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MOLECULAR MODELING AND DRUG DISCOVERY OF POTENTIAL INHIBITORS FOR ANTICANCER TARGET GENE MELK (MATERNAL EMBRYONIC LEUCINE ZIPPER KINASE)

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ABSTRACT
Maternal embryonic leucine zipper kinase (MELK), a member of the AMP serine/threonine kinase family, exhibits multiple features consistent with the potential utility of this gene as an anticancer target. Reports show that MELK functions as a cancer-specific protein kinase, and that down-regulation of MELK results in growth suppression of breast cancer cells. There are many inhibitors which bind to kinases and are in clinical trials too. In our study we have taken a library of different inhibitors and docked those using GLIDE Induced Fit. From docking result we can conclude that Syk inhibitor II, Rho kinase inhibitor IV, p38 MAP Kinase Inhibitor III, HA 1004, Dihydrochloride and IKK -2 inhibitor VI have good binding affinity towards MELK and may have anticancer activity.

KEYWORDS: Maternal embryonic leucine zipper kinase (MELK), Homology Modeling, Schrodinger Glide, Maestro, Bioinformatics.

INTRODUCTION

Today's research tools and experiments help scientists zoom in ever closer on the mechanics of many kinds of cancer. In the past, clinicians defined most cancers by phenotype, but now molecular signatures identify many cancers. The work on cancer markers also reveals some of the steps that initiate and promote this diverse family of diseases. As a result, some of today's cancer researchers believe that targeted therapeutics--aiming attacks at defective molecules--turning in its development. As a result, new tools that compare the activity of these genes in normal and mutated states could point to new ways to stop the division, or kill the cancer[1].

Microarray, protein array and analysis of cancer pathways show a number of interrelated markers responsible for carcinogenesis. Since analyses using those technologies often yield confusing results due to accidental errors, their results must be confirmed by real-time PCR, western blotting, and immunohistochemical staining[2]. Many genes have been detected with differential expression in malignant tumors, compared to normal tissues. Those candidate molecular markers play various roles in the cell, and the expression status suggests the oncogenetic process. In this way there are several genes which are asscoiated with cancer, one among them is Maternal Embryonic Leucine Zipper Kinase (MELK).

In this study the protein of interest MELK, a member of AMP serine/theronine kinase family which is implicated in stem cell renewal, cell cycle renewal, cell cycle progression and pre mRNA splicing[3]. Even the smallest MELK fragment is catalytically active comprises the N terminal catalytic domain. Microarray analysis of multiple human tumor samples and cell lines suggests that MELK expression is frequently elevated in cancer relative to normal. Due to its multiple active features interlocking MELK with drug screening provides new clues related to the relevant hits and drug leads[4]. With the advancement in the field of computer science and technology, nowadays it is becoming more interesting and time saving to study and screen these hits employing the powerful concepts of bioinformatics and chemonformatics.

In Silico modeling is a multidisciplinary method integrating mathematical models with experimental and clinical data[5,6]. Comparative and homology modeling of protein structure is most widely used approach to predict the 3D structure of the target protein based on known protein homologues. Docking is a method which predicts the preferred orientation of one molecule to the second when bound to each other to form a stable complex[7]. The prediction of putative protein ligand interaction studied by computational docking methods is of increasing importance in the field of structure based drug design[8].

Therefore, this study is aimed at modeling the structure of the target protein (MELK) using prime module of Schrodinger V.2010[9,10] and docking by Glide tool (Schrodinger 2010)[11,12] to identify inhibitors for MELK in pursue of finding and designing potential inhibitors for this target protein. The results obtained from this study would be useful in both understanding the inhibitory mode of MELK as well as in rapidly and accurately predicting the activities of newly designed inhibitors on the basis of docking scores. These models also provide some beneficial clues in structural modification for designing new inhibitors for the treatment of cancer with much higher inhibitory activities against MELK.

