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A Short Review on the Prediction of Biological Activities for the New and Novel Chemical Substances by PASS online System and Case study of Aripiprazole by PASS Prediction

Senthil Periyasamy[1*] and Selvaraj Subbiah[2*]

1*Research scholar [Reg. No: 8425], PG & Research department of chemistry, Sriparama kalyani college, Alwarkurichi-627412, Tamilnadu, India, Email:prksenthil@gmail.com, Mob: 7204263360

2*Associate Professor & HOD, PG & Research department of chemistry, Sriparama kalyani college, Alwarkurichi-627412, Tamilnadu, India, Email:drselvarjspkc@gmail.com Mob: 9442064252.

*Affiliated to Manonmanium sundaranar university, Abishekapatti, Tirunelveli-627012, Tamilnadu, India.

ABSTRACT

Reverse screening is applied if the biological activity of the new chemical subatances is unknown. Prediction of the Activity Spectrum of Substances (PASS) is applied to find out the biological interactions of macromolecular targets with the new substances and it is freely available websource. The current version of the PASS system predicts more than 6000 kinds of biological activity. Herein, we represent the review on the new chemical substance's biological spectra predicted by the PASS system and case study of Aripiperazole's biological functions compared with PASS prediction.

KEYWORDS: Reverse Screening, PASS, Chemical Substances and Aripiprazole.

*Corresponding Authors:

Dr.SelvarajSubbiah

*Associate Professor & HOD,

PG & Research department of chemistry,

Sriparamakalyani college, Alwarkurichi-627412,

Tamilnadu, India,

Email:drselvarjspkc@gmail.com Mob: 9442064252.

1. INTRODUCTON

Finding the drug interactions and their adverse side effects when it interact with the macromolecular targets of the human/animals/plants is a complex problem in an ancient era. But in modern chemical biology, Computational and Molecular Modeling study has a given a lot of insights into the drug discovery and their interactions with the macromolecular targets of the living systems. Many sources were currently available[1-2] and able to predict the biological activity of the chemicals exist in the databases or synthetically derived. Molecular properties and bioactivity studies of the substances were clearly be done with cheminformatics tools[3-4]. In contrast to the conventional virtual screening, Reverse screening is widely applied and used to predict the biological functions of the new chemicals[5-6]. Target identification[7-8] and Binding site prediction[9-10] are the preliminary stages to finding the protein-drug complex and their interactions.

1.1. PREDICTION OF THE ACTIVITY SPECTRUM OF SUBSTANCES [PASS]:

Pass system requires only structural information of the chemical substances such as smiles notation or MDL MOL files either the synthesis yet to be done or completed, it can predict the biological activity of the chemical substances. Biological activity is due to the interaction between the chemical substances and protein targets/enzyme/receptors. As described by Filimonovet al.[11] recently modified PASS system in 2007 can predict 3300 types of biological activity (Table 1) while in 2004, the software could only able to predict 1000 types and predicts with a mean prediction accuracy of about 95%. In the PASS system, there are two technical terms involved namely active (Pa) and in-active (Pi) in expressing the biological activity of the chemical substances.

New compounds biological spectra prediction in the PASS system is based on Structure-Activity relationships (SAR base) and the traning set includes 117332 known biological active substances (drugs, drug-chemical probes, leads and toxic compounds). The activity spectra is arranged in the descending order. Thus, the more probable one is ranked at the first and less probable is ranked at the lowest in the biological activity spectra. Chemical substances activities with this probability (P) factor: $P_a > P_i$ are considered as feasible for the particular compound.

Table 1.Number of biological activities by PASS system described by Filimonov et al.

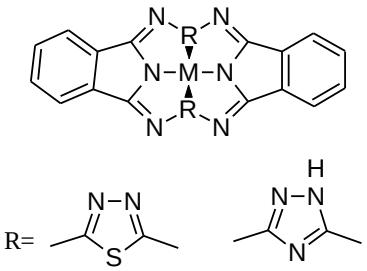
Entry	Biological Spectra (Catagories)	Number of Activities	Examples
1	Pharmacotherapeutic effects	374	Antihypertensive, Anticonvulsant, Nootropic, Antidiabetic etc.
2	Mechanisms of action	2755	Feruloyl esterase inhibitor, Transcription factor STAT3 inhibitor, Sphingosine-1-phosphate receptor 1 antagonist etc.
3	Adverse and Toxic effects	50	Carcinogenic, Mutagenic, Hematotoxicetc
4	Metabolic terms	121	CYP1A inducer, CYP1A1 inhibitor, CYP3A4 substrate etc.

We examined the biological activity done for the newly synthesized chemical substances and fall in the four catagories (Table 1) mention with their structure and the PASS probability score, P_a and P_i.

