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ORIGINAL ARTICLE

Marine Bacterial Compounds Evaluated by In Silico Studies as Antipsychotic Drugs Against Schizophrenia

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Abstract

Schizophrenia (SCZ) is one of the brain disorders which affects the thinking and behavioral skills of patients. This disorder comes along with an overproduction of kynurenic acid in the cerebrospinal fluid and the prefrontal cortex of SCZ patients. In this study, marine bacterial compounds were screened for their suitability as antagonists against human kynurenine aminotransferase (hKAT-1) which causes the synthesis of kynurenic acid downstream which ultimately causes the SCZ disorder according to the kynurenic hypothesis of SCZ. The marine actinobacterial compound bonactin shows more promising results than other tested marine compounds such as the histamine H2 blocker famotidine and indole-3-acetic acid (IAC) from docking and in silico toxicological studies carried out here. The obtained results of the Grid-based Ligand Docking with Energetics (Glide) scores of extra-precision (XP) Glide against the target protein hKAT-1 on IAC, famotidine, and bonactin were − 6.581, − 6.500 and − 7.730 kcal/mol where Glide energies were − 29.84, − 28.391, and − 47.565 kcal/mol, respectively. Bonactin is known as an antibacterial and antifungal compound being extracted from a marine *Streptomyces* sp. Comparing tested compounds against the drug target hKAT-1, bonactin alone showed the best Glide score and Glide energy on the target protein hKAT-1.

Keywords Computational biology · Schizophrenia · Kynurenic acid · Protein binding · Drug interactions · Toxicology

Introduction

Severe mental illnesses cause death in patients about 10–25 years earlier than for the general population, and the mortality rates among people with schizophrenia (SCZ) are 2 to 2.5 times higher than those for the general population (WHO 2013). As for SCZ, the major ionotropic excitatory receptors such as ligand-gated ion channel receptors amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl D-aspartate, and kainite in the central nervous system (CNS) are endogenous antagonists of kynurenic acid (KYNA) (Palmer et al. 2005; Passera et al. 2011). KYNA is converted from kynurenine

Dhinesh Kumar Thiyagarajamoorthy and Charli Deepak Arulanandam contributed equally to this work.

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catalyzed by the human kynurenine aminotransferase (hKAT) (E.C.2.6.1.7) which represents a transamination enzyme belonging to the family of pyridoxal 5-phosphate (PLP)-dependent enzymes. There are four hKAT enzymes known (hKAT-1, -2, -3, and -4; see Nematollahi et al. 2016) where hKAT-1 seems to be mostly involved in KYNA production. The kynurenine aminotransferase isozymes (KAT-1, -2, -3, and -4) have been associated to SCZ. These enzymes are members of the pyridoxal-5-phosphate (PLP) dependent enzyme family which converts L-kynurenine to kynurenic acid (Alireza et al. 2016). The next isoform of hKAT discovered was KAT-3, showing the highest identity and similarity to KAT-1 but there is no crystallographic study on hKAT-3 as yet (Yu et al. 2006). Rat and human brain mitochondrial aspartate aminotransferase was reported to be able to catalyze the transamination of kynurenine to KYNA and, therefore, was named KAT-4 (Guidetti et al. 2007). KAT-4 is the last member of KATs, and though not extensively characterized as yet, one crystal structure of hKAT-4 was deposited in the PDB. Among the individual mammalian KATs, KAT-1 and KAT-3 share similar genomic structures, show high sequence identity, and may, therefore, have overlapping biological functions (Qian et al. 2009). Enzyme inhibitory assays and binding studies showed that estradiol disulfate is a strong inhibitor of KAT-1 and KAT-2 (IC50, 291.5 and 26.3 μM, respectively), with estradiol, estradiol 3-sulfate, and estrone sulfate being much weaker (IC50 > 2 mM). Therefore, it was suggested that estrogen levels can dictate the balance of kynurenic acid in the brain (Gayan et al. 2017). The kynurenine synthesis begins with transaldimination between the amino group of L-kynurenine (L-KYN) and the cofactor of PLP being catalyzed by aminotransferase (Rossi et al. 2004; Rossi et al. 2010). The amino acids tryptophan and phenylalanine are inhibitors of hKAT-1 and show cysteine-conjugated β-lyase activity. There is also sulfur and selenium conjugated compound activation which leads to liver and kidney associated carcinogenesis often caused by environmental pollutants (Han et al. 2009). The kynurenine biosynthesis plays a significant role in mammals in tryptophan degradation and in the exploitation of neuroactive compounds (quinolinic acid and picolinic acid) (Schwarcz, 2004).

The postmortem reports of SCZ patients revealed a high content of kynurenic acid in the cerebrospinal fluid (CSF), and the prefrontal cortex and a low level of glutamate in CSF (Gattaz et al. 1982; Schwarcz et al. 2001; Erhardt et al. 2001). The major symptoms of SCZ include hallucinations, delusions, cognitive deficits, and abnormal behaviors. Patients with SCZ are often at greater risk for cardiovascular diseases and obesity (American Psychiatric Association 2013; Hert et al. 2009). SCZ affects more than 21 million people worldwide but is not as common as many other mental disorders. It is more common among males (12 million), than among females (9 million).

SCZ also commonly gets expressed at earlier age among men (WHO 2018). The best current knowledge of the SCZ disorder is linked with variable phenotypic and multiple genotypic expression interactions with environmental factors (Iannitelli et al. 2017; Jablensky 2010). SCZ positive family history of presence or absence of SCZ symptoms will be helpful in resolving heterogeneity than symptom-based typologies (Erhardt et al. 2001). Due to psychotic disorders like the SCZ, millions of people are suffering because of limited resources and compromised public health care systems. This holds particularly for lower to middle income countries where treatment is suboptimal with only 25% of the patients receiving treatment. The thorazine derivatives prolixin, haldol, and loxapine are antipsychotic drugs otherwise called neuroleptics which are linked to neurological stress. These drugs have antagonistic effects on positive symptoms of this disorder. Famotidine (Kiszkiel et al. 2012) is a repurposed drug (used for heartburn since the 1980s) and it is used to treat SCZ. It can penetrate the blood–brain barrier (BBB) with a dose of 200 mg/day/person. This is a relatively high dose affecting the histamine system in the human brain to control SCZ (Meskanen et al. 2013). This marketed drug also shows adverse effects in clinical trials such as anaphylaxis, asthenia, arthralgia, alopecia, bronchospasm, paresthesia, and tinnitus. During clinical studies with 35 pediatric patients <1 year of age with GERD symptoms, agitation was observed in five patients upon famotidine treatment which resolved when the medication was discontinued (http://www.rxlist.com/pepcid-drug.htm#side_effects_interactions). This drug is also present in the aquatic environment as a contaminant (Gros et al. 2006).

