COMBINED PEPTIDOMIMETIC AND HIGH THROUGHPUT VIRTUAL SCREENING IDENTIFY NOVEL INHIBITORS OF FASCIN-CATALYZED ACTIN-BUNDLING

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ABSTRACT

Objective: Cancer is a disease of complex and multifactorial etiology characterized by unregulated cell division and metastasis. Metastasis is a biophysical event which involves reorganization of extracellular matrix and changes in actin cytoskeletal dynamics leading to the formation of mechanosensory filopodia and migratory lamellipodia at the leading edge. Although several proteins are involved in the regulation of actin dynamics, the role played by fascin is unique and its expression has been positively correlated with metastatic cancer phenotypes. Methods: Combined Peptidomimetic (pepMMsMIMIC) and high throughput virtual screening on MOE platform have been used to scan for fascin inhibitors. Results: 12 unique aromatic and peptide based compounds have been identified with high affinity for actin-bundling sequence of fascin designated as 29FGKVNASASSLKKK43-H-139 Q-141 S-259 R-383 R-389 based on GBVI/WSA free energy of binding. Conclusions: These 12 compounds are expected to exhibit potent anticancer activities due to their unique interaction with fascin and ultimately are expected to break new frontiers in the treatment of cancer.

Keywords: Fascin, Anticancer, Novel drug, In-silico.

INTRODUCTION

The high morbidity associated with cancer has strong correlation with metastasis [1]. This migration may not be a simple diffusion through plasma or lymph but a complex choreography of biochemical events directed by complex and largely unresolved intracellular and intercellular signaling [2] which dictate cell detachment from primary location and directional migration to secondary tissues [3]. Despite the complexity of the overall process, local actin dynamics-mediated biophysical translocation is clearly observable. This is presented as formation of mechanosensory filopodia and migratory lamellipodia at the leading edge [4]. Against this backdrop, research has intensified into deconstructing actin dynamics in normal and cancer cells while the key regulators are emerging [5] as potential pharmacological targets with high promise as cancer chemotherapy [6,7].

Fascin has received significant attention in recent times as a key regulator of cytoskeletal and filopodial actin dynamics. At the leading edge, filopodia comprises bundles of unipolar, formins-nucleated actin filaments with fascin crosslink [8]. In highly motile cancer cells, increased expression of fascin has been observed [9] thus, presenting as a potential target for cancer chemotherapy. However, migrastatin and its analogues are the only widely available inhibitors of fascin [6-7]. Macrolactone an analogue of migrastatin inhibits metastasis via interaction with β-trefoil-IV residues of fascin which lies proximal to the two actin-binding sites located within β-trefoil domains I-IV [10] [hg 1.1 a, b]. It then becomes imperative to screen the vast majority of chemical library available to find new compounds with the capability of direct and stable interaction with the actin-binding residues of fascin.

In this work, peptidomimetic-based in silico screening for chemical compounds with actin-bundling residues of fascin binding fingerprints were queried with compounds from approximately 17 million conformers developed from approximately 4 million commercially available chemical collection in MM/NSC database using the crystal structure of fascin from the protein-data bank (PDB ID: 3LLP) [11,12,13]. The best 400 compounds were retrieved for high throughput virtual screening and scoring analysis using MOE [Molecular Operating Environment 2011.10] platform [14].

METHODS AND MATERIALS

Retrieval of fascin 3d structures and peptidomimetic virtual screening

The three-dimensional structure of human fascin was retrieved from the Protein Data Bank [ID 3LLP] and uploaded into the pepMMsMIMIC server at http://nms.lifesci.unsw.edu.au/pepMMsMIMIC. The structure is managed using the jmol applet on the server. The residue selected for peptidomimetic query were previously identified as either fascin actin-bundling residues (29FGKVNASASSLKKK43)[5] or proximal to these domain (H-139 Q-141 S-259 R-383 R-389) [8]. The scoring method selected for this analysis is fingerprint-based filtering of shape similarity. A total of 400 unique compounds were retrieved ranked according to their fingerprint similarity which is estimated by weighted similarity index Sw [15].

