Novel dihydropyrimidine derivatives as potential HDAC inhibitors: in silico study

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Abstract Dihydropyrimidine derivatives possess many biological activities due to presence of pyrimidine ring structure in various nucleic acids, vitamins, coenzymes, uric acid and their derivatives. They have possessed broad spectrum actions like antibacterial, antifungal, antiviral, anticancer and antihypertensive etc. Before synthesis of compounds, it is good to predict biological activity using in silico methods. Here, we have selected some of N (3a–f) and O (4a–f) manich bases of dihydro pyrimidine derivatives emphasized on histone deacetylase 4 (HDAC-4) inhibitions activity. We have used the different software tools like Lipinski’s rule of five; pass online; osiris property explorer and docking studies to predict anti cancer activity. All the selected compounds exhibited potential drug like molecule with anti cancer activity. Among all compound the substitution with methoxy group (3c) exhibited more drugs like property and substation with hydrogen (4a) showed high anti neoplastic activity; whereas substitution with dichloro groups (4e) showed more drug docking scores. These were compared with standard drugs tamoxifen and 5-flourouracil. The approach of predicting anticancer activity using in silico method may be more useful to select and synthesis novel compounds in research as well as in industry.

Keywords Dihydropyrimidines · In Silico · Lipinski’s rule · Pass online · Osiris property explorer · HDAC-4 enzyme

Introduction

In recent years a paradigm shift was observed from normal traditional drug design strategies to the Computer Aided Drug Design (CADD) as potential tool to predict biological activity. To facilitate the discovery of novel therapeutic agents, rational drug design methods in combination with structural biology offer great potential (Dutta et al. 2010). Computational drug discovery is an effective strategy for accelerating and economizing drug discovery and development process. Because of the dramatic increase in the availability of biological information at macro and micro level, the applicability of computational drug discovery has been extended and broadly applied to nearly every stage in the drug discovery and development workflow, including target identification and validation, lead discovery and optimization and preclinical tests. Over the past decades, computational drug discovery methods such as molecular docking, pharmacophore modeling and mapping, de novo design, molecular similarity calculation and sequence-based virtual screening have been greatly improved (Ou-Yang et al. 2012). This move resulted as advances in the fields of pharmacy, biochemistry, molecular biology and cell biology, facilitated by developments in genomics and proteomics are producing a large number of novel biological targets that might be exploited for therapeutic interventions.

Here, we have selected some of novel N (3a–f) and O (4a–f) manich bases of dihydropyrimidine derivatives (Fig. 1) and checked their potential as anti cancer activity using human histone deacetylase (HDAC-4) enzyme inhibition as target site. Literature also revealed that these pyrimidine pharmacophore derivatives are playing a vital role in many biological processes due to ring system being present in nucleic acids, several vitamins, coenzymes, uric acid and other purines (Sahu

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and Siddiqui 2016), and abundant occurrence in nature (Mayer et al. 1999). The synthetic and natural dihydropyrimidine derivatives possessed various biological activities like antimicrobial (El-Sayed et al. 2009; Shah et al. 2010), anti-inflammatory (Nofal et al. 2011; Bahekar and Shinde 2003), anti-malarial (Narayanaswamy et al. 2014), antitubercular (Narayanaswamy et al. 2013), anticonvulsant (Shah et al. 2010), analgesic (Nofal et al. 2011), anticancer (Mayer et al. 1999; Abadi et al. 2009), anti HIV (Giffin et al. 2008), antifungal (Zou et al. 2012), Antihypertensive (Atwal et al. 1991) activities. Here, we have assessed some of N and O mannich bases of dihydropyrimidine derivatives through in silico methods like Lipinski rule, pass online, orisis and docking studies have