Around 70% of the Earth is covered by the oceans which are sources of microbial bioactive compounds. Marine compounds (Kwon et al. 2006) play a significant role in drug discoveries against several pathogens like *Escherichia coli* and *Staphylococcus aureus*. Such compounds were selected from different marine bacteria, especially *Actinobacteria* occurring in different habitats. Commonly, *Actinobacteria* such as *Streptomyces* provide promising drug candidates against pathogens like bacteria, viruses, and even eukaryotic parasites. We retrieved compounds from marine bacteria from databases such as ChemSpider (http://www.chemspider.com/) and PubChem (https://pubchem.ncbi.nlm.nih.gov/). From the list of marine actinobacterial compounds (Table 1), the genus *Streptomyces* was more proliferative than the genus *Thermoactinomyces*, *Marinispora*, *Janibacter*, etc. (Kanoh et al. 2005; Maskey et al. 2003). The selected compounds showed already distinct properties like antimicrobial (abyssomicin B, himalomycin A), (Li et al. 2005; Shiono et al. 2002) antifungal (bonactin) (kock et al. 2005), antiviral (resistomycin) (Maskey et al. 2004), and anticancer (chinikomycin A and chinikomycin B) (Liu et al. 2007) and some compounds have dual properties like anticancer and antibacterial (resistoflavine) (Jensen et al. 2007) or anticancer and antimalarial effects (trioxacarcin A and trioxacarcin B) (Mitchell et al. 2004).

Table 1 Active compounds from marine *Actinobacteria*

Compounds	Sources	Classification	Properties	CID/CSID	References
Abyssomicin B	*Verrucosispora* sp.	Polyketide	Antibacterial	CID 101727942	Bister et al. (2004)
Actinofuranones A	*Streptomyces* sp.	Polyketide	Cytotoxic	CSID 9835603	Cho et al. (2006b)
Actinofuranones B	*Streptomyces* sp.	Polyketide	Cytotoxic	CSID 9820943	Cho et al. (2006b)
Arcyriaflavin A	*Z (2)0392*	Alkaloid	Anticancer	CID 5327723	Liu et al. (2007)
Areniolide	*Salinispora arenicola*	Macrolide	Antibacterial	CSID 8917007	Jensen et al. (2007)
Aureoverticillactam	*Streptomyces aureoverticillaris*	Macrocyclic lactam	Anticancer	CSID 8044227	Mitchell et al. (2004)
Azamerone	*Streptomyces* sp.	Meroterpenoid	-	CSID 9859638	Cho et al. (2006a)
Bonactin	*Streptomyces* sp. *BD21-2*	Ester	Antibacterial, antifungal	CID 11741721	Schumacher et al. (2003)
Chalcomycin	*Streptomyces* sp. *M491*	Macrolide	Anticancer and antibacterial	CSID 4940919	Ding et al. (2008)
Chinikomycin A	*Streptomyces* sp. *M045*	Manumycin derivatives	Anticancer	CSID 9448084	Maskey et al. (2003)
Chinikomycin B	*Streptomyces* sp. *M045*	Manumycin derivatives	Anticancer	CSID 9440210	Li et al. (2005)
Cyclomarin A	*Streptomyces* sp.	Peptide	Anti-inflammatory, antiviral	CSID 8947744	Renner et al. (1999)
Daryamide B	*Streptomyces* sp. *CNQ-085*	Polyketid	Anticancer, antifungal	CID 16099484	Asolkar et al. (2006)
Daryamide C	*Streptomyces* sp. *CNQ-085*	Polyketid	Anticancer, antifungal	CID 16099483	Asolkar et al. (2006)
Glaciapyrrole A	*Streptomyces* sp. *NPS008187*	Pyrrolosesquiterpenes	Antibacterial	CSID 24690200	Macherla et al. (2005)
Helquinoline	*Janibacter limosus*	Quinone	Antibacterial	CSID 8641491	Asolkar et al. (2004)
Himalomycin A	*Streptomyces* sp. *B6921*	Quinone	Antibacterial	CSID 27022966	Maskey et al. (2003)
Komodoquinone A	*Streptomyces* sp. *K53*	Quinone	Neuritogenic activity	CSID 9931447	Aoyagi et al. (1992)
Maridomycin	*Marinispora*	Macrolide	Anticancer, antibacterial	CSID 16736966	Kwon et al. (2006)
Mechercharmycin A	*Thermoactinomyces* sp.	Peptide	Antitumor	CID 44569200	Kanoh et al. (2005)
Pyrizinostatin	*Streptomyces* sp. *SA-2289*	Enzyme inhibitor	Pyroglutamyl peptidase inhibition	CID 127007	Aoyagi et al. (1992)
Resistoflavine	*Streptomyces chibaensis AUBN(1)/7*	Quinone	Anticancer, antibacterial	CSID 171446	Kock et al. (2005)
Resistomycin	*Streptomyces corchorusii AUBN(1)/7*	Quinone	Antiviral	CSID 4445287	Shiono et al. (2002)
Saliniketal A	*Salinispora arenicola*	Polyketide	Anticancer	CID 102400689	Liu et al. (2007)
Saliniketal B	*Salinispora arenicola*	Polyketide	Anticancer	CID 102400690	Williams et al. (2007)
Salinosporamide A	*Salinispora tropica*	Gamma-lactam Beta-Lactone	Anticancer	CID 11347535	Jensen et al. (2007)
Streptokordin	*Streptomyces* sp. *KORDI-3238*	Methylpyridine	Anticancer	CID 11579160	Jeong et al. (2006)
Thiocoraline	*Micromonospora*	Peptide	Anticancer, antibacterial	CID 70698112	Romero et al. (1997)
Trioxacarcin A	*Streptomyces ochraceus*	Complex compounds	Anticancer, antimalarial	CID 3067465	Aouiche et al. (2014)
Trioxacarcin B	*Streptomyces bottropensis*	Complex compounds	Anticancer, antimalarial	CID 3086133	Aouiche et al. (2014)

CID, PubChem ID; *CSID*, ChemSpider ID

Already reported histamine H2 receptor antagonists such as famotidine and indole-3-acetic acid (IAC) were used to compare with test compounds (Fraczek et al. 2013; Rossi et al. 2010). Table 1 shows selected marine bacterial compounds including sources and mechanisms against hKAT-1. One of the high GC content bacterial groups are the *Actinobacteria*, providing a significant role in drug discovery and development. Generally, microbial secondary metabolites including antibiotics like penicillin, methicillin, clindamycin, and ciprofloxacin have distinct functionality with antipathogenic and anticancer properties. Overall, available pharmaceutical antibiotics are for two thirds retrieved from *Actinobacteria* sources, especially *Streptomyces* spp. (Fraczek et al. 2013; Aouiche et al. 2014).

Different procedures or protocols are used for the development of pharmacokinetics and pharmacodynamics worldwide. One of the promising fields of pro-drug identification and development in recent years are in silico methods like molecular modeling and molecular docking studies. The computational studies applied widely for the design of drugs make use of the exact protein–ligand complex geometry by computational tools with the accuracy of distinct docking programs (Friesner et al. 2004). The common computational scheme utilize the scoring function for evaluating the binding affinity based on physical or virtual database docking molecules with the receptor (Meng et al. 2011). Several publications are dealing with virtual screening of chemical databases, the comparison of different docking methods, and scoring functions or improved screening hit rate methodology (Friesner et al. 2004). In silico molecular docking studies are made possible by software like Schrödinger-Maestro, AutoDock, and Gold. The molecular docking studies are commonly followed by worldwide available techniques for novel active compound identification based on the virtual screening of structures (Kubinyi 1998; Friesner et al. 2006). Especially, drug identification works proceed by using molecular docking software like Glide (Grid-based Ligand Docking with Energetics) including protein–protein docking and ligand–protein docking.