2. REVIEW OF LITERATURE FOR THE PASS PREDICTION

2.1. Biological Spectra and Effects (Entry 1-4, Table 1):

Macroheterocycles reported by Islyaikin et al[12] whose antitumor activity was predicted by PASS system and the synthesized heterocycles treated with metal salts like Copper(IV), Cobalt(V) and Nickel (IV) formed metallomacroheterocycles (1). The P_a score 15 for the three complex with 96% accuracy.

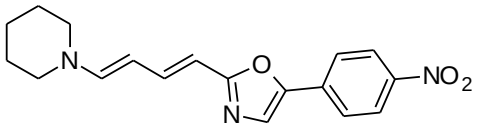


M= Cu(IV), Co(V), Ni(IV).

(1)

Fig. 1 Metallomacrocycles (1) lead for Antitumor activity.

The probability of active (P_a) found for Antimicrobial is 78 and 1 for inactive (P_i) predicted by the PASS system. The least score (P_a/P_i) is found for Antiparkinsonic (32/27), Immunomodulator (31/26) and Antiadrenogenic (24/23) for the oxazol-1,3-butadiene[13] derivatives (2).

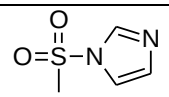
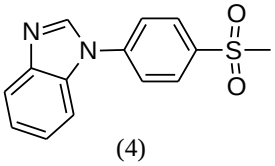
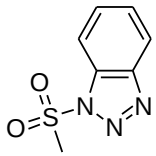


(2)

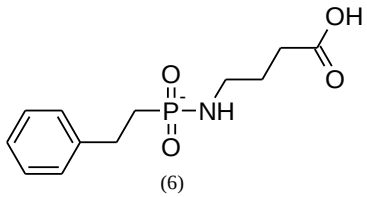
Fig. 2 Antimicrobial substances (2): potential leads of oxazol-1,3-disubstituted derivatives.

The four kinds of biological activity is found different for sulphonamide (3, 4 & 5) analogues synthesized by Polyakova et al[14]. The inhibition activity for Antihypertensive (3) is absent but the probable activity (3) is higher in score for vascular treatment (Table 2).

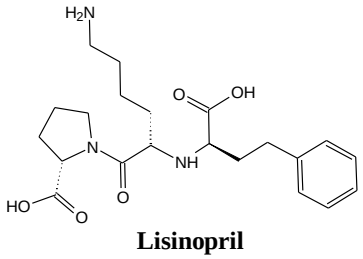
Table 2. Different substitution of imidazole-sulphonamide analogues with varies activity.

Structure	Active, P_a	Inactive, P_i	Activity Spectra
 (3)	1.000 1.000 0.878	0.001 0.071 0.000	Vascular (periferal)disease treatment Dermatologic Antihypertensive
 (4)	0.825 0.792 0.639 0.579 0.607	0.005 0.005 0.010 0.003 0.112	Cardiovascular analeptic Restenosis Agent Antihypertensive CAMP Phosphodiesterase inhibitor Antiishemic
 (5)	1.000 0.900 0.875 0.656 0.444	0.005 0.008 0.166 0.035 0.091	Vascular (periferal)disease treatment Antitrypanosomal Dermatologic Antiishemic CAMP Phosphodiesterase inhibitor

Laguninet al[15] selected the chemical substances were already deposited with MDDR 99.2 database[16] and found the prediction for Antihypertensive activity with dual mechanism of action. In comparison with **Lisnopril**, a drug medicinally used for the treatment of high blood pressure and heart attacks, compound (6) was shown maximum probable activity for Antihypertensive with dual mechanism of actions: ACE (angiotension-converting enzyme) and NEP (neutral endopeptidase) inhibitors.



(6)



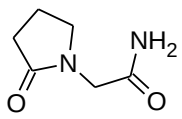
Lisinopril

Active, P_a & P_i: 0.855 & 0.002(NEP inhibitor) Active, P_a & P_i: 0.115 & 0.012 (NEP inhibitor)
Active, P_a & P_i: 0.805 & 0.003(ACE inhibitor) Active, P_a & P_i: 0.607 & 0.004 (ACE inhibitor)

Fig. 3 Antihypertensive of (6) in comparison with Lisinopril.

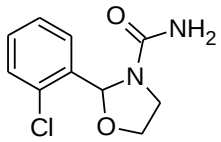
Cognition-enhancers newly designed by Geronikaki and coworkers[17] found much promising activity exhibited by five membered heterocyclics (7, 8) when compared with Piracetam, the

probable activity (P_a) for the thiazole and pyrrolidine derivatives approximately the same obtained by the PASS system.