MATERIALS AND METHODS

Target Selection & Modelling of MELK

Sequence of catalytic domain of MELK (E.C:2.7.11.1) was obtained from SWISSPROT database (ID Code: Q14680). The search for template sequence was performed using BLASTp program and the search was performed in the PDB database. This structure was modelled based on the template sequence of the chain A of Kinase And Ubiquitin-Associated Domains Of Mark3PAR-1 holding the PDB ID 2QNJ. The structure was modeled with the help of commercial software SCHRÖDINGER Prime module (Schrödinger, 2010). The modeled structure was imported and corrections were carried out by Protein Preparation wizard software, where hydrogens were added automatically and refinement of the structure was also done. Energy minimization was done by using OPLS_AA force field and refinement was carried out until average mean square deviation of the non hydrogen atoms reached 0.3A0 and the resulting optimized structure was used for further studies[13].

Grid Generation

Ligand docking jobs cannot be performed until the receptor grids have been generated. Receptor grid generation requires a “prepared” structure: an all atom structure with appropriate bond orders and formal charges (Schrodinger, LLC). Residues 150- 178 in MELK (T loop) was scaled by vander waal’s radii of 1.0A0 with partial atomic charge less than 0.25A0, gird was generated around these residues and enclosed by a box at the centeroid of selected residues.

Ligand Preparation

Ligands were downloaded from EMD. There are three inhibitor libraries such as, Library I: Tyrosine & cAMP dependent protein kinase/protein kinase G /protein kinase C. Inhibitor Library II: cMGC –cyclin dependent,mitogen activated &Glycogen synthase

kinases. Inhibitor Library III: cMGC, CaMK- Ca2+/Calmodulin dependent kinase, STE – Ser/Thr Protein Kinase.

The .sdf files of these inhibitors were downloaded and prepared them using the Ligprep module of the Maestro software. The ligands did not have correct bond orders and bond angles were subjected to a full minimization with OPLS_2005, followed by assigning appropriate ionization state of each ligand by using the "ionizer" option.

Ligand Docking and Scoring

Prepared ligand and receptor were used as the initial coordinates for docking purposes. We have used MELK as the target receptor. The principle ligand can be docked by two methods: (1) Assuming that the ligand is flexible and the receptor is rigid and (2) Assuming that the ligand is rigid and the receptor is flexible. So here we have used both strategies of ligand docking. In both processes we have used GLIDE for docking .During the first docking process, the receptor was treated as fixed while ligand was flexible. After docking, the results were used for binding energy calculations and docking scores.

RESULTS AND DISCUSSION

Comparative Modeling

The protein sequence of MELK consists of 325 amino acids (ID Code: Q14680) was obtained from Swiss Prot and modeled using Prime (Schrodinger 2010). The best template was selected based on the percentage of identity, similarity and query coverage with BLAST programme[14,15]. Prime calculates alignments using a combination of sequence and secondary structure information. Structures are built using atom positions from the aligned portions of the template(s), taking solvent, ligand, force field, and other contributions into account via a series of algorithms. Briefly, the OPLS2000 all-atom force field is used for energy scoring of proteins; the OPLS2001 force field for ligands and other non-amino acid residues, a Surface Generalized Born (SGB) continuum solvation model, is used for treating solvation effects; and side chain rotomer and backbone dihedral libraries derived from PDB non-redundant structures are used for building backbone and side chains. Portions of the query sequence that do not align to the template, such as loops, are built using an ab initio procedure that incorporates solvation[16].

The modeled MELK protein was corrected by protein preparation wizard of Schrodinger. It would automatically add missing hydrogen atoms, correct metal ionization states to ensure proper formal charge and force field treatment. Structures that are missing residues near the active site should be repaired by Prime (a Schrodinger's program) and fix the orientation of any disoriented groups i.e. Amide groups of Asn & Gln. Adjust the ionization & tautomerisation state of protein. Optimize the charge state of His residues. The amino acid flips are labeled for easy identification (Fig 1a).

The modeled protein was validated by Ramachandran Plot generated using Ramachandran Server. The plot value was found to be 74.69% in the favored region, 18.75% of the residues lie in additional allowed region and 5.31% in the generously allowed region. Only 1.25% of the residues located in the disallowed region. (Fig 1b). The statistics of nonbonded interactions between different atom types were detected and value of the error function was analyzed by ERRAT. Good high resolution structures generally produce values around 95% or higher. For lower resolutions (2.5 to 3A) the average overall quality factor is around 91%. Here the overall quality of the modeled structure was 85.94% (Fig 1c)[17] .

