl pyrimidine derivatives by using Insilco molecular tool. Several compounds bearing pyrazole moiety are acknowledged to exhibit anti-inflammatory [13], antidepressant [14], anticancer [15], antiobesity [16], anticonvulsant [17], antibacterial [18] and antiviral [19-20] activities. Pyrimidine derivatives also exert anticonvulsant, antimicrobial, antiviral [21-24], antibiotic, antitubercular activities. Hydrazinyl derivatives exhibit antiviral activity [25-34]. Therefore, the present investigation comprises molecular docking of some novel pyrazole contain hydrazinyl pyrimidine derivatives and to evaluate their anti-viral activity.

The current study incorporates the use of Insilco molecular modeling tool AutoDock Vina. The receptor grid that was generated will helps in locating the protein active site and preparing the grid for the ligands to be docked in the shape and properties of the receptor are represented on a grid by many different sets of fields that provide progressively more precise scoring of the ligand poses. The binding energies of mentioned analogs, further clarify the design of potential drug candidates against Pokeweed Antiviral Protein.

MATERIALS AND METHODS

Dataset ligands and Ligand Optimization

The 2Dstructures (figure1) of 15 compounds were generated from the ACD/Chemsketch Software (Table1). The generated ligands cleaned and performed 3D optimization then saved in the MDL Molfile format. The ligands were then converted to a PDBQT file format using the Open Babel chemistry toolbox.

Molecular Docking Studies

The three-dimensional structure of Pokeweed Antiviral Protein (figure2) (PDB ID: 1J1S) was downloaded from Brook heavenProtein Data Bank (https://www.rcsb.org) and saved as a Brookhaven protein data bank file and the structure was optimized by deleting unbound water molecules which are

over 1 Å, adding hydrogen atoms to satisfy the valences, adding missing amino acids to stabilize side chains and energy of the whole structure was minimized using AUTODOCK suite of MGL Tools.

Auto dockVina was used for molecular docking studies. A grid was generated around the co-crystallized ligand. The co-ordinates (x = 32.63, y =26.25, z = 16.59) were generated with the help of MGL Tools & Pharmit: interactive exploration of chemical space (http://pharmit.csb.pitt.edu/). Prepared pdbqt files for both target & ligands. Created in house batch file of ligands & amp; target and docking performed in the absence of water molecules for all 15 molecules. The molecules were analyzed after docking and visualized in the discovery studio for the interactions with the active site amino acids.

Binding interactions and efficiency of the binding were calculated in terms of dock Score, which is a combination of hydrophilic, hydrophobic, metal binding groups, Van der Waals energy, freezing rotatable bonds and polar interactions with receptor.

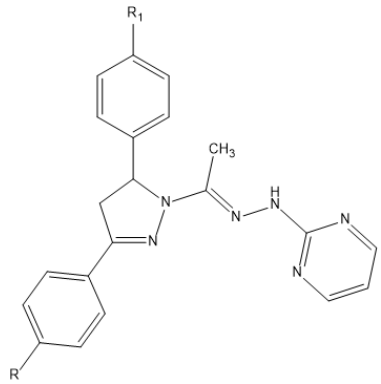


Figure 1: pyrazole contain hydrazineyl pyrimidine derivatives (1)

SL NO	COMPOUND NO	R_1	R
1	1a	H	H
2	1b	CH_3	H
3	1c	Cl	H
4	1d	NO_2	H
5	1e	F	H
6	1f	OCH_3	H
7	1g	OCH_3	CH_3
8	1h	F	CH_3
9	1i	NO_2	CH_3
10	1j	Cl	CH_3
11	1k	CH_3	CH_3
12	1l	H	CH_3
13	1m	$N(CH_3)_2$	CH_3
14	1n	$N(CH_3)_2$	H
15	1o	NHC_2H_5	CH_3

Table 1: ligands used in the study

RESULTS AND DISCUSSION

Molecular docking studies were performed in order to find the possible protein ligand interactions of the dataset ligands. The potential active site amino acids of 1JIS complex were predicted using CASTp. The target protein and inhibitors were geometrically optimized. All the 15 compounds were docked against active site of target protein using AUTODOCK VINA. Additionally, these also assisted in identifying the conformational changes of the ligand in the protein environment. About 100 different protein-ligand complex conformations for each docked complex were generated through AUTODOCK suite of MGL Tools, the confirmation with lowest binding energy was displayed as the best binding

ISSN: 0975-8585

energy. Binding energy of the dataset ligands were shown in Table 2 along with the interaction amino acids and number of amino acids.