Docking simulation on MOE platform

Flexible ligand-docking was performed using MOE (molecular operating environment, 2011.10) platform [14]. The 3D of fascin used in pepMMsMIMIC server for peptidomimetic screening was uploaded into the MOE for high throughput virtual screening and poses scoring. Water molecules and other non amino acid component were removed followed by 3D protonation and parameterization using the protein preparation pull-down menu, all the missing atoms, incorrect bond stretch and length were corrected. The LigX menu was used to tether heavy atoms and recheck the parameters before docking. The docking simulation was done using the following protocols: Poses were generated using triangle matcher placement [14]. Receptor + solvent mode was assigned to the receptor while the ligand (site) is defaulted to bind on selected residues including 29FGKVNASASSLKKK43 [5], H-139 Q-141 S-259 R-383 and R-389 [8]. The first scoring was estimated using London dG defined by the equation below:

$$
\Delta G = c + E_{\text{pKa}} + \sum_{i=1}^{n_{\text{bases}}} c_{\text{bases}} f_{\text{bases}} + \sum_{i=1}^{n_{\text{lig}}} c_{\text{lig}} f_{\text{lig}} + \sum_{i=1}^{\text{atoms}} \Delta E_{\text{dG}}
$$

$$
\Delta D_{\text{vap}} = c_{\text{vap}} \sum_{\text{at}} \left( \int_{-\infty}^{\infty} u^{1/2} \text{d}u \right) \left( \int_{-\infty}^{\infty} u^{1/2} \text{d}u \right)
$$
RESULTS

Identification of novel fascin-catalysed actin-bundling inhibitors

pepMMsMIMIC is a web-oriented peptidomimetic compound virtual screening was used to identify 400 unique compounds (data not shown) from the list of 17 million compounds developed from approximately 4 million commercially available chemical collection in MMsINC database using the 3D structure of fascin obtained from the protein databank (3LLP) and fingerprint similarity of H139 Q141 S259 R385 R389 representing the conserved residues proximal to the putative actin-binding site of fascin-1 [8] and 29GFQW/NASASSLKKK43 (fig 1.1 ab) which is the structural motif for the actin bundling activity and fascin regulation via ser39 phosphorylation by PKC [5]. This screening method generates best five lowest-energy conformation using Rotate вер. 1.0 software and subsequently docking these compounds into the pockets of the proteins using defined pharmacophoric features such as the tryptophan, histidine and tyrosine side chains, hydrogen-bond donor/acceptor, positively and negatively ionizable groups, aromatic and hydrophobic features. Finally, the binding is scored in order of their weighted similarity index Sw [10]. To isolate the compounds with exceptional binding affinity for fascin in the 400 compounds retrieved from the pepMMsMIMIC webserver were imported to our MOE database for docking and rescoring. The receptor is prepared by removal of water molecules and extra chain present, followed by protonation and parametrization. The receptor for docking on MOE was defined as receptor-solvent while the site atoms were defined as selected residues similar to the residues used for initial screening. Poses were generated by aligning ligand triplet of atoms on triplet of alpha spheres as described in triangle matcher mode in MOE in each pose generated, the London dG scoring function was first used to estimate the free energy of binding. While forcefield refinement scheme was used which is more accurate than the GridMin but computationally more expensive. Finally, post refinement rescoring was done by GBVI/WSA dG which takes into cognizance of the contribution of cumbolic electrostatic term, solvation electrostatic term, van der Waals contribution and surface weighted by exposure [14,19]. The combination of these methods is highly predicted to yield a robust dataset of compounds exhibiting specific interaction with actin-bundling residues of fascin. Furthermore, we predefined -9.0 kcal/mol as the cutoff binding energy this step ultimately identified 12 of the starting 400 compounds as exhibiting high affinity for the actin-bundling domain of fascin (figure1.0). The free energy of binding and features of the compounds are shown on table 1.0. It must be understood that efforts have been made towards establishing a correlation between the free energy of binding and IC50 of compounds [20]. This mathematical relationship strongly indicates low IC50 values positively correlate with low free energy of binding; we therefore speculate that these compounds would have low IC50 during wet screening experiments.