Methods

Protein of hKAT-1 as a Drug Target

The human kynurenine aminotransferase 1 (hKAT-1) is the target protein of this study. This enzyme has a major role in catalyzing kynurenic acid from kynurenine. An abnormal production of kynurenic acid has been associated to SCZ (Trotta et al. 2016), Alzheimer's disease, acquired immune deficiency syndrome (AIDS), dementia (Gupta and Kulshreshtha, 2017; Guillemin et al. 2005), and Huntington's disease (Quinti et al. 2017). The target protein was retrieved from Protein Data Bank (PDB ID: 3FVU) which was used as a target for the analysis of novel drug candidates for SCZ (Kanoh et al. 2005). It had two domains named A and B. When the native drug of IAC binds to the protein, it shows hydrophobic pockets like ASN185, PHE339, ARG398, GLY36, PHE125, LYS255, and LLP and it interacts with ASN185, ARG398, and π-π stacks with PHE125. hKAT-1 (3FVU) has three high resolutions (1.50–1.55 Å), crystal structures complexed with glycerol (GOL), IAC, and Tris that were able to occupy the binding position on the substrate and cause hKAT-1 inhibition (Han et al. 2009; see Fig. 1) and Fig. S1 also shows the sequence chain view of target protein hKAT-1(3FVU). This protein has one polymer, the type of the chain is a polypeptide (L), and it has 422 residues in length (UniProtKB-Q16773) [available from https://www.uniprot.org/uniprot/Q16773].

Glide Docking (Protein–Ligand)—Schrödinger

The docking programs were run between hKAT-1 (3FVU) and the marine *Actinobacteria* compounds listed in Table 1. Figure 2 shows the native ligand (IAC), the marketed drug famotidine, and marine *Actinobacteria* compound bonactin test ligand against the SCZ disorder evaluated by Schrödinger software (Schrödinger 2008) with XP Glide (Solanki et al. 2008) as well as other Glide parameters. The crystallographic macromolecule of the protein from PDB included heavy atoms with cofactors, metal ions, and water and it consists of a lack of information about topologies, bond orders, or formal atomic charges and unassigned ionization and tautomeric states. The protocols were following Glide Manual 5.526 with small modifications (Glide, 2009). Glide bond orders and ionization states have to be properly assigned. The primary process of protein preparation can be performed in the Protein Wizard panel. The prepared protein that was refined having the hydrogenated structure of the ligand and the ligand–receptor complex can be used for Glide docking. This was concentrated to determine the dimer or presence of duplicate binding sites in multimer and the duplicate chains that were redundant of the protein–ligand complex. At duplicate binding sites of the multimer protein–ligand complex, the binding sites and the associated chains and molecules must be removed or deleted. Some of the parameters were checked such as water molecule orientation, steric clashes, and resolving H-bond conflicts.

Similar concepts like for the protein preparation were followed for ligand preparations using the LigPrep panel, which maintain some parameters such as pH 7 ± 1, force field-OPLS_2005, and generate tautomers. The panel of LigPrep included conversion, corrections, and generated variation, optimization, and elimination of unwanted structures. The input structures had a single low-energy 3D structure with corrected chiralities, various ionization states, tautomers, stereo chemistries, and ring confirmations. These generate the ligand protonation states linked to specified pH ranges by the ionization function which included retaining the original state, neutralization, generate possible states at target pH

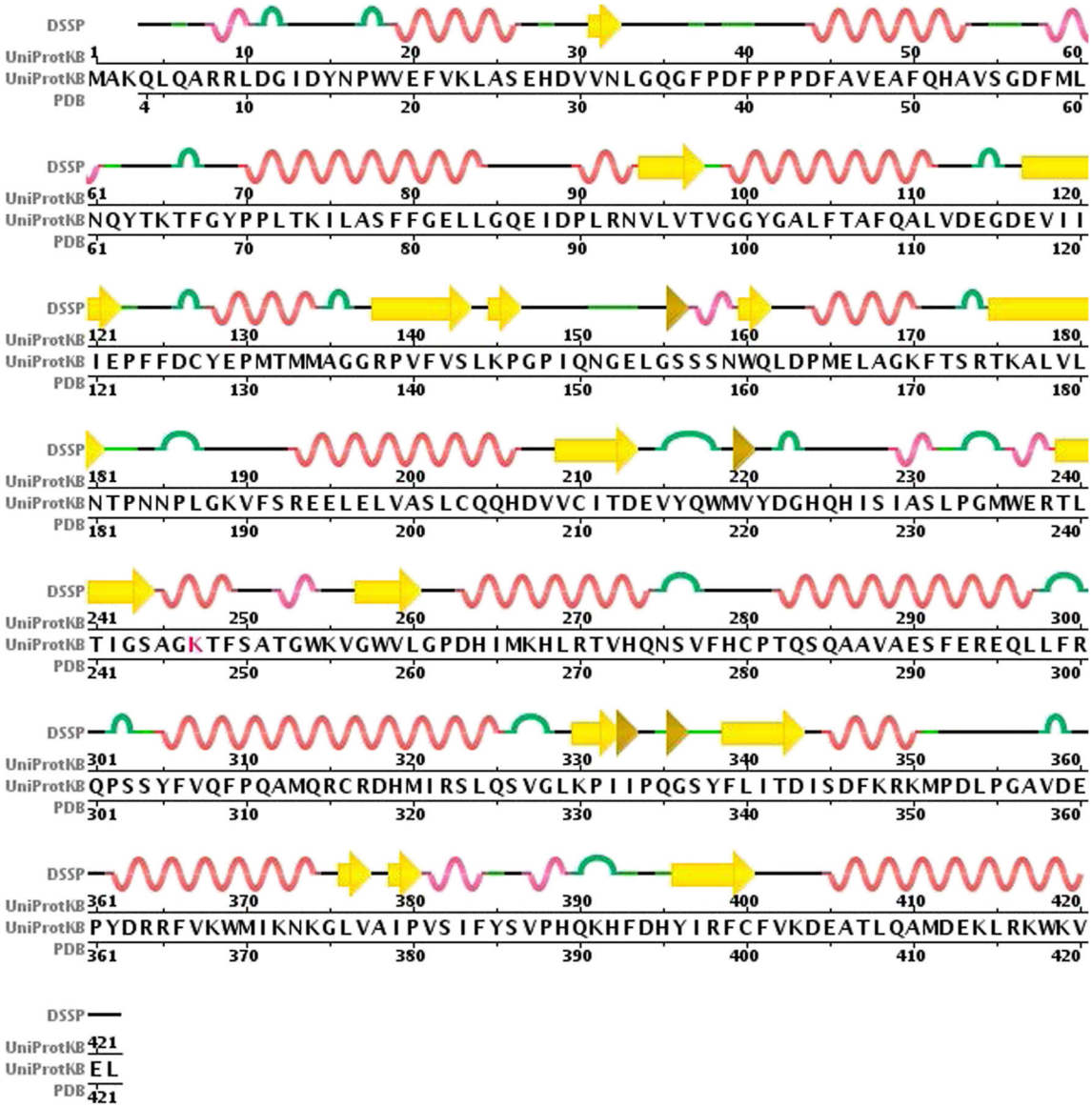

Fig. 1 *Sequence chain view of hKAT-1.* Yellow/yellowish orange—E, beta strand/B: beta bridge; green—T: turn; pink—G: 3/10-helix; dark green—S: bend; red—H: alpha helix; black—empty; no secondary structure assigned (available from https://www.rcsb.org)