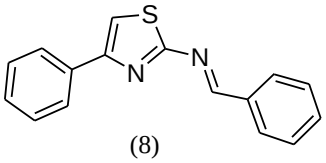
Piracetam

Active, P_a & P_i: 0.725 & 0.008
Cognition disorders treatment



(7)

Active, P_a & P_i: 0.752 & 0.007
Cognition disorders treatment

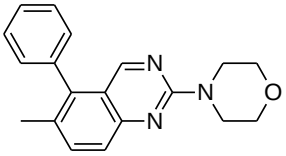


(8)

Active, P_a & P_i: 0.754 & 0.007
Coginition disorders treatment

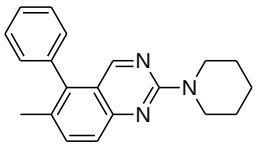
Fig. 4 Cognition enhancers prediction of (7 & 8) with Piracetam

Novel quinazolines as described by Goel et al[18] predicted the biological activity spectra for anxiolytic and GABAergic agents followed by biological assay data (9, 10 & 11) on mice and reported the activity order for both pharmacological functions in the descending order: 11>9>10.



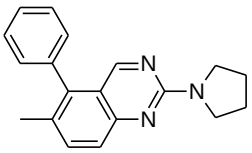
(9)

Active, P_a & P_i: 0.693 & 0.010 (Anxiolytic)
Active, P_a & P_i: 0.458 & 0.075 (GABAergic)



(10)

Active, P_a & P_i: 0.706 & 0.009 (Anxiolytic)
Active, P_a & P_i: 0.642 & 0.009 (GABAergic)

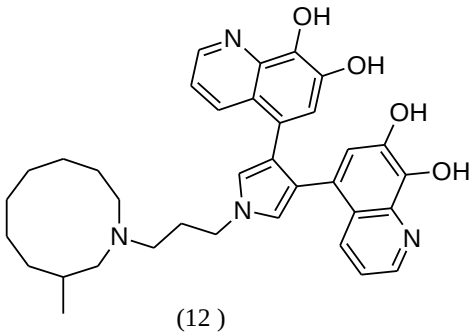


(11)

Active, P_a & P_i: 0.708 & 0.009 (Anxiolytic)
Active, P_a & P_i: 0.411 & 0.068 (GABAergic)

Fig. 5 Quinazolines (9-11) as anxiolytic and GABAergic agents.

The cytotoxic activity of Halitulin (12)[19,22]isolated from marine sponge, *Haliclonatulearensis* evaluated aginst for P-388 murine leukemia, A-549 human carcinoma, HT-29 human colon carcinoma and MEL-28 human melanoma is 0.025, 0.012, 0.012 and 0.025 µg/ml respectively and predicted the biological spectra for the highest activity of psychosexual dysfunction treatment (P_a/P_i: 0.814/0.014) and Antineoplastic activity (P_a/P_i: 0.420/0.097) reported by Dembitsky et al.



(12)

Halitulin

Fig. 6 Halitulin (12) isolated from marine sponge, potential probe as antineoplastic agent.

Antimicrobial activity determined for the synthesized 2-substituted-3-mercapto-1,4-napthoquinones (13) and found potent analogues of thiols (R=1, 2, 3). All these analogues were tested against Gram negative and postive strains. Very good probable activity score (P_a, R=1,2,3): 0.877, 0.853 & 0.786) is predicted for this thiols among the other synthesized analogues[20].

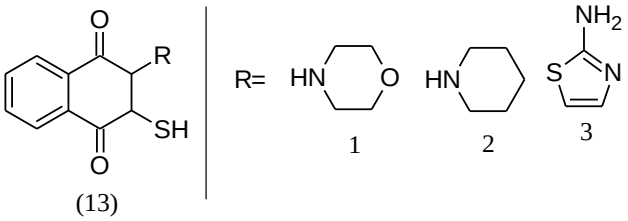


Fig. 7 Substituted 1,4-naphtoquinones (13) as antimicrobial probes.

New Thiazolidinones[21] were found as potential Anti-Inflammatory agents with dual Cyclooxygenase (COX) and Lipooxygenase (LOX) inhibition activity and all the analogues (1-9) substituted with different phenyl groups. The probable (P_a) activity for all the analogues were observed more than 0.350.

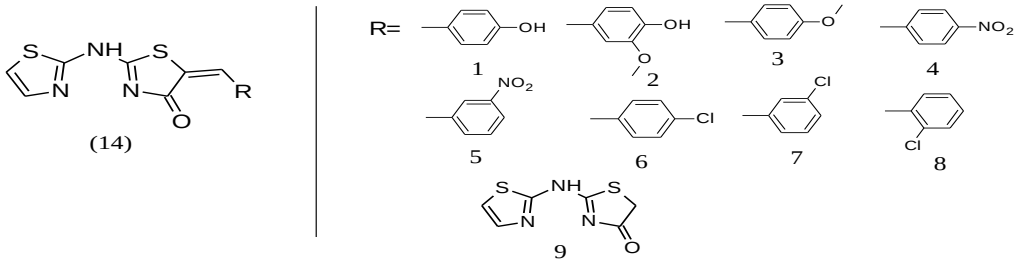


Fig. 8 Antiinflammatory substances (14) substitued with different aryl groups.