Deconstructing the fascin-bundling pattern of individual compounds

Taking advantage of the presentation of protein-ligand complex in 2D format available on MOE [17] we provide an information-rich 2D interaction between the actin-bundling domain of fascin and selected compounds [17]. The diagrams well accentuate the hydrogen bonds, contours, solvent exposure, covalent interactions and the contribution of pi-cloud of electrons. The interaction between MMs02455752 and actin-bundling region of fascin is shown in (Fig 2.0). This compound is 6-methoxy-S-chloro 9-amino substituted acridine ring joined by an octane 1,8-diamine chain. The interaction is largely driven by hydrogen bonding interaction between the electron withdrawing effect of chlorine atoms on hydroxyl group hydrogen of ser 409 and carboxyl-amido hydrogen of gl142 and the pi-electron density of acridine heterocyclic ring which interacts with the imidazole cation of his 392 and the e-amino nitrogen of Lys-42. Visibly, the cationic centers of the basic amino acids (histidine-392 and lysine-42) well interact with the electron-rich heteroaromatic aromatic center of acridine thus, accounting for a total of -2.0 kcal/mol of energy while chlorine-mediated hydrogen bond accounts for -2.2 kcal/mol. Although, bis-acridines have been used in the management of cancer, prion accumulation and microbial infections, the underlying mechanisms have been linked to DNA-acridine adduct formation [21]. This study may have provided a unique and new insight into the full complement of bis-acridines anti-cancer bioactivity.

MMs03916843 is a structure on di-p-hydroxy m-methylaminobromobenze linked by glutamidio chain. Hydrogen bonding interaction and pi-electrons are responsible for the stabilization of the interaction. The N-N linkage between the methyl-amino group and the glutamido-nitrogen interacts with glutamate 13 with an energy of -4.1 kcal/mol while the phenyl ring pi-electrons interacts with the cationic center of e-amino group of lysine 460 with energetic value of -0.6 kcal/mol. The flexibility of the carbon- nitrogen bond allows spatial occupation of this compound into the actin-bundling pocket proximal to the reactive residues as shown by the contour scheme (fig 2.1). The MM02455752 structure is built on the depotosing derervative in ZINC database so possibly newly developed without any known bioactivity. However, some alky-haloaryl-derivatized compounds have been identified as antitumour agents with which MMs03916844 has shown a shared structural similarity [22].

Hydrogen-bonding interaction between the partially charged oxygen atom of the oxoacetyl substituent of benzothipene-3-carboxylate and caticonic center of the guanilino group of arg389 is the stabilizing force between MMs-02115720 and fascin (fig 2.2). Although, hydrogen bonding accounts for -6.3 kcal/mol, nitrogen-nitrogen single bond between the hydrazinyl bridge constitute a central flexible diazine unit which may play important role in correctly localizing this compound into similar contour within actin-bundling residues of fascin and may further drive stability of the complex [23]. Similarly, a quantitative structure-activity relationship (QSAR) study has identified benzothiophene derivatives as potent anticancer agents [24] and the mechanism has been linked to histone deacetylase inhibition. In a related study, other groups have identified the anticancer mechanism as due to DNA-binding and topoisomerase I and II inhibition [25].

MMs02455752 is structurally analogous to MMs02455724 but unlike the later, it has 3- methyl substituents on the two acridine rings. As expected, absence of chlorine blocks the contribution of hydrogen bonding but the pi-electron contribution is preserved. The fused acridine heterocyclic aromatic rings proximal to His392 and lys42 donates pi-electron density which spatially interacts with imidazole cationic center histidine 392 and e-amino nitrogen center of lys 42 (fig 2.3). The total energies for this
interaction is -2.1 kcal/mol. As this compound is in the class of bis-acridines, their anti-cancer properties have been previously exploited [21].

MMs02185018 has two substituted 1,3,5-triazin moieties bridged by cyanophenyl group. Although, one of the triazin and its substituents are exposed, the cyanophenyl bridge and the second triazin residues are more buried into the actin-binding domain of fascin. These buried moieties interact with Lys34 and His392 via pi-electron density (fig 2.4). The inflexibility of carbon-carbon bond between triazin C5 and cyanophenyl groups may play significant role on exposing the dimethylbutanoylamino moieties.