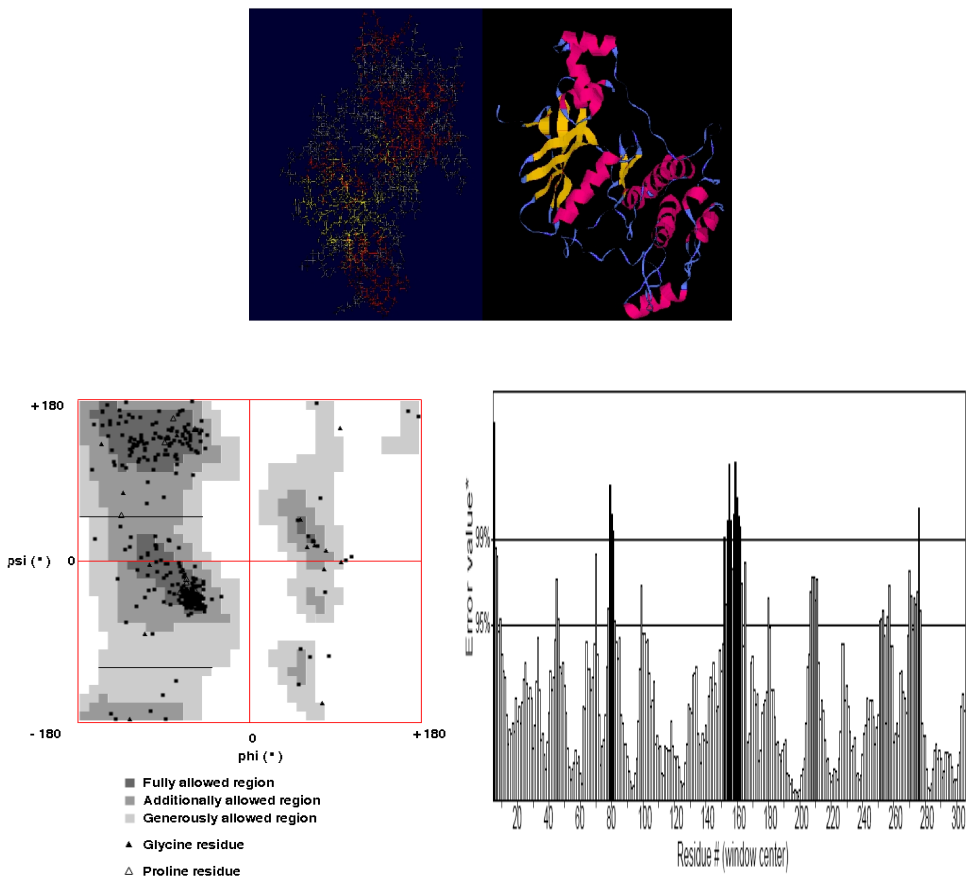

Fig.1: (a) Modelled structure of MELK; (b) Ramachandran plot for modelled structure, (c) ERRAT result depicting overall quality factor of modeled protein.

Table.1 Results of Rigid and flexi docking

Library	Name	Rigid Docking		Flexible Docking	
		Docking score	Glide energy	Docking Score	IFD score
I	Syk Inhibitor II	-7.61056	-47.7673	-8.665	-584.504
	TGF-b RI Kinase Inhibitor	-5.53351	-40.566	-6.916	-579.415
	Rho Kinase Inhibitor IV	-5.51495	-43.3678	-8.511	-577.193
	Rho Kinase Inhibitor III, Rockout	-5.18095	-29.337	-6.505	-574.442
	Akt Inhibitor V, Triciribine	-5.18045	-38.7507	-8.301	-571.99
II	p38 MAP Kinase Inhibitor III	-6.74722	-54.5136	-5.099	-576.604
	GSK-3b Inhibitor XI	-6.23652	-50.3448	-7.316	-573.94
	Tpl2 Kinase Inhibitor	-6.15229	-49.5944	-7.441	-579.024
	SB 202474, Neg Con for p38 MAPK Inhibition Studies	-6.13233	-38.3767	-5.5126	-574.738
	SU9516	-5.58957	-35.3004	-4.969	-574.57
	STO-609	-5.46368	-30.2732	-6.7605	-576.422
	HA 1077, Dihydrochloride Fasudil	-5.46029	-37.9937	-4.859	-573.37
	Aurora Kinase/Cdk Inhibitor	-5.41953	-37.3932	-3.9878	-576.465
III	HA 1004, Dihydrochloride	-6.585459	-40.965977	-8.5215	-579.512
	IKK-2 Inhibitor VI	-5.941003	-40.36515	-4.9539	-571.628
	Rho Kinase Inhibitor	-5.868228	-44.336402	-7.1848	-574.95
	Bisindolylmaleimide V	-5.814733	-45.128181	-6.434	-568.88
	IKK Inhibitor X	-5.79807	-42.248421	-4.764	-570.822
	Cdk2/5 Inhibitor	-5.457889	-40.02811	-6.007	-578.53
	H-8, Dihydrochloride	-5.435378	-37.845612	-6.512	-576.792
	Bisindolylmaleimide III, Hydrochloride	-5.409017	-42.556535	-7.1779	-575.784