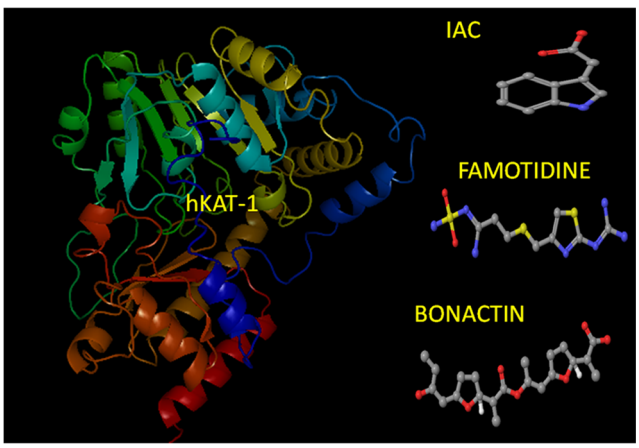

Fig. 2 *hKAT-1 with ligands of IAC, famotidine, and bonactin*. Model protein of hKAT-1 and structure of ligands

ranges, and generate distinct stereochemical combinations up to a maximum (32-default).

The prepared protein included an all atom structure with appropriate bond orders and formal changes requiring the generation of a receptor grid. In the panel of receptors, the grid generation contained the presence of co-crystallized ligands, a receptor grid corresponding to the determination of active site sizes, and a position setup for Glide constraints. This panel from the application menu had four setting tabs such as receptor that were able to define the receptor, Van der Waals radius scaling, per atom Van der Waals radius, and charge scaling. Site was positioning the scoring grids and was prepared from the structure in the workspace. Constraints that were responding to receptor–ligand interactions, including the evaluation of binding modes, structural or biochemical data for

docking suitability, and rotatable groups that kept the hydroxyl groups flexible, such as belonging to Ser, Thr, and Tyr.

Glide ligand docking was calculated by receptor grids and ligands that were prepared by LigPrep or MacroModel (software) and unparametrized elements such as arsenic or atom types of ligands that were automatically skipped by Glide and not supported by OPLS (optimized potentials for liquid simulations) force fields. Docking was performed by a ligand docking panel that had six steps:

Settings including docking ligand choices like specifying grid, selecting the precision (SP, XP, or HTVS)

Setting of flexibility options using force field-OPLS_2005

Ligands—selection of docking ligands or scoring and set size limits for skipping, cores termed reference ligand, used for docking the other ligands or for RMS (root mean square) deviation calculation

Constraints applied by ligand-relevant feature identification and specified atoms

Similarity select the molecules based on the "similarity property principle" that means to share similar biological activity by closely related chemical structures and physiochemical properties and output that finalized the docking output of ligands that pass successfully through various scoring stages of Glide.

The GlideScore based on ChemScore included a steric clash term, added buried polar terms devised by Schrödinger to penalize electrostatic mismatches, and had modifications to other terms:

GScore a * vdW + b * Coul + Lipo + H-bond + Metal + BuryP + RotB + Site (GScore = GlideScore; vdW = Van der Waals energy; Coul = Coulomb energy; Lipo = lipophilic; H-bond = hydrogen bonding term; Metal = metal binding term; BuryP = penalty for buried polar groups; RotB = penalty for freezing rotatable bonds; and Site = polar interactions at the active site; $a = 0.065$ $b = 0.130$).

Statistical Analysis

Famotidine was used as a control drug for the statistical analysis such as standard deviation and correlation coefficient, and IAC and bonactin were comparative targets. This work was done using Microsoft Excel for mean and standard deviation analysis and Origin software for significant analysis through descriptive statistics of correlation coefficient. Results described as mean ± standard deviation and $p < 0.05$ were considered as significant.

Quantitative Structure–Activity Relationship Analysis

Potent compounds were checked whether druggable or not by VEGA (Virtual models for property Evaluation of chemicals within a Global Architecture) software. Here, the major parameters like toxicity and carcinogenicity were analyzed. The following models were used for potent ligands.

Mutagenicity (Ames Test) Model

CAESAR (version 2.1.13) – QSAR (quantitative structure–activity relationship) classification model for mutagenicity (Cassano et al. 2014) is based on a support vector machine combined with a set of ToxTree rules developed by Benigni/Bossa and the model extends the original CAESAR Mutagenicity model 1.0 developed by Politecnico di Milano (PM), Italy (http://www.caesar-project.eu/); SarPy/IRFMN version 1.0.7 is based on a set of rules built with SarPy software and developed by Istituto Mario Negri (IMN), Italy; SarPy software was developed by PDM, Italy. The ISS (version 1.0.2) is based on Benigni-Bossa (Istituto Superiore di Sanit'a) rule set as implemented in ToxTree 2.6 and KNN/Read-Across (version 1.0.0) developed by Istituto di Ricerche Farmacologiche Mario Negri (IRFMN).

Carcinogenicity Model CAESAR (Version 2.1.9) and ISS (Version 1.0.2)

QSAR (quantitative structure–activity relationship) classification model for carcinogenicity is based on a neural network and developed by the Kemijskiinstitut Ljubljana, Slovenia. The model extends the original CAESAR Carcinogenicity model 1.0. (Floris et al. 2016). The results are given as membership function values of class positive and non-positive, and compounds are assigned to the class having a value > 0.5 and an ISS model based on Benigni-Bossa (Istituto Superiore di Sanita) rule set as implemented in ToxTree 2.6.

Developmental Toxicity Model/ Reproductive Toxicity Library CAESAR (Version 2.1.7) and PG (Version 1.0.0)

QSAR (quantitative structure–activity relationship) classification model for developmental toxicity is based on a random forest classification. The model extends the original CAESAR DevTox model 1.0 (Rissdörfer et al. 2014) and is developed by IMN, Italy. PG model implements a virtual library of toxic compounds as described in the study from Procter and Gamble.

Estrogen Receptor Relative Binding Affinity Model (IRFMN) (Version 1.0.1)

Relative binding affinity (RBA) classification model for endocrine disruptor screening is based on the model (SAR and QSAR) published to SAR and QSAR in Environmental Research (Roncaglioni et al. 2008; Jensen et al. 2008).