MMs02460092 shares similar structures with MMs0245724 and MMs0245893 whose anticancer potencies have been discussed previously. However, the defining features of MMs0246092 include an hexanediamine bridge rather than octane1,8-diamine bridge in the previous molecules (fig 1.0). It also has a unique 3-propoxyl group. The heterocyclic acridine ring proximal to Lys41 interacts with this residue using pi-electron (fig 2.5).

Fig (2.6) shows the interaction between fascin and MMs024089; a di-1,3-dioxoethanold-2-oyl ethoxyethyl derivative of 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane. While the 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane moiety has observable interaction with fascin residues, the isoidone 1,3-dione substitute eventually participate in hydrogen bonding with Arg269. The isoidone rings also offers pi-electrons for interaction with Gly393 and His392 with a total energy of -5.4 kcal/mol. previously, phenyl-isoidone derivatives have been classified as anticancer agents due to their cytotoxicity [26] and in some experiments, chaperone protein Hsp90 inhibition.

MMs03919433 has been previously recognized as collagenase substrate in the quantitative determination of collagenase (Fluka 27637). It is a peptide mimic containing phenyl-Gly-Pro-Gly-Pro-Ala-OH. This structural uniqueness is observed in the recognition and binding pattern with fascin. First, the flexibility of the inter-residue bond allows for packing closely into the actin-bundling domain of fascin with less exposed few exogenous atoms. Secondly, the ligand residues make specific contact with the residues of fascin allowing for establishment of hydrogen bonding interaction with fairly high negative energies (fig 2.7). Specific hydrogen bonding interactions are made with Gln13 (-2.4 kcal/mol), Gly390 (-2.0 kcal/mol) Gln11 (-1.4 kcal/mol) and Arg389 (-1.0 kcal/mol) pi-electron of phenylglycinamide group also interacts with e-amino cation of Lys460 contributing an energy of -0.7 kcal/mol. The use of peptides as novel class of anticancer drugs has been given priority in recent times [27] and MMs03919433 may emerge as the newest in the list.

In (2.8) the interaction between MMs03128586 and fascin is shown. The ligand is built on benzoyloxylphenyl-methylidenhydrazinyl structures joined together by 1,7-heptadiolic moiety. The flexibility of the 1,7-heptadiolic moiety is largely responsible for placement of the two benzoyloxylphenyl-methylidenhydrazinyl groups into the actin-binding domain of fascin with consequent formation of hydrogen bonding interaction between the amido oxygen of heptadiolic moiety and Arg389 which accounts for -3.8 kcal/mol of energy. The anticancer potency of benzyl-benenate the core component of MMs03128586 may not have been reported but its antiparasitic activity is well known [28]. It is also a major composition of the essential oils of Kaempferia rotundula L. and Kaempferiaangustifolia Roscoe rhizomes from Indonesia used as insecticidal ethnopharmaherapeutic agent[29]. MMs0245724 is an isomer of MMs0245724, the only structural difference is the location of the 2-methoxyl substituent on carbon-2 of the acridine ring in the former while it is on carbon-6 in the later. This alteration has very subtle effect on residue recognition and binding of MMs0245724; in that the distance between His393 and the proximal acridine ring is slightly longer (3.96 and 4.62 angstrom) (fig 2.9) compared with MMs0245724 (3.95 and 4.33 angstrom, fig 2.1). It may be oversimplifying to state that this physical restraint is responsible for the loss of chlorine interaction as with sar409 and glu141 as observed for MMs0245724 but it certainly does play responsible for the free energy of binding difference 56.83 kcal/mol (table 1.0).

Fig. 3.0 shows another structural analogue of MMs0245724; in this structure (MMs0242072), 6-chloro group is absent in the acridine ring. The binding of this analogue is principally via pi-electron to His392 and Gly393 with observed weaker free energy of binding to fascin compared to the previous ones.