Table.2 Lipinski's parameters for drug likeliness

Library	Name	MW	Toxicity Risk Assessment	clogP	logs	Drug-Likeness Prediction	Overall Drug Likeliness Score
I	Syk Inhibitor II	449.256	LR	0.46	-3.59	-9.08	0.42
	TGF-b RI Kinase Inhibitor	272.303	LR	Feb.65	-3.66	-1.36	0.24
	Rho Kinase Inhibitor IV	467.41	LR	0.34	-1.98	Mee.27	0.88
	PKR Inhibitor	268.29	MR	0.8	-2.44	02.Jun	0.72
	Rho Kinase Inhibitor III, Rockout	194.23	LR	Feb.65	-3.43	-1.11	0.54
	Akt Inhibitor V, Triciribine	320.303	MR	-1.39	-2.55		
II	p38 MAP Kinase Inhibitor III	404.503	LR	Mäe.69	-5.15	02.Aug	0.54
	GSK-3b Inhibitor XI	349.343	LR	-1.76	-0.95	Jan.91	0.86
	Tpl2 Kinase Inhibitor	404.827	LR	Mäe.92	-6.04	-6.67	0.24
	SB 202474, Neg Con for p38 MAPK Inhibition Studies	279.336	LR	Feb.95	-3.79	0.24	0.64
	SU9516	241.245	LR	Jan.35	-2.32	Jan.96	0.98
	STO-609	374.346	MR	04.Feb	-6.96	0.32	0.08
	HA 1077, Dihydrochloride Fasudil	364.290	LR	0.92	-1.77	3.0	0.91
	Aurora Kinase/Cdk Inhibitor	435.407	LR	Mäe.38	-6.3	-1.94	0.23
III	HA 1004, Dihydrochloride	366.266	HR	0.21	-2.29	Mäe.26	0.58
	IKK-2 Inhibitor VI	261.299	LR	Jan.86	-4.47	0.86	0.66
	Rho Kinase Inhibitor	319.421	LR	Jan.52	-2.49	Mäe.56	0.89

	Bisindolylmaleimide V	341.362	LR	02.Jan	-3.19	Mäe.78	0.84
	IKK Inhibitor X	322.748	LR	Feb.98	-4.3	Feb.59	0.72
	Cdk2/5 Inhibitor	301.752	LR	0.99	-3.21	Jan.93	0.84
	H-8, Dihydrochloride	338.253	LR	0.43	-1.77	02.Sep	0.9
	Bisindolylmaleimide III, Hydrochloride	420.891	LR	0.89	-3.06	Feb.24	0.48