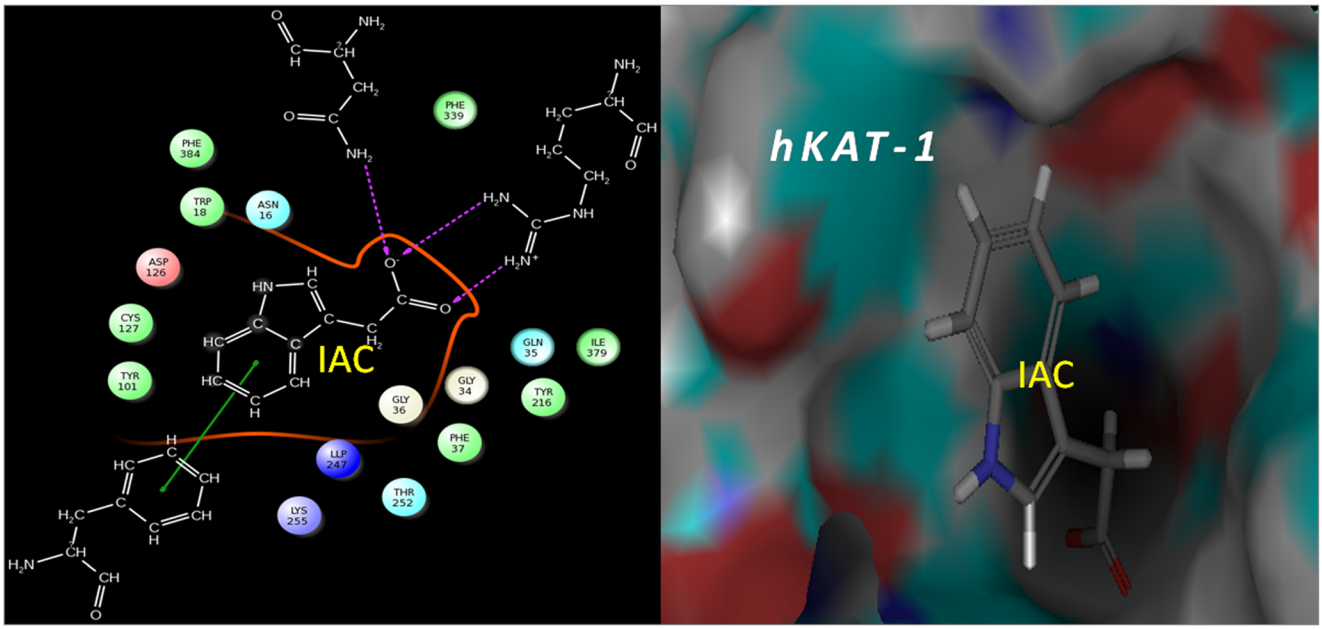

Fig. 3 *IAC–H-bond interactions and binding surface against hKAT-1*. Chemical structure of ligand, and binding sites and surface image of IAC with hKAT-1

Fish Acute (LC50) Toxicity Classification SARpy/IRFMN (Version 1.0.2) and KNN/Read-Across (Version 1.0.0)

QSAR classification model for fish acute (LC50) toxicity based on fragments built by SarPy software is developed by PM, Italy, and IRFMN, Italy. KNN (Read-Across) model for fish acute (LC50) toxicity is developed by IRFMN, Italy.

Fathead Minnow LC50 96 h (EPA) (Version 1.0.7)

QSAR model for Fathead Minnow LC50 (96 h) is based on a multiple linear regression. The model extends the original model implemented in the T.E.S.T. software. The original model was developed by US EPA inside the T.E.S.T. software and can be freely accessed at http://www.epa.gov/nrmrl/std/cppb/qsar/.

Daphnia Magna LC50 48 h EPA (Version 1.0.7) and DEMETRA (Version 1.0.4)

QSAR model for *Daphnia magna* LC50 (48 h) is based on multiple linear regressions. The model extends the original model implemented in the T.E.S.T. software. The original model was developed by US EPA inside the T.E.S.T. software and can be accessed freely at http://www.epa.gov/nrmrl/std/cppb/qsar/. DEMETRA Acute toxicity for Water Flea (*Daphnia magna*) for pesticides, LC50 48-h exposure, was built as a hybrid model upon two ANNs and a single PLS. It is based on the model built for DEMETRA project (http://www.demetra-tox.net).

Results

Binding Energies and H-Bond Interactions of IAC

Preliminary docking studies started with the native ligand of IAC, docked to hKAT-1 by Glide with three different modes such as SP, XP, and HTVS. The Glide XP (Schrödinger 2008) was focusing on both protein–ligand penalty desolvation and exact structural motif identification linked to enhanced binding affinity. The docking functions were within the rigid-receptor approximation and deviated some abilities from the restrictions of the van der Waals potential of the receptor confirmation in docking built into the potential energy function employed to predict the ligand binding mode (Solanki et al. 2008). The XP results of IAC (Fig. 3) interacted with ARG398, ASN185 with the length of hydrogen bonds being within 1.74248 to 2.04732 Å and the Glide energy and docking score being − 29.84 and − 6.581 kcal/mol, respectively. In the SP, HTVS Glide energies and docking scores were − 29.419 and − 29.646, and − 6.841 and − 6.838 (kcal/mol) (see also Table 2) (Jensen et al. 2008).

Binding Energies and H-Bond Interactions of Famotidine

Famotidine is currently used as a drug to control the SCZ disorder and it is an antagonist of histamine H2 receptors on the basolateral membrane of parietal cells, reduces the basal and nocturnal gastric acid secretion, and leads to acidity and gastric volume reduction. Concentrations of 0.008 to 0.094 μg/L were found in waste water samples at low level.

Table 2 Glide parameters and H-bond interactions of IAC, famotidine, and bonactin

Compounds	Dock	GScore	G-energy	GEVDW	GEMODEL	GCOU	D-score	H-bond	Length
IAC	XP	− 6.581	− 29.840	− 16.497	− 38.357	− 13.344	− 6.580	ARG398…=O	1.62994
								ARG398… O^-	1.74248
								ASN185… O^-	2.04732
	SP	− 6.841	− 29.419	− 16.650	− 49.562	− 12.770	− 6.841	ARG398… =O	1.62682
								ARG398… O^-	1.75117
								ASN185… O^-	2.06902
	HTVS	− 6.838	− 29.646	− 15.567	− 47.211	− 13.078	− 6.837	ASN185… =O	2.12953
								ARG398… =O	1.75551
								ARG398… O^-	1.5882
Famotidine	XP	− 6.500	− 41.686	− 28.391	− 54.220	− 18.828	− 3.988	NH_2…ASP126	1.80098
								ASP185… =O	1.97807
								ARG398… =O	1.62994
								ASN185… O^-	2.04732
	SP	− 5.955	− 46.540	− 18.947	− 70.088	− 26.213	− 5.113	NH_2…LLP247	1.46436
								ARG398… =O	1.8382
								ASN185… =O	1.95337
								GLY36… O^-	1.69674
	HTVS	− 4.497	− 43.782	− 29.484	− 57.067	− 14.608	− 2.325	NH_2…ASP126	1.75488
								NH_2…LLP247	1.61512
								ASN16… =O	2.12953
Bonactin	XP	− 7.730	− 47.565	− 31.675	− 61.043	− 15.891	− 7.729	ARG398… =O	1.72491
								ARG398… O^-	1.63683
								ASN185… =O	2.15360
								ASN16… O	2.22786
	SP	− 6.613	− 43.254	− 21.425	− 64.049	− 18.828	− 6.612	ARG398… =O	1.81093
								ASN185… =O	1.59542
								ARG398… O^-	1.69674
	HTVS	− 4.172	− 37.484	− 26.693	− 44.623	− 10.791	− 4.171	OH…LLP24	1.73752
								ASN16… =O	2.5029
								GLY36… =O	1.84035
								LYS255… OH	2.47907

A docking study of famotidine provided scoring results about the interactions with hKAT-1 substrate. Interactions were high and scores are lower than that with bonactin and higher than that with IAC. The details of interaction in XP mode are provided in Fig. 4 for ASP126, ASP185, ARG398, and ASN185 (Table 2) with a salt bridge and π-π stacking. In the session using Glide, energy and docking scores were − 41.686 and − 3.988 kcal/mol, respectively. The docking scores were very low compared to the native ligand. The results of SP and HTVS Glide energies and docking scores were − 5.955 and − 4.497 kcal/mol and − 5.113 and − 2.325 kcal/mol, respectively.