MMs02374885 is di-1,4-dihydropyrrolo[1,2-α,phenyl-3-carboxylic acid linked together by amino-propyl-methyl amino-propylamine chain. The interaction with actin binding domain of fascin is driven by hydrogen bonding interaction between fascin Glu24 carboxylic acid and pyrrole nitrogen of dihydropyrrol-3-carboxamidate, between carbamidate oxygen of ligand and Arg389 and pi-electron between dihydropyrrol-3-carboxamidate and Lys41(fig 3.1).

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<th>Table 1.0: High affinity fascin binding inhibitors and their corresponding free energies</th>
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<tr>
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dG (GBV/WSA dG)
Fig. 1.0: Collection of 12 compounds with high affinity for actin-bundling domain of fascin.

Fig. 1.1: Fascin-1 3D structure a) shows the different trefoil domains of fascin-1; trefoil-1 (red), trefoil-2 (green), trefoil-3 (blue) and trefoil-4 (yellow) b) cartoon representation of fascin trefoils with side chain depicting actin-bundling residues (**FGFKNASASSLKKK**) and proximal residues H-139 Q-141 S-259 R-383 R-389.

Fig. 2.0 Surface diagram (upper right) and 2D depiction for the interaction of MMs02455724 with fascin actin-bundling residues. (bottom right) The designation of binding residues, interaction type and bond energies.
Fig. 2.1: Surface diagram (upper right) and 2D depiction for the interaction of MM03916843 with fascin actin-bundling residues. (bottom right) The designation of binding residues, interaction type and bond energies.

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<tr>
<td>6-ring</td>
<td>N</td>
<td>p-cation</td>
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<td>-0.6</td>
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Fig. 2.2: Surface diagram (upper right) and 2D depiction for the interaction of MM03115720 with fascin actin-bundling residues. (bottom right) The designation of binding residues, interaction type and bond energies.

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<td>O</td>
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Fig. 2.3: Surface diagram (upper right) and 2D depiction for the interaction of MM02458931 with fascin actin-bundling residues. (bottom right) The designation of binding residues, interaction type and bond energies.

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Fig. 2.4: Surface diagram (upper left) and 2D depiction for the interaction of MMs02185018 with fascin actin-bundling residues. (bottom right) The designation of binding residues, interaction type and bond energies.

Fig. 2.5: Surface diagram (upper right) and 2D depiction for the interaction of MMs02460092 with fascin actin-bundling residues. (bottom right) The designation of binding residues, interaction type and bond energies.

Fig. 2.6: Surface diagram (upper right) and 2D depiction for the interaction of MMs03924089 with fascin actin-bundling residues. (bottom right) The designation of binding residues, interaction type and bond energies.
Fig. 2.7: Surface diagram (upper right) and 2D depiction for the interaction of MM03919433 with fascin actin-bundling residues. (bottom right) The designation of binding residues, interaction type and bond energies.

Fig. 2.8: Surface diagram (upper right) and 2D depiction for the interaction of MM03128586 with fascin actin-bundling residues. (bottom right) The designation of binding residues, interaction type and bond energies.

Fig. 2.9: Surface diagram (upper right) and 2D depiction for the interaction of MM02456592 with fascin actin-bundling residues. (bottom right) The designation of binding residues, interaction type and bond energies.
DISCUSSION