Table 2: Binding Energy, No of H-bonds, Interacting amino acids, H-bond lengths of ligand data set.

Compound No	Binding Energy (Kcal/mol)	No of H-bonds	Interacting amino acids	H-bond lengths (Å)
1a	-8.9	2	ARG:178, GLY: 208	2.66, 2.43
1b	-9	2	ARG:178, GLY: 208	2.67, 2.43
1c	-9	2	ARG:178, GLY: 208	2.66, 2.43
1d	-8.5	1	GLY: 208	2.81
1e	-9	2	ARG:178, GLY: 208	2.67, 2.43
1f	-8.8	2	ARG:178, GLY: 208	2.59 2.43
1g	-8.3	1	LYS:209	2.47
1h	-8.7	1	LYS:209	2.50
1i	-8	1	LYS:209	2.49
1j	-8.7	1	LYS:209	2.48
1k	-8.7	1	LYS:209	2.49
5l	-8.6	1	GLY: 208	2.51
1m	-8.4	1	GLY: 208	2.48
1n	-8.9	2	ARG:178, GLY: 208	2.67, 2.43
1o	-8	1	GLY: 208	2.48

Among the docked ligands, compound 1b, 1c, 1e reported lowest binding energy of -9 Kcal/mol. Binding energy of all the compounds ranged from -9 (compound 1a) to -8.4 (compound 1o). Compounds 1a, 1b, 1c, 1e, 1f, 1n possess two hydrogen bonds each with ARG:178 and GLY:208 amino acids. Compounds 1d, 1g, 1h, 1i, 1j, 1k, 1l, 1m, 1o had one hydrogen bond interaction with LYS: 209 residue.Vanderwalls interactions were observed with GLU:205 and Leu: 121 residues in compounds 1a.

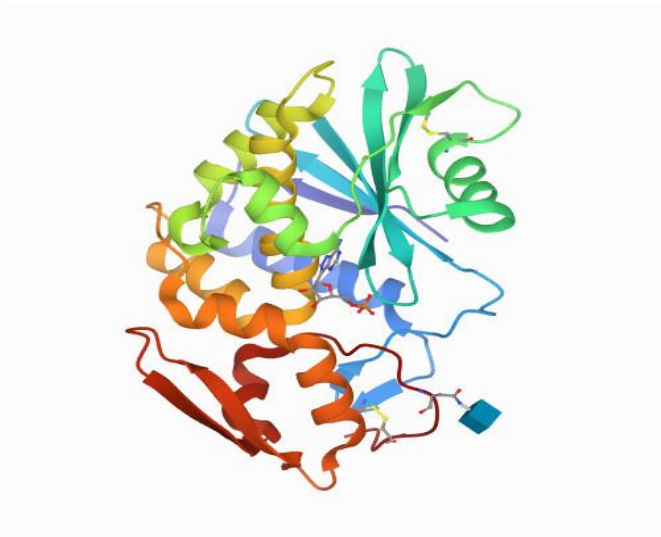
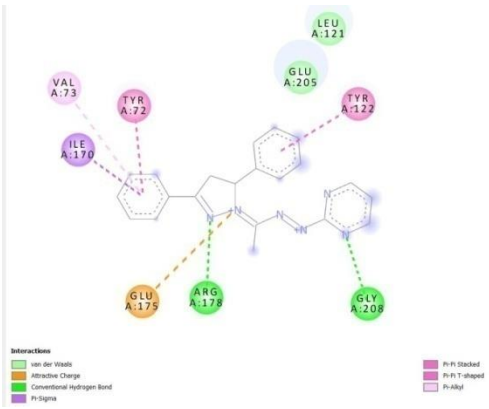
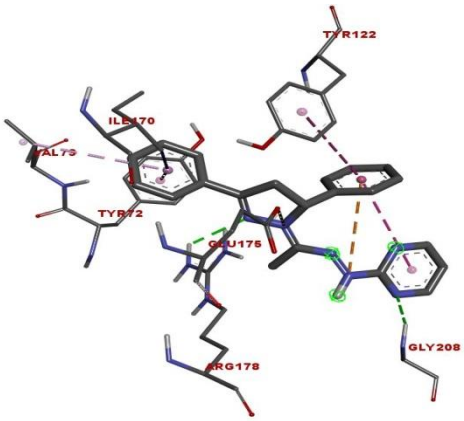


Figure 2: 3D structure of Pokeweed Antiviral Protein (PDB ID: 1J1S)