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**N-Mannich Bases**

| Code | R₁ | R₂ | Mol.formula |
|------|----|----|-------------|
| 3a   | H  | H  | C₁₉H₁₈N₆O   |
| 3b   | H  | Cl | C₁₉H₁₇ClN₆O |
| 3c   | H  | OCH₃ | C₂₀H₂₀N₆O₂  |
| 3d   | Cl | H  | C₁₉H₁₇ClN₆O |
| 3e   | Cl | Cl | C₁₉H₁₆Cl₂N₆O |
| 3f   | Cl | OCH₃ | C₂₀H₁₉ClN₆O₂ |

**O-Mannich Bases**

| Code | R₁ | R₂ | Mol.formula |
|------|----|----|-------------|
| 4a   | H  | H  | C₁₉H₁₈N₆O   |
| 4b   | H  | Cl | C₁₉H₁₇ClN₆O |
| 4c   | H  | OCH₃ | C₂₀H₂₀N₆O₂  |
| 4d   | Cl | H  | C₁₉H₁₇ClN₆O |
| 4e   | Cl | Cl | C₁₉H₁₆Cl₂N₆O |
| 4f   | Cl | OCH₃ | C₂₀H₁₉ClN₆O₂ |

![Fig. 1 Selected dihydropyrimidine derivatives of N (3a–f) and O (4a–f) mannich base series compounds were represented for in silico biological activity.](image)
been applied and identified and predicted their potency and toxicity scores.

**Some of selected selected dihydropyrimidine derivatives**

Pyrimidine is a basic moiety present in DNA or RNA of several basic structure components, its derivatives of dihydropyrimidines possessed various biological activities (Kumarachari et al. 2016). Before synthesis of compounds it would be better approach to apply available In silico methods to predict probable biological activities. Here, we have selected some of N-Mannich (3a–f) and O-Mannich (4a–f) bases of dihydropyrimidines derivatives have been considered for In Silico studies to know their drug likeness, to predict the biological activity spectrum, to assess toxicity and to identify protein–ligand interactions. These molecule were designed against HDAC inhibition activity through their maldock score has been obtained. These structures were used further to predict the anti cancer activity.

**Methods**

**In silico tools**

*Lipinski’s rule of five*

Lipinski rule of five is help to distinguishing between drug like and nondrug like molecules. It predicts the probability of success or failure of drug likeness of a molecule. If a molecule contains molecular mass less than 500 Da, lipophilicity score less than 5, hydrogen bond donors score less than 5, hydrogen bond acceptors score less than 10 and molar refractivity score between 40 and 130, then it is considered as a drug-like molecule (Lipinski 2004).

**PASS online**

PASS (Prediction of Activity Spectra for Substances) is a software product designed as a tool for evaluating the general biological potential of an organic drug-like molecule. PASS provides simultaneous predictions of many types of biological activity based on the structure of compounds. Thus, PASS can be used to estimate the biological activity profiles for virtual molecules, prior to their chemical synthesis and biological testing (Filimonov et al. 2014). The biological activity spectrum of a chemical compound is the set of different types of biological activity that reflect the results of the compound’s interaction with various biological entities. Biological activity is defined qualitatively (yes/none) suggesting that the biological activity spectrum represents the “intrinsic” property of a substance depending only on its structure and physical–chemical characteristics. Though this may be a generalization, it provides the possibility for combining information from many different sources in the same training set, which is necessary because no one particular publication comprehensively covers all the various facets of the biological action of a compound.

**Osiris property explorer**

Prediction of toxicity, drug likeness and drug score can be done by the computer programmer. OSIRIS provides the basis to avoid the experimental study of potentially harmful substances. In Osiris toxicity risk assessment predicts mutagenicity, tumorogenicity, irritating and reproductive effects. The Osiris property explorer is an integral part of Acetlion’s in-house substance registration system developed by Thomas sander at Acetlion’s pharmaceuticals limited, Switzerland (Molecular Properties Prediction 2017). It lets us draw chemical structures and calculates on-the-fly various