Global cancer epidemiological statistics reveal that cancer is the leading cause of death and second leading cause of death in economically developed and developing countries according to 2008 estimates [30]. This statistics has engendered intensive research into the mechanism of cancer pathogenesis but the more insight we gain into these mechanisms, the more complex it becomes to find a cure to cancer [31]. First, cancer cells share almost similar transduction pathways with normal cells [32,33,34], they become immune evasive phenotypes [35] and develop mechanisms for therapeutic compound efflux through ABC transporters [36] and increased expression of broad-range of detoxifying enzymes [36] thereby eliminating selective toxicity of therapeutic compounds, evading immuno-surveillance mechanisms and de-accumulation of therapeutic compounds. One property that seems restricted to few normal cells but exhibited by all cancer cells and immune cells is migration [31]. Our understanding of this biophysical event has been beneficial to the development of therapeutics agents for cancer management. Migrastatin [7] together with their analogues were developed on the principle of migration inhibition in cancer cells [8]. The atomic details of the interaction between macroketone and fascin target is well understood and the data show that macroketone interacts with β-trefoil IV residues while fascin-mediated actin-bundling principally occurs within β-trefoil I and III [5]. It has been presented that ser39 in the β-trefoil I exists within the spatial crevice of macroketone binding and the protein kinase C-mediated phosphorylation of this serine residue is associated with loss of actin bundling functions [35]. It is logically inconsistent to assume that inhibition of serine39 phosphorylation by protein kinase C (PKC) has significant contribution to macroketone bioactivity as inhibition of phosphorylation will correlate with increased F-actin bundling [9]. The proximity of macroketone binding to the 29- FGKVKNASASLKKK-43 motif may be responsible for actin-bundling inhibitory action [5]. But our data still suggest the presence of glycerol in this groove may further serve to enhance the stability of the interaction as the free energy of binding recorded is relatively high (data not shown).

In contrast to the binding pattern of macroketone, we have targeted the fascin residues involved in actin bundling activity and we have identified 12 compounds out of approximately 17 million compounds available in the MMsINC database exhibiting high affinity to the actin-bundling residues. Out of the 12 compounds, five (5) belongs to the bis-acridine family. Anticancer potency of bis-acridine has been documented [21]. Here, we present fascin...
inhibition as a new mechanism for bis-acridine-anticancer properties different from their adduct formation with DNA [26]. The high affinity of bis-acridine-based compounds to the actin-bundling domains has been shown to involve pi-electron center of their heterocyclic aromatic rings and the cationic surface of fascin-bundling domains which is rich in basic amino acids such as Lys and His residues. Same argument holds for the rest of the compounds as they are derivatives of aromatic or heterocyclic aromatics compounds such as allyloxy-halobenzenes (MMs03916843), benzophenone (MMs03115720), 1, 3, S-triazin-2-yl-5-cyanobenzene (Mms02185018), dioxa-isindole (MMs03924869), benzyl benenate (MMs03128586) and phenylhydroindolenol-gerole (MMs02374885). We also discovered a peptide-based compound used as reagent in qualitative determination of collagenase activity (MMs03919433) this compounds further raises the possibility of peptide based anticancer agent which has been given some considerations in recent times [20].

CONCLUSION
Fascin is widely reputed as a biomarker for metastatic tumour, this is due to increased gene expression and this expression pattern correlates well with cancer migration and worse disease outcome and higher morbidity. Migrastatin and its analogues have been correlated well with cancer migration and worse disease outcome and higher morbidity. Migrastatin and its analogues have been widely used as cancer chemotherapy on the principle of fascin inhibition. We have discovered 12 new classes of compounds with high affinity for the F actin-bundling residues of fascin. These compounds are essentially aromatic in structure forming highly stable complexes from electrostatic interaction between the electron rich pi-cloud of electron on the aromatic moieties and highly cationic centers of actin-bundling residues of fascin contributed by rich lysine and histidine residues. With these new compounds, we expect oncologists and pharmaceutical researchers to explore them as anticancer agents with the ultimate hope that cancer mortalities will be significantly reduced.

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CONCLUSION
Fascin is widely reputed as a biomarker for metastatic tumour, this is due to increased gene expression and this expression pattern correlates well with cancer migration and worse disease outcome and higher morbidity. Migrastatin and its analogues have been correlated well with cancer migration and worse disease outcome and higher morbidity. Migrastatin and its analogues have been widely used as cancer chemotherapy on the principle of fascin inhibition. We have discovered 12 new classes of compounds with high affinity for the F actin-bundling residues of fascin. These compounds are essentially aromatic in structure forming highly stable complexes from electrostatic interaction between the electron rich pi-cloud of electron on the aromatic moieties and highly cationic centers of actin-bundling residues of fascin contributed by rich lysine and histidine residues. With these new compounds, we expect oncologists and pharmaceutical researchers to explore them as anticancer agents with the ultimate hope that cancer mortalities will be significantly reduced.

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