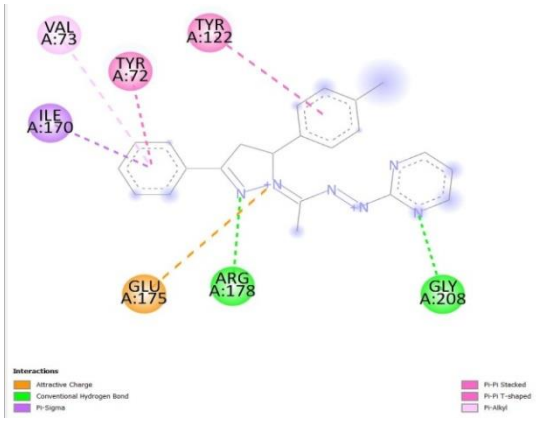
ISSN: 0975-8585



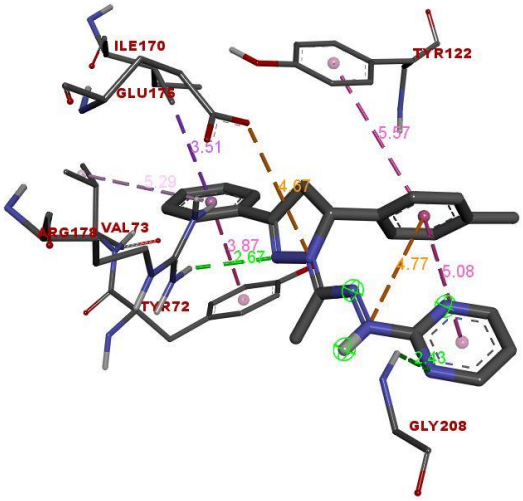
1a-2D



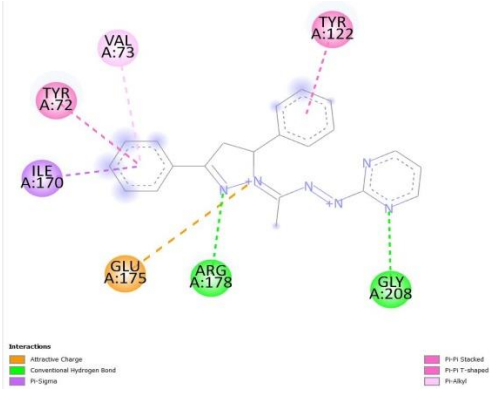
1a-3D



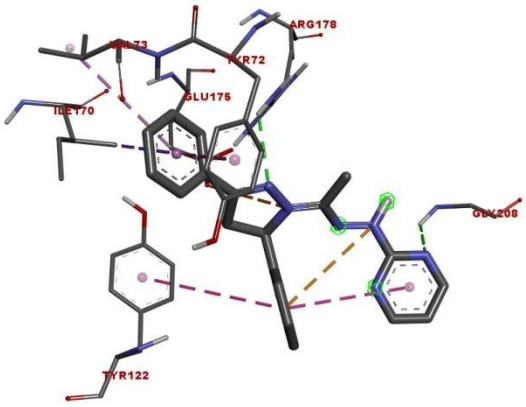
1b-2D



1b-3D

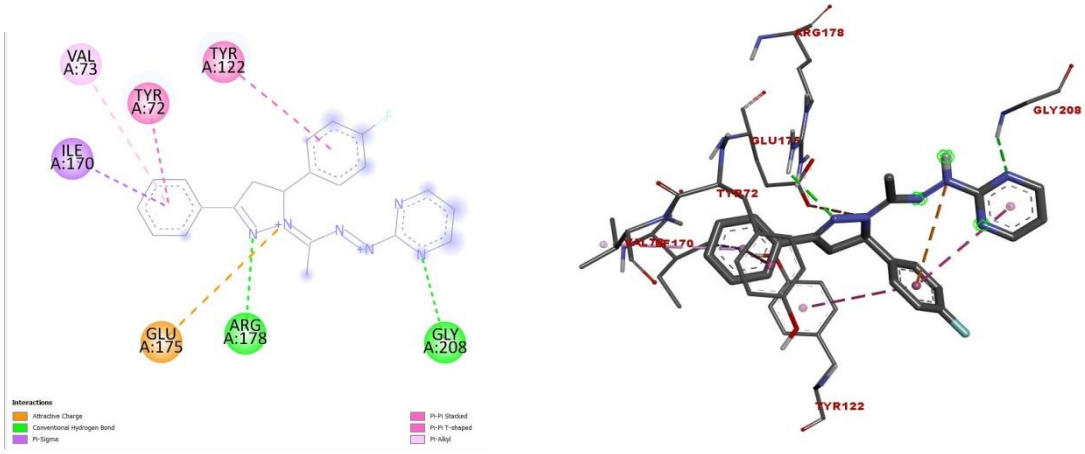


1c-2D

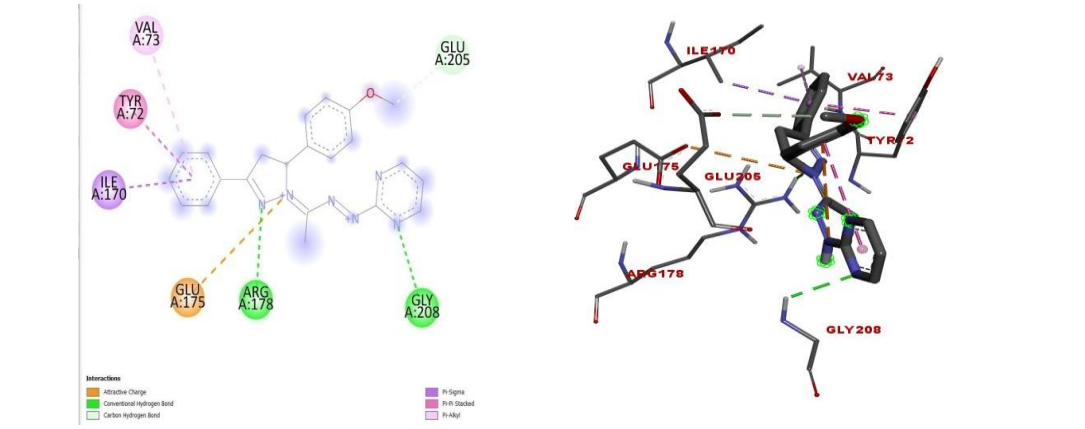


1c-3D

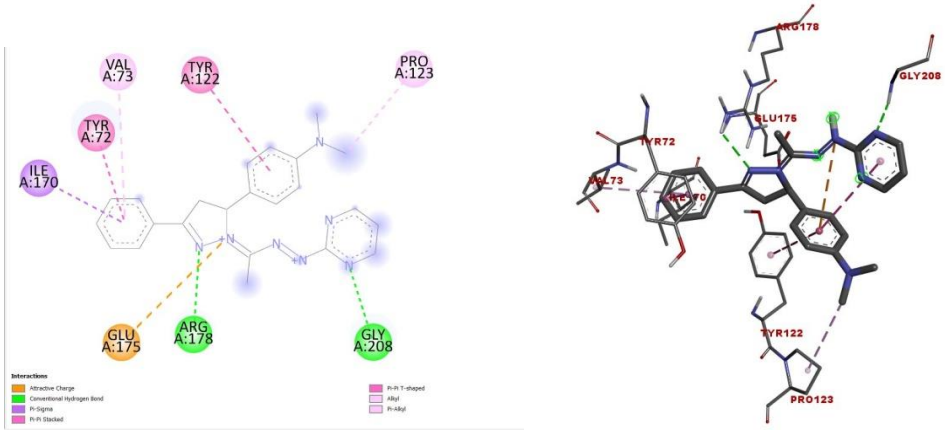
ISSN: 0975-8585



1e-2D **1e-3D**



1f-2D **1f-3D**



1n-2D **1n-3D**

Figure3: 2D and 3D interaction of ligand with target protein according to lowest binding energy of compounds 1a (-8.9), 1b (-9), 1c (-9), 1e (-9), 1f (-8.8) and 1n (-8.9)

CONCLUSION

Among the docked ligands, compound 1a, 1b, 1c, 1e, 1f and 1n reported lowest binding energy and the target receptor associated with good antiviral activity.