| Table 1 Lipinski five rules applied on some of dihydropyrimidine derivatives |
|----------------------------|-----------|---------|---------|---------|---------|---------|---------|---------|
| Compounds | MF        | MW < 500 | Log P < 5 | MR [40–130] | HBD < 5 | HBA < 10 | PSA < 140 | Violations |
| 3a        | C19H18N6O | 346.3858 | 2.34    | 102.58  | 3 | 4 | 85.94 | 0       |
| 3b        | C19H17ClN6O | 380.831 | 2.95    | 107.38  | 3 | 4 | 85.94 | 0       |
| 3c        | C20H20N6O2 | 376.4118 | 2.18    | 109.04  | 3 | 5 | 95.17 | 0       |
| 3d        | C19H17ClN6O | 380.831 | 2.95    | 107.38  | 3 | 4 | 85.94 | 0       |
| 3e        | C19H16Cl2N6O | 415.276 | 3.55    | 112.19  | 3 | 4 | 85.94 | 0       |
| 3f        | C20H19ClN6O2 | 410.857 | 2.79    | 113.85  | 3 | 5 | 95.17 | 0       |
| 4a        | C19H18N6O | 346.3858 | 3.16    | 102.95  | 3 | 6 | 87.22 | 0       |
| 4b        | C19H17ClN6O | 380.831 | 3.77    | 107.76  | 3 | 6 | 87.22 | 0       |
| 4c        | C20H20N6O2 | 376.4118 | 3.00    | 109.42  | 3 | 7 | 96.45 | 0       |
| 4d        | C19H17ClN6O | 380.831 | 3.77    | 107.76  | 3 | 6 | 87.22 | 0       |
| 4e        | C19H16Cl2N6O | 415.276 | 4.37    | 112.56  | 3 | 6 | 87.22 | 0       |
| 4f        | C20H19ClN6O2 | 410.857 | 3.61    | 114.22  | 3 | 7 | 96.45 | 0       |
| Tamoxifen | C25H27NO  | 357.4880 | 5.91    | 123.83  | 0 | 2 | 12.47 | 1       |

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drug-relevant properties whenever a structure is valid. Prediction results will be valued and color coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption will be shown in red color. Whereas a green color indicates drug-confirm behavior.

Docking studies

Docking studies are useful for the prediction of protein–ligand interactions. The ability of a ligand to bind to a specific protein is related to molecular structure, orientation and conformation. During binding process there are enthalpy and entropy changes in the protein–ligand system, associated with alteration of both intra- and inter-molecular structures of protein and ligand. These conformational changes allow the ligand to bind to the receptor active site in a more stable manner. In general, protein–ligand interactions of pharmaceutical interest principally involve non-covalent interactions, including hydrogen bonds, ionic interactions, hydrophobic interactions, π–π interactions and cation–π interactions.

Results

Lipinski’s rule of five

The Lipinski’s rule of five is used for predicting whether selected and designed compounds have the property of drug like molecule or not. This is based on the selected compound satisfy the five rules of drug remain small (Lipinski et al. 2001), hydrophobic ring system hydrophobic packets on protein surface activity (Bondensgaard et al. 2004; Hajduk et al. 2000), structure homology for biological for endogenous substances (Sangameswaran et al. 1986) and biological activities (DeSimone et al. 2004). However, as per Lipinski’s rule, we have analyzed all selected dihydropyrimidine derivatives (3a–e) and (4a–e) series molecular weight of the compounds were less than < 500 kd and molecular surface activity within the range (40–130), hydrogen bond donor (HBD) capacity < 5, Hydrogen bond acceptor < 10 and polar surface area should be < 140° were desirable to act as drug like molecule. Among all compounds were within the limit, but the standard drug tamoxifen is violated the Lipinski rule with higher log P value that more than > 5. All selected compounds passed the Lipinski’s filters (Table 1), and hence all are considered to be drug-like molecules.
PASS online