Binding Energies and H-Bond Interactions of Marine Compounds

The marine compounds (Table 1) were used against the target enzyme (hKAT-1) (Akladios et al. 2012) and its docking scores and energy scores are surprising. Most of the compounds such as IAC, famotidine, and bonactin were reviving. According to the XP Glide results, among others bonactin, abyssomicin B, helquinoline, resistoflavine, resistomycin, daryamide A and daryamide B, trioxacarcin A, and trioxacarcin B provided a list of marine compounds based on ascending Glide scores. The XP Glide energy and docking score results of bonactin were − 47.565 and − 7.729 kcal/mol (Table 2). Those interacting with a number of hydrophobic pockets (Fig. 5) were ASN16, ASN185, and ARG398. Bonactin isolated from *Streptomyces* sp. contains a chemical group of esters which seems to make it more suitable. Its PubChem identification number is 11741721. It has antibacterial and antifungal activities. The Glide scores and docking scores of bonactin by SP and HTVS were − 6.613 and − 4.172, and − 6.612 and − 4.171 kcal/mol (Table 2). Figure 6 shows important energy scores of different Glide parameters for IAC, famotidine, and bonactin. Table 2 shows some of the major parameters such as Glide energies and interactions of docking results of IAC, famotidine, and bonactin. Commonly, the H-bond formations occurred due to electronegative atoms such as O_2, Cl, I, and Br. The H-bond interactions are affected by the furan ring moiety of bonactin, showing a hit on amino acids belonging to hKAT-1. Bonactin has an acid moiety, furan ring moiety, and ester groups (Figs. 5 and 2). The docking scores of trioxacarcin A, trioxacarcin B, and helquinoline in XP were − 7.689 and − 7.026 kcal/mol and Glide energies were − 48.605 and − 31.530 kcal/mol. Trioxacarcin B is a complex compound and was isolated from *Streptomyces* sp. The trioxacarcin PubChem identification number is 3086133 and it has anticancer and antimalarial activities and the quinone group of helquinoline was isolated from *Janibacter* sp. The ChemSpider ID of helquinoline is 8641491 and it has antibacterial properties. Figure 7 shows comparable docking and Glide scores of IAC, famotidine, bonactin, trioxacarcin, and helquinolone plotted as bar diagrams in Origin software. According to the Glide scores, bonactin was more dominant than other compounds against hKART-1 and it showed best results from the evaluated actinobacterial marine compounds. There was no effective significant value with famotidine to IAC in the Glide energy, GEVDW, and GEMODEL. Famotidine compared to IAC showed a p value of 0.02 in the docking scores. Overall, significant p values were

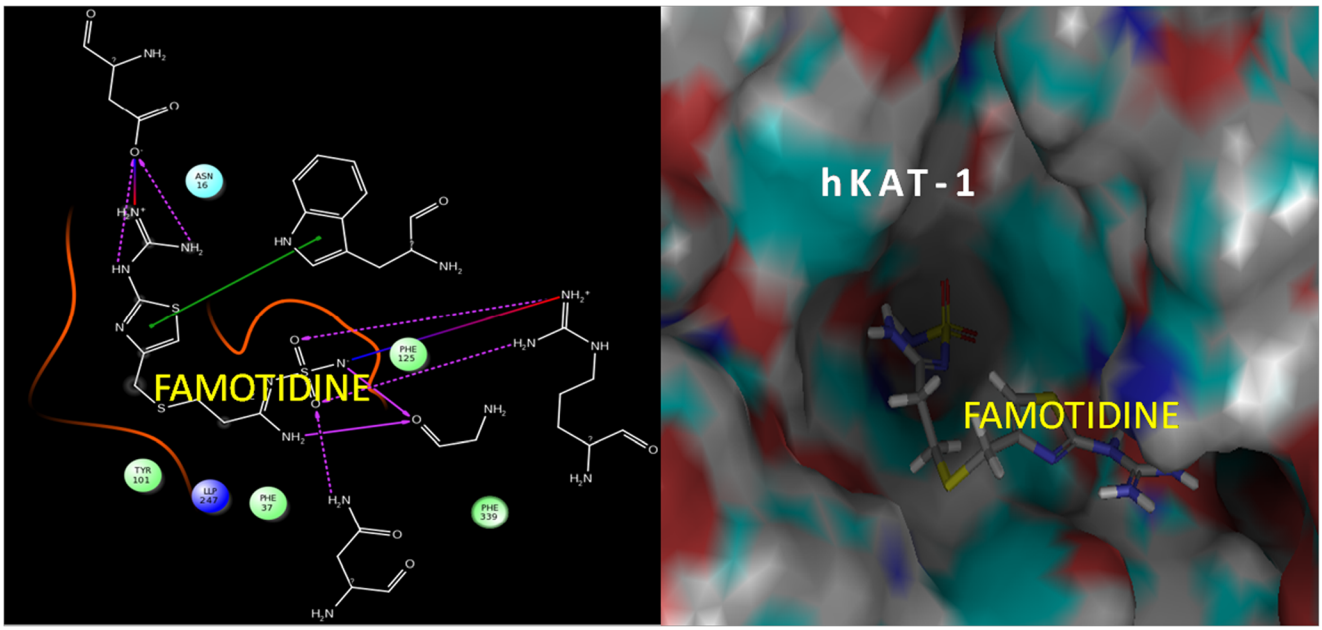

Fig. 4 *Famotidine–H-bond interactions and binding surface against hKAT-1*. Chemical structure of famotidine, and binding sites and surface image of famotidine with hKAT-1