*LR: Low Risk; MR: Medium Risk; HR: High Risk

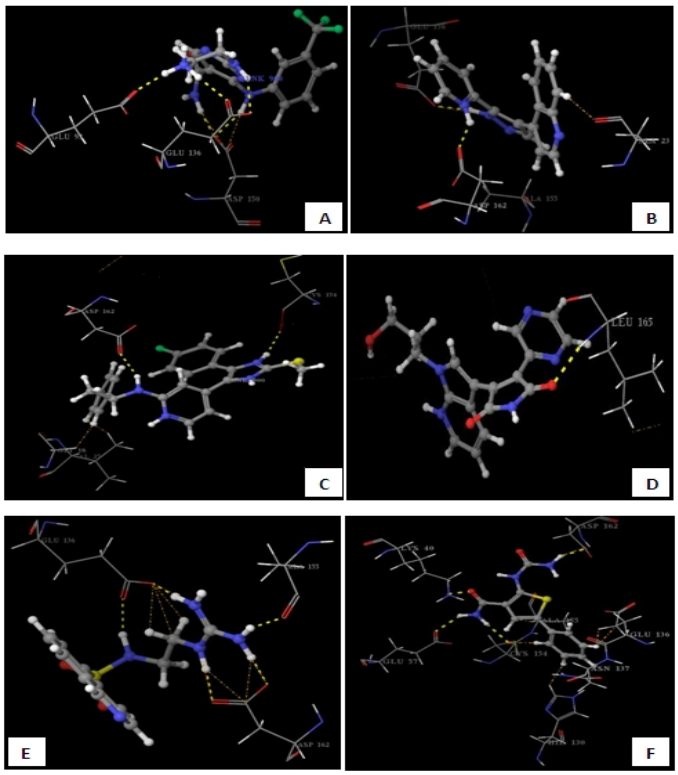

Fig. 2: Glide docking poses after rigid body docking. (A) Syk Inhibitor II; (B) TGFBR2 Inhibitor; (C) P38 MAP Kinase Inhibitor; (D) GSK-3b Inhibitor XI; (E) HA 1004, Dihydrochloride; (F) IKK-2 Inhibitor VI

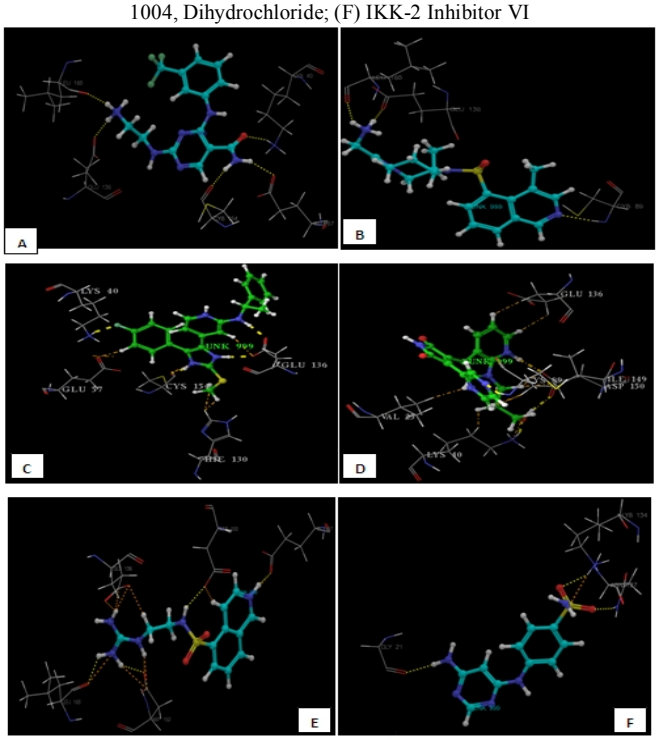

Fig. 3: (A) Syk Inhibitor II; (B) Rho Kinase Inhibitor IV; (C) P38 map kinase inhibitor III; (D) GSK -3b inhibitor ifd; (E) HA 1004, Dihydrochloride; (F) Cdk2/5 Inhibitor

Docking

We have applied the GLIDE docking method to inhibitors to build a binding affinity model for MELK. For the prediction of results mainly four parameters are considered, which G-score, Glide energy, H-bonds and Good van-der-walls interactions. On the basis of these parameters the binding affinity of ligand towards receptor are discussed. The more negative value of G-score indicates good binding affinity of the ligand with receptor. The minimum energy for the formation of complex between ligand and receptor indicates good binding affinity. More H-bonds in the structure shows ligand having good binding mode to receptor. Good vdw interaction means ligand structure having large numbers of bulky group due to which van-der-waals interactions are formed. H-bond interaction also relates to antagonist and agonist action of ligand with receptor.

Out of 96 compounds in Library I (Tyr kinases & AMP dependent protein kinase / protein kinase G /Protein kinase c) six compounds showed binding affinity with MELK and gave docking score (Table 1). The compound Syk inhibitor II was found to have high docking score of -7.61055. It interacts with the modeled protein at sites: Glu 93, Glu 136, Asp 150 (Fig 2).The other ligands which showed good docking score are listed in Table 1.