The PASS online software generates the pass online scores for selected compounds on basis of online program PASS. Its application of wide varieties pharmacological properties could be confirmed by different experimental studies. Comparative biological activity based on structural formula of the chemical compounds is necessary to obtain PASS prediction at the earliest stage of the Investigation. The structure of the chemical compounds was drowning through ACD lab Chem Skech software, which predicts the possible mechanism of actions as good as biological activities (Filimonov et al. 2014). We have predicted biological activity of N-mannich (3a–f) and O-mannich bases (4a–F). Based on calculated pass online scores of N and O-Mannich bases predicted the anticancer activity. Here, the compounds N mannich (3a–f) possess more antimititic activity, among all compounds compound 3a showed more antimitotic activity with high score with 0.534, whereas Omannich (4a–F) compounds were showed antineoplastic activity.
activity, among all compound 4a showed more activity with 0.669, however, these were less score than selected standard drug tamoxifen estimated as 0.821.

**Osiris property explorer**

Osiris property explorer is use full to calculate the drug relevant property on valid structure (Molecular Properties Prediction 2017). This software predicts mutagenicity and poor intestinal absorption with red colour, where as green colour indicates drug confirms behaviour. It also predicts the ADME toxicity studies (Taj et al. 2011). This OSIRIS property explorer is known estimate harmful substances, mutagenesis and toxicity for the compounds to be tested. Here all the selected compounds were found to be drug like and non toxic candidates by toxicity assessment studies. The cLog P values should be < 5 for better activity. Here, we have analyzed some of dihydropyrimidine (3a–e) and (4a–f)
have shown better activity than standard drug tamoxifen and 5-flouro uracil (Fig. 2).

**Docking studies**

Docking studies were designed to study the hybrid compound formulated to predict the estimated of biological activity based on docking engine of targeted enzymes (Thomsen and Christensen 2006). These were predicted based on pre stored data of more than 200 structurally diverse complexes with known PDB binding activity (Wang et al. 2004). Here we have selected human histone deacetylase 4 (HDAC4) (PDB ID: 4CBT) was employed to identify the HDAC inhibitory potential of the molecules. Molegro virtual docker was used for docking. All the compounds showed more docking score than that of co-crystal ligand and 4e shows the highest score. 3e, 3f, 4a, 4b, 4e, 4e showed significant H-bond interactions whereas tamoxifen showed no hydrogen bond interactions. 4e, 4a showed highest interactions.
In silico pharmacological activity prediction has been increased in pharmaceutical industry and employed number increased to deal with modern molecular modeling (Hughes et al. 2011). It is a process to estimate the biological actions by using available computational based software’s methods provided intricate aspects of molecular recognition (Weigelt 2010). Before design and synthesis of new compounds, it is better to predict the pharmacological properties of final products. Here, we have selected N-mannich (3a–f) and O Mannich (4a–f) dihydropyrimidine derivatives (Fig. 1) by considering their simple synthetic possibilities and expected potential HDAC-4 enzyme anti cancer activity of compounds (Fig. 1). We have selected tamoxifen drug as standard compound for comparison. However, Lipinsky rule 5 is a well known in silico method (Yusof and Segall 2013; Congreve et al. 2003; Nakashima et al. 2013) to estimate drug likeness property, which was optimized considering different parameters of absorption, distribution, metabolism, excretion and toxicity parameters as integral part of drug discovery studies (Di et al. 2009). We have observed all our compounds were satisfied the properties of drug like molecules of Lipinski rule, among all compound 3c has been exhibited with least log P value and other parameters were indicated in Table 1.

Another important method has been used is orisis toxicity prediction software (Molecular Properties Prediction 2017). Where, it is important to measure the safety parameters and side effects of compounds were based on structural orientation. Here, we have assessed the mutagenic and toxicity of all selected dihydropyrimidine derivatives was represented in Fig. 2. All compounds were exhibited less toxicity and mutagenic properties based on their less cLog P values were presented in Fig. 2. Among all the compound 3c has been exhibited 2.49 value which was comparable with tamoxifen indicated is 4.72. The pharmacological activity prediction is very important to select the compounds. Here, we have used pass online software to estimate anti cancer activity and ACD lab chemsketch software. We have used this software to predict anti cancer activity. Among all compounds N mannich series (3a–f) has been predicted with antimitotic activity, where as O mannich series (4a–f) has been exhibited anti neoplastic activity. The compound 4a has been showed more score of 0.669, but it was less than tamoxifen exhibited pass online score 0.821 (Table 2).