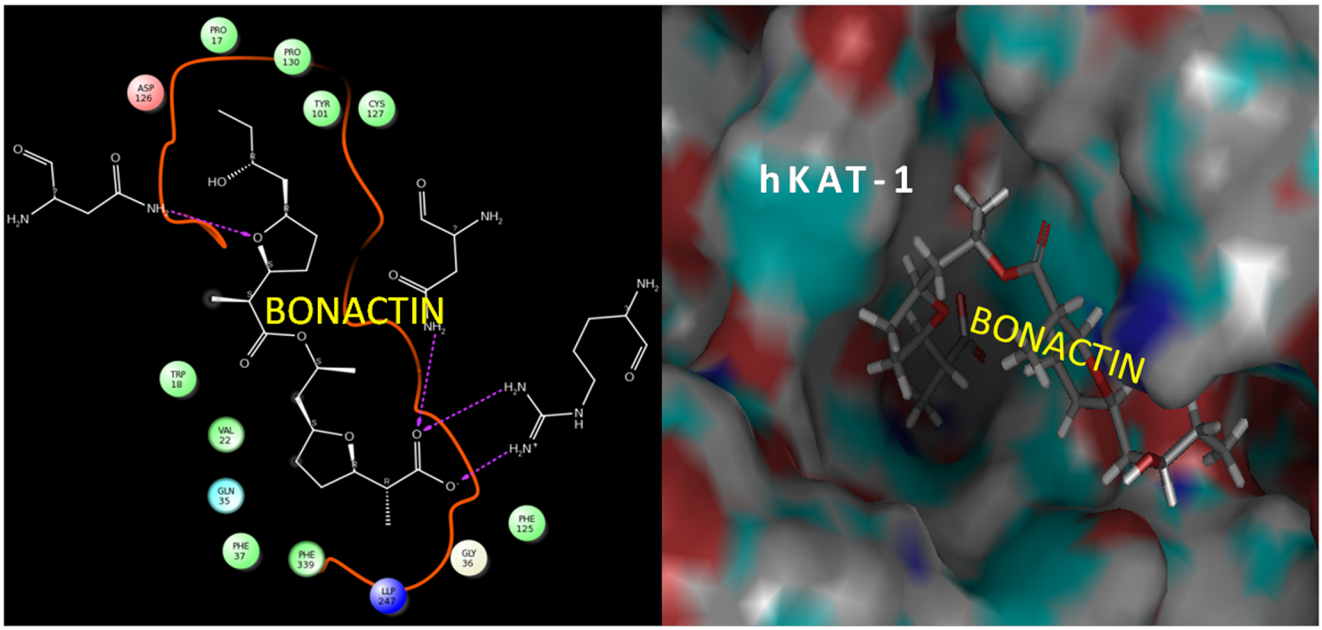

Fig. 5 *Bonactin–H-bond interactions and binding surface against hKAT-1.* Chemical structure of bonactin, and binding sites and surface image of bonactin with hKAT-1

observed between famotidine and bonactin: 0.04 in docking score, 0.009 in Glide energy, 0.03 in GEVDW, and 0.004 in GEMODEL (Fig. 8).

Quantitative Structure–Activity Relationship Model

Mutagenicity

In silico mutagenicity studies were performed with four different in silico mutagenicity prediction models such as Tool M-1 (CAESAR-2.1.9); M-2 (ISS-1.0.2); M-3 (SaRPY/IFMN 1.0.7); and M-4 (ISS 1.0.2). The bonactin and IAC had no mutagenic property based on four mutagenicity assessment tools (see Table 3). All three showed that famotidine was not mutagenic but Tool M-4 shows famotidine as a mutagen.

Carcinogenicity

The carcinogenicity prediction was done by two different tools: Tool C-1 (CAESAR-2.1.9) and Tool C-2 (ISS-1.0.2) (Table 3). Based on the results, Tool C-1 showed that IAC

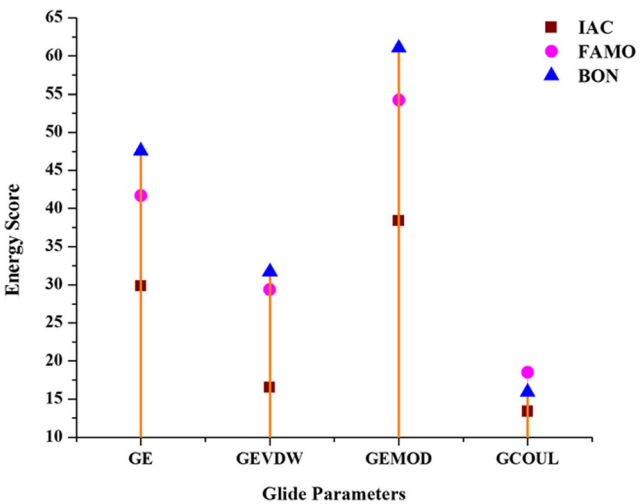

Fig. 6 *Important parameters of IAC, famotidine, bonactin except in GCOUL, and bonactin showed significant differences.* IAC - indole-3-acetic acid; FAM - famotidine, and BON - bonactin

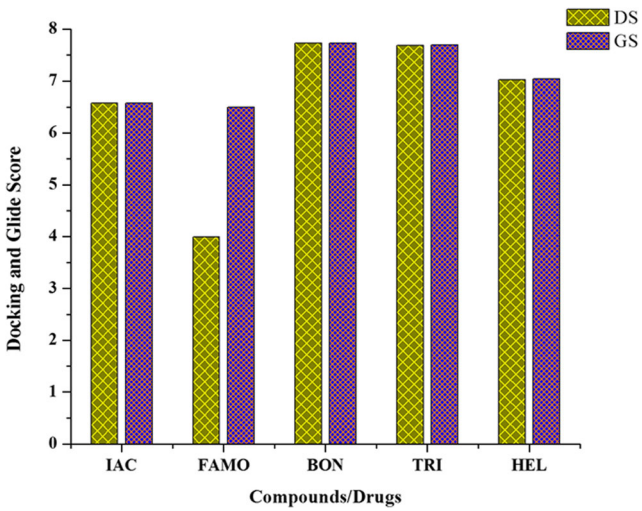

Fig. 7 *Docking and Glide scores of IAC, famotidine, bonactin, trioxacarcin, and helquinoline.* IAC - indole-3-acetic acid; FAMO - famotidine, BON - bonactin; TRI - trioxacarcin; HEL - helquinoline

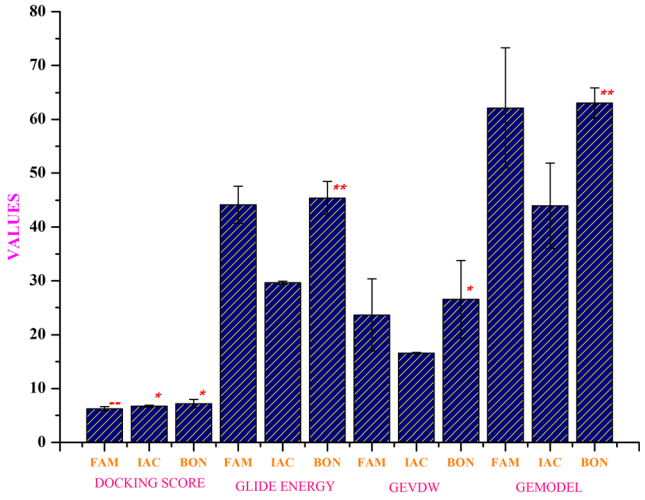

Fig. 8 *Statistical analysis of scores and energies.* *About the significance *p* values of IAC and bonactin with famotidine

and famotidine were carcinogenic except bonactin and Tool C-2 showed that all three were not carcinogenic.

Estrogen Receptor Relative Binding Affinity Model (IRFMN) 1.0.1

RBA was assessed to study the endocrine disrupting property of three compounds such as bonactin, famotidine, and IAC that are predicted as inactive (IA). These three compounds will not have effects on the endocrine system (see also Table 4).