TGF-b RI Kinase Inhibitor, a cell-permeable diheteroaryl-substituted pyrazole compound that acts as a potent, selective, reversible, and ATP-competitive inhibitor of TGF-β Receptor I kinase. It regulates a wide array of cellular processes including cell differentiation, cellular senescence, immune response, wound healing, and apoptosis. In our study it binds to MELK and forms hydrogen bonds with Asp 162 , Ala 155 and showed covalent interaction with Ala 23 (Fig 2).

Library II contains cyclin dependent, Mitogen activated and glycogen synthase kinase (cMGC) inhibitors (Table 1). In this library p38 map kinase inhibitor showed a highest binding score. With MELK it forms 2 hydrogen bonds (Lys 154,Asp162) and covalent interactions with Val 25,GLY 18.In induced fit docking, the ligands are docked into the binding site of the receptor where the receptor is held rigid and the ligand is free to move. P38 map kinase inhibitor generated different poses with MELK.From docking score and Glide energy we can say that p38 MAP kinase inhibitor III having good binding affinity with MELK and p38 MAP kinase inhibitor III may develop as a drug that target MELK.

GSK-3b Inhibitor XI is a cell-permeable azaindolylmaleimide compound that acts as a potent, specific, and ATP-competitive inhibitor of GSK-3β.From Glide score & energy we can say that it is having good binding affinity towards MELK.Studies showed that GSK-3b inhibitors lead to decreased cancer cell proliferation and survival via negative regulation of NF-jB activity, p53-dependent apoptosis, and enhancing the TRAIL-induced cell death.[18 - 20].

Library III contains cMGC, Ca2+/Calmodulin dependent kinase (CaMK) ,Ser/Thr Protein Kinase (STE) inhibitors, in these inhibitors HA1004,Dihydrocholoride showed a high docking score. It is a cell permeable and ATP competitive inhibitor of protein kinase A. It interacts with Asp162, Glu136 &Ala155.

Numerous studies showed that IKK-2 is an important regulator of the nuclear factor-κB (NF-κB) which has been implicated in survival, proliferation and apoptosis resistance of lymphoma cells(*). In our study also it showed strong binding with MELK using Hydrogen bond and covalent bond interaction with target. Its glide score is -5.94.

Induced Fit Docking

The results of the induced fit docking are given in Table I, which displays the best docked poses. From the results of the induced fit docking, it is clear that there are some considerable changes in the docking scores and energies of the docked complexes. By comparing the results of flexible receptor docking and rigid receptor docking, we see that there is slight variation in their docking score. The variation in the results may also be explained due to the strategy adopted in induced fit methods[21]. The docked poses are shown in fig. 3.

Finding Drug Likeliness Using Lipinski Drug Filter

To find drug- likeness of inhibitors we used OSIRIS Property Explorer tool. It allows you draw chemical structure of compounds and calculates various drug relevant properties such as Molecular weight, toxicity risk assessment, clogp, solubility logS, drug likeness and drug likeness score. According to prediction, compounds with higher Molecular weights are less likely to be absorbed and therefore to ever reach the place of action. Drugs those have molecular weight below 450 are more promising. In the present study all the inhibitors which show minimum docking score possess low molecular weight (>450). Toxicity risk assessment is an indication about a compound whether it is mutagenic, tumourigenic, irritant effect or it posses any reproductive effect. In our study most of the compounds showed LR except PKR inhibitor, Akt Inhibitor V, Triciribine and STO-609. The logP value of a compound, which is the logarithm of its partition coefficient between n-octanol and water $\log(c_{octanol}/c_{water})$, is a well established measure of the compound's hydrophilicity. Almost all compounds showed values below 5 and it indicates that they have reasonable absorption (Table.2).

CONCLUSION

Thus the *Insilco* method adopted in the present study helped in identifying the inhibitors using Schrodinger software. A comparison of the induced fit and virtual docking gives the role of protein flexibility. It is obvious from the results that a combined method of soft docking and side chain optimization gives better results. From the results and discussion we conclude that Syk inhibitor II, Rho kinase inhibitor IV, p38 MAP Kinase Inhibitor III, HA 1004, Dihydrochloride and IKK -2 inhibitor VI have good docking score. This is open possibility to use and develop these inhibitors to inhibit MELK.

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