Another important property of docking studies was based on target site of enzyme binding site involvement in the hybrid of selected compounds. Here, we have selected the targeted site id HDAC-4 enzyme inhibition is for docking to predict anti cancer activity. All compounds were exhibited high score of docking score than co crystal ligand indicates that these may be exhibit better biological activity of the compounds (Fig. 3). However, the approaches for drug discovery have the option to screen through conventional and in silico methods. Here, we have hypothetically represented merits of in silico drug screening general approaches over conventional methods (Fig. 4). This approach may save lots of time and financial burden for designing the new molecule and predict the pharmacological actions of drug. This may help to identify the potential compounds from the bulk groups.

Figure 4 Hypothetical representation of advantages of in silico approaches over conventional drug development process

Discussion

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Conclusion

In summary, we conclude that it is a best method to screen the compounds with some of available in silico methods to predict desired the biological activities. Here, we have selected some of dihydropyrimidine derivatives and processed for in silico biological activity. All the compounds exhibited good anti cancer activity. Whereas, compound
substitution with methoxy group (3c) exhibited more drugs like property and substitution with hydrogens (4a) showed high anti neoplastic activity; whereas substitution with dichloro groups (4e) showed more drug docking scores. The approach may predict the potential compounds and save time and money.

References

Abadi AH, Ibrahim TM, Abouzid KM, Lehmann J, Tinsley HN, Gary BD et al (2009) Design, synthesis and biological evaluation of novel pyridine derivatives as anticancer agents and phosphodiesterase 3 inhibitors. Bioorg Med Chem 17:5974–5982
Atwal KS, Swanson BN, Unger SE, Floyd DM, Moreland S, Hedberg A et al (1991) Dihydropyrimidine calcium channel blockers. 3. 3-carbamoyl-4-aryl-1, 2, 3, 4-tetrahydro-6-methyl-5-pyrimidine-carboxylic acid esters as orally effective antihypertensive agents. J Med Chem 34:806–811
Bahekar SS, Shinde DB (2003) Synthesis and anti-inflammatory activity of some [2-amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1, 6-dihydropyrimidine-5-yl]-acetic acid derivatives. Acta Pharm 53:223–229
Bondensgaard K, Ankersen M, Thogersen H, Hansen BS, Wulff BS, Bywater RP (2004) Recognition of privileged structures by G-protein coupled receptors. J Med Chem 47:888–899
Congreve M, Carr R, Murray C, Jhoti H (2003) ‘A rule of three’ for fragment-based lead discovery? Drug Discov Today 8:876–877
DeSimone RW, Currie KS, Mitchell SA, Darrow JW, Pippin DA (2004) Privileged structures: applications in drug discovery. Comb Chem High Throughput Screen 7:473–494
Di L, Kerns EH, Carter GT (2009) Drug-like property concepts in pharmaceutical design. Curr Pharm Des 15:2184–2194
Dutta S, Sutrathdar S, Sachan K (2010) Computer-aided drug design—a new approach in drug design and discovery. Computer 4:025
El-Sayed WA, Nassar IF, Adel A-H (2009) C-Furyl glycosides, II: synthesis and antimicrobial evaluation of C-furyl glycosides bearing pyrazolines, isoazolines, and S, 6-dihydropyrimidine-2 (1H)-thiones. Monatshefte für Chem Chem Mon 140:365–370
Filimonov DA, Lagunin AA, Gloriozova TA, Rudik AV, Druzhilovskii YM, Odhav B (2013) Synthesis and antitubercular activity of 2-(substituted phenyl/benzyl-amino)-6-(4-chlorophenyl)-5-(methoxy carbonyl)-4-methyl-3, 6-dihydropyrimidin-1-ium chlorides. Chem Biol Drug Des 81:219–227
Narayanaswamy VK, Nelakuditi S, Shinde DB (2003) Synthesis and anti-inflammatory activity of some [2-amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1, 6-dihydropyrimidine-5-yl]-acetic acid derivatives. Acta Pharm 53:223–229