Toxicity

In the toxicity study, Tool T-1 (PG–1.0.0) shows three compounds as nontoxic. Tool T-2 (CAESAR - 2.1.7) shows only bonactin as nontoxic, but famotidine and IAC as toxic (see also Table 3).

Aquatic Toxicity Prediction

Aquatic toxicity was assessed for bonactin, famotidine, and IAC. The analysis of LC50 values in milligrams/liter was done by three different model organisms like the teleost fathead minnow and the water flea *Daphnia magna*.

Fish Toxicity

The tool FA-1 results of fish acute toxicity for bonactin, famotidine, and IAC are given in Table 4. It shows that bonactin and famotidine belongs to the same toxicity class but are less toxic than IAC. The results of Tool FA-2 (Table 4) show famotidine as nontoxic and bonactin has a lower toxicity than IAC. The Tool FM-1 of EPA 1.0.7 LC50 values of fathead minnow shows that bonactin with 6.96 mg/L was noticed as a very low toxic level compared with IAC and famotidine (Table 4).

Daphnia magna Toxicity

The toxicity assessment results using tool DM-1 for *Daphnia magna* show famotidine with low LC50 and bonactin with high LC50. IAC was predicted as belonging to toxicity class 3. Tool DM-2 assessment shows bonactin with a very low LC50 value with class (2) toxicity against *Daphnia magna* acute toxicity compared to famotidine and IAC (see also Table 4).

According to aquatic toxicity studies, bonactin was not toxic to aquatic model organisms such as the teleost fathead minnow and *Daphnia magna*.

Discussion

As in other medical fields, psychiatric drug identification and development is warranted. With regard to SCZ, neuroleptics, among others thorazine, perphenazine, and thioridazine, and

Table 3 QSAR results of IAC, famotidine, and bonactin

Toxicology									
Compounds	Mutagenicity (M)				Carcinogenicity (C)		Toxicity (T)		Affinity (A)
	Tool M-1	Tool M-2	Tool M-3	Tool M-4	Tool C-1	Tool C-2	Tool T-1	Tool T-2	Tool A-1
IAC	NM	NM	NM	NM	**C**	NC	NT	**T**	IA
Famotidine	NM	NM	NM	**M**	**C**	NC	NT	**T**	IA
Bonactin	NM	NM	NM	NM	NC	NC	NT	NT	IA

Tool M-1, (CAESAR-2.1.9); Tool M-2, (ISS-1.0.2); Tool M-3 (SaRPY/IFMN-1.0.7); Tool M-4 (ISS-1.0.2); Tool C-1, (CAESAR – 2.1.9); Tool C-2, (ISS – 1.0.2); Tool T-1, (PG – 1.0.0); Tool T-2, (CAESAR – 2.1.7)

NM, non-mutagenic; *M*, mutagenic; *C*, carcinogenic; *NC*, noncarcinogenic; *NT*, nontoxic; *T*, toxic; *IA*, inactive

Table 4 Aquatic toxicity prediction by different in silico QSAR model and tool for IAC, famotidine, and bonactin

Aquatic toxicity prediction by different in silico models and tools										
	Fish acute				Fathead minnow 24 h		*Daphnia magna* 48 h			
	Tool FA-1		Tool FA-2		Tool FM-1		Tool DM-1		Tool DM-2	
Compounds	LC50 (mg/mL)	Toxicity class	LC50 (mg/mL)	Toxicity class	LC50 (mg/mL)	Toxicity class	LC50 (mg/mL)	Toxicity class	LC50 (mg/mL)	Toxicityclass
IAC	10–100	2	14.34	3	24.05	3	14.05	3	10.28	3
Famotidine	1–10	2	Nil	Nil	208.27	2	2.38	2	17.81	2
Bonactin	1–10	3	8.77	2	6.96	2	28.26	2	0.3565	2

Fish acute toxicity prediction by Tool FA-1 = KNN/Read-Across 1.0.0; fish acute toxicity prediction by Tool FA-2 = SarPy/IRFMN 1.0.2 and Tool FM-1 = EPA 1.0.7; *Daphnia magna* acute toxicity prediction by Tool DM-1 = EPA 1.0.7; *Daphnia magna* acute toxicity prediction by Tool DM-2 = DEMETRA 1.0.4

more recently atypical antipsychotics have been reported to only partially control SCZ symptomatology. Famotidine is associated with a reduction in the overall SCZ symptoms approximately of 10% (Meskanen et al. 2013; Citrome, 2017; Brugnoli et al. 2016). In this study, IAC, famotidine, and marine *Actinobacteria* compounds (Table 1) were used for docking studies against the hKAT-1 (PDB ID: 3FVU) protein (see Fig. 1) (Berman et al. 2014); hKAT-1 shows a response to the SCZ disorder by using in silico molecular docking including the XP Glide method (Friesner et al. 2004). The secondary structure of the hKAT-1 protein consists of 45% helicoidal structures which include 193 residues and 23 helices; 15% were beta sheets which included 65 residues and 19 strands. The docking studies were done using Schrödinger-Maestro by three different Glide modules such as XP (extra-precision), SP (standard precision), and HTVS (high-throughput virtual screening) (Han et al. 2009; Solanki et al. 2008). Glide docking searches the protein–ligand according to positional, orientational, and conformational space available on the ligand as it is feasible and accomplished through the application of hierarchical filters such as docking time and binding affinity predictions. IAC, famotidine, and bonactin are inactive when using the estrogen receptor relative binding affinity model (IRFMN) 1.0.1 for an evaluation.

Conclusion

The control of psychiatric diseases is difficult because of their unpredictable effects since they are linked to various environmental and genetic factors. To predict a suitable compound against the SCZ disorder, we assessed the marine actinobacterial compound toxicological and hKAT-1 inhibition properties by this in silico study. According to our docking study, the natural drug bonactin has most promising antipsychotic properties compared to other tested marine actinobacterial compounds and it may provide higher effects than the marketed antipsychotic drug (famotidine) and the native ligand IAC. Commonly, the use of natural compounds for untreatable diseases is increasing, but only little research is currently allocated for mental illnesses using natural compounds.

Among all the compounds tested in our docking studies, bonactin (CID 11741721) had the best inhibitory properties. Based on the docking scores and energies, it shows highest inhibitions against the hKAT-1 protein. The marine actinobacterial compound bonactin seems, therefore more effective against the targeted protein hKAT-1 than the other tested marine *Actinobacteria* compounds, IAC and famotidine, to treat SCZ.

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Compliance with Ethical Standards

Ethics Approval and Consent to Participate Not applicable.

Human and Animal Rights No animals/humans were used for this study.

Conflict of Interest The authors declare that they have no conflict of interest.

Acronyms *IAC*, indole-3-acetic acid; *XP*, extra-precision; *hKAT*, human kynurenine aminotransferase; *kcal/mol*, kilocalories/mole; *Glide*, grid-based ligand docking with energetics; GEMODEL/GEVDW (depending on authors); *RBA*, relative binding affinity; *IMN*, Istituto Mario Negri; *SCZ*, schizophrenia; *CNS*, central nervous system; *KYNA*, kynurenic acid; *CSF*, cerebrospinal fluid; *BBB*, blood–brain barrier; *AIDS*, acquired immune deficiency syndrome; *SP*, standard precision; *HTVS*, high-throughput virtual screening

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