ISSN: 0975-8585

REFERENCES

[1] Mukesh B, Rakesh K. IJRAP 2011;2:1746-51.
[2] Geraghty RJ, Aliota MT, Bonnac LF. Viruses 2021;13(4):667-69.
[3] Barbieri L, Battelli MG, Stirpe F. 1993;21:237-82.
[4] Stirpe F, Barbieri L, Battelli MG, Soria M, Lappi DA. Biotechnol 1992;10(4):405-12.
[5] Endo Y, Glück A, Wool IG. J Mol Biol 1991;221(1):193-207.
[6] Correll CC, Munishkin A, Chan YL, Ren Z, Wool IG, Steitz TA. Proc Nat Acad Sci 1998;95(23):13436-41.
[7] Barbieri L, Aron GM, Irvin JD, Stirpe F. Biochem J 1982;203(1):55-9.
[8] Irvin JD, Kelly T, Robertus JD. Arch Biochem Biophy 1980;200(2):418-25.
[9] Irvin JD. Arch Biochem Biophy 1975;169(2):522-8.
[10] Bolognesi A, Barbieri L, Abbondanza A, Falasca AI, Carnicelli D, Battelli MG, Stirpe F. 1990;1087(3):293-302.
[11] Kataoka J, Habuka N, Masuta C, Miyano M, Koiwai A. Plant Mol Biol 1992;(5):879-86.
[12] Honjo E, Dong D, Motoshima H, Watanabe K. The J Biochem 2002;131(2):225-31.
[13] El-Sayed MA, Abdel-Aziz NI, Abdel-Aziz AA, El-Azab AS, ElTahir KE. Bioorg Med Chem 2012;20(10):3306-09.
[14] Secci D, Bolasco A, Chimenti P, Carradori S. Curr Med Chem 2011;18(33):5114-19.
[15] Shamroukh AH, Rashad AE, Abdel-Megeid RE, Ali HS, Ali MM. Archive der Pharmazie 2014,228-34.
[16] Srivastava BK, Soni R, Patel JZ, Joharapurkar A, Sadhwani N, Kshirsagar S, Mishra B, Takale V, Gupta S, Pandya P, Kapadnis P, Solanki M, Patel H, Mitra P, Jain MR, Patel PR. Bioorg Med Chem Lett 2009;19(9): 2546-53.
[17] Secci D, Bolasco A, Chimenti P, Carradori S. Curr Med Chem 2011;18(33):5114-19.
[18] Desai NC, Satodiya HM, Kotadiya GM, Vaghani HV. Archive der Pharmazie.2014, 347(7), 523-32.
[19] Ouyang G, Cai XJ, Chen Z, Song BA, Bhadury PS, Yang S, Jin LH, Xue W, Hu DY, Zeng M. J Agr Food Chem 2008;56 (21):10160-83.
[20] el-Sabbagh OI, Baraka MM, Ibrahim SM, Pannecouque C, Andrei G, Snoeck R, Balzarini J, Rashad AA. European J Med Chem 2009; 44(9): 3746-53.
[21] Piotrowska DG, Andrei G, Schols D, Snoeck R, Łysakowska M. European J Med Chem 2017;126(6):84-100.
[22] Hwang JY, Windisch MP, Jo S, Kim K, Kong S, Kim HC, Kim S, Kim H, Lee ME, Kim Y, Choi J. Bioorg Med Chem Lett 2012 ;22(24):7297-301.
[23] Rashad AE, Hegab MI, Abdel-Megeid RE, Micky JA, Abdel-Megeid FM. Bioorg Med Chem 2008;16(15):7102-6.
[24] Wang YY, Xu FZ, Zhu YY, Song B, Luo D, Yu G, Chen S, Xue W, Wu J. Bioorg Med Chem Lett 2018;28(17):2979-84.
[25] Dawood KM, Abdel-Gawad H, Mohamed HA, Badria FA. Med Chem Res 2011;20(7): 912-19.
[26] Fathalla OA, Zaghary WA, Radwan HH, Awad SM, Mohamed MS. Archive der Pharmazie. 2002; 25(3):258-69.
[27] El-Sabbagh OI, Rady HM. European J Med Chem 2009; 44:3680-86.
[28] El-Sayed WA, El-Essawy FA, Ali OM, Nasr BS, Abdalla MM, Abdel-Rahman AAH. Monatshefte fur Chemie 2010;14(1):1021–28.
[29] Rashad AE, Mohamed MS, Zaki MEA, Fatahala SS. Archive der Pharmazie Life Science 2006;33(4);664-69.
[30] Zemtsova MN, Zimichev AV, Trakhtenberg PL, Belenkaya RS, Boreko EI. Pharma Chem J 2008; 42(10): 21-23.
[31] Jin Y, Tan Z, He M, Tian B, Tang S, Hewlett I, Yang M. Bioorganic & medicinal chemistry Bioorg Med Chem Lett 2010;18(7); 2135-40.
[32] Zhan P Liu H, Liu X, Wang Y, Pannecouque C, Witvrouw M, Clercq EDe. Bioorg Med Chem Lett 2010;19(5): 652-63.
[33] Tian B, He M, Tang S, Hewlett I, Tan Z, Jiebo Li, Jin Y, Yang M. Bioorg Med Chem Lett 2009;19(8): 2162-67.
[34] Vicini P, Incerti M, Colla PL, Loddo R. 2009;44:1801-07.