Lipinski CA (2004) Lead- and drug-like compounds: the rule-of-five revolution. Drug Discov Today Technol 1:337–341
Lipinski CA, Lombardo F, Dominy BW, Feeney PJ (2001) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 46:3–26
Mayer TU, Kapoor TM, Haggarty SJ, King RW, Schreiber SL, Mitchison TJ (1999) Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen. Science 286:971–974
Molecular Properties Prediction (2017) OSIRIS property explorer. http://www.organic-chemistry.org/prog/peo/. Accessed 14 Apr 2017
Nakashima S, Yamamoto K, Arai Y, Ikeda Y (2013) Impact of physicochemical profiling for rational approach on drug discovery. Chem Pharm Bull 61:1228–1238
Narayanaswamy VK, Nayak SK, Pillay M, Prasanna R, Coovadia YM, Odhav B (2013) Synthesis and antitubercular activity of 2-(substituted phenyl/benzyl-amino)-6-(4-chlorophenyl)-5-(methoxy carbonyl)-4-methyl-3, 6-dihydropyrimidin-1-ium chlorides. Chem Biol Drug Des 81:219–227
Narayanaswamy VK, Gleiser RM, Chalannavar RK, Odhav B (2014) Antimosquito properties of 2-substituted phenyl/benzylamino-6-(4-chlorophenyl)-5-methoxy carbonyl-4-methyl-3,6-dihydropyrimidin-1-ium chlorides against Anopheles arabiensis. Med Chem 10:211–219
Nofal ZM, Fahmy HH, Zarea ES, El-Eraky W (2011) Synthesis of new pyrimidine derivatives with evaluation of their anti-inflammatory and analgesic activities. Acta Pol Pharm 68:507–517
Ou-Yang SS, Lu JY, Kong XQ, Liang ZJ, Luo C, Jiang H (2012) Computational drug discovery. Acta Pharmacol Sin 33:1131–1140
Sahu M, Siddiqui N (2016) A review on biological importance of pyrimidines in the new era. Int J Pharm Pharm Sci 2016:14
Sangameswaran L, Fales HM, Friedrich P, De Blas AL (1986) Purification of a benzodiazepine from bovine brain and detection of benzodiazepine-like immunoreactivity in human brain. Proc Natl Acad Sci USA 83:9236–9240
Shah T, Gupta A, Patel M, Chaudhari V, Patel H, Patel V (2010) Synthesis and in vitro study of biological activity of heterocyclic N-Mannich bases of 3,4-dihydropyrimidine-2 (1H)-thiones. Indian J Chem Sect B Org Incl Med 49:578
Taj T, Kamble RR, Gireesh TM, Hunnur RK, Margankop SB (2011) One-pot synthesis of pyrazole derivatised carbazoles as antitubercular, anticancer agents, their DNA cleavage and antioxidant activities. Eur J Med Chem 46:4366–4373
Thomsen R, Christensen MH (2006) MolDock: a new technique for high-accuracy molecular docking. J Med Chem 49:3315–3321
Wang R, Fang X, Lu Y, Wang S (2004) The PDBbind database: collection of binding affinities for protein–ligand complexes with known three-dimensional structures. J Med Chem 47:2977–2980
Weigelt J (2010) Structural genomics-impact on biomedicine and drug discovery. Exp Cell Res 316:1332–1338
Yusof I, Segall MD (2013) Considering the impact drug-like properties have on the chance of success. Drug discov Today 18:659–666
Zou Y, Zhao Q, Liao J, Hu H, Yu S, Chai X et al (2012) New triazole derivatives as antifungal agents: synthesis via click reaction, in vitro evaluation and molecular docking studies. Bioorg Med Chem Lett 22:2959–2962