Antifungal activity predicted for the substituted 2-arylhydroxynitroindoles (15) as described by Kokurkinaet al[23] and evaluated by PASS system followed by QSAR study.

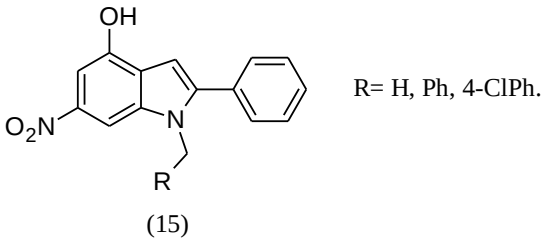
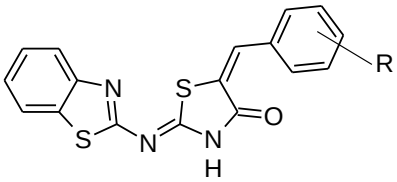


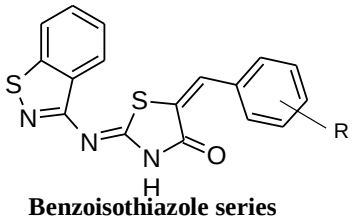
Fig. 9 Antifungal probes of substituted nitroindoles (15).

Filimonov, Poroikov and coworkers[24] have described the synthesis of thiazolidinone's derivatives as COX/LOX inhibitors and they modified fragments of thiazolidinone's skeleton to

improve the activity. The two skeleton is modified thiazolidinone (16, 17) in contrast to the earlier reported in 2008. They performed PASS evaluation followed by docking.



Benzothiazole series
(16)

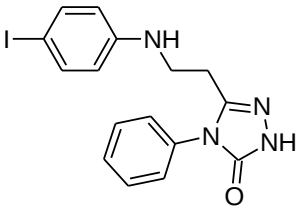


Benzoisothiazole series
(17)

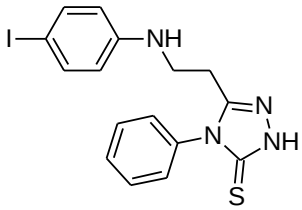
R= H, 2-NO_2, 3-NO_2, 4-NO_2, 2-Cl, 3-Cl, 4-Cl, 3-OCH_3, 4-OCH_3, 3-OH, 4-OH, 3,5-OCH_3.

Fig. 10 Modified thiazolidinones as antiinflammatory probes (16-17) with dual function.

Similarity search for the newly synthesized N-(4-iodophenyl)-β-alanine hydrazide derivatives (18-21) is examined with Chemspider/Chemical structure look up service in contrat to the PASS system[25]. This similarity search is based on Tanimoto coefficient (TC). If TC is higher than the similarity thershold then the query molecule and the molecule in the databases are considered to be similar.



(18)



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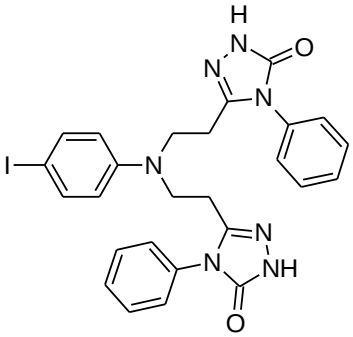

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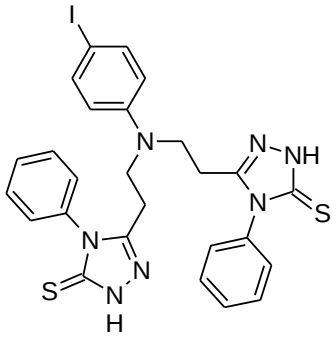

(21)

Fig. 11 Similarity search of β-alanine hydrazide (18-21) derivatives.

The TC is calculated by using the equation: TC: $N_{AB}/N_A + N_B\text{-}N_{AB}$), where, N is the number of bits sets for the each molecule (A, B) and N_{AB} is common bits sets for the two molecule. For the

compounds (18-21), found TC > 70% similarity thershold.After the similarity search followed by biological prediction, all these compounds tested for antibacterial and antifungal activity.

The Potential phosphonates[26] of thiazolobenimidazoles (26-28) is developed for anticancer and the biological activity is predicted by the PASS for the probable activity (P_a/P_i) of (26): 0.672/0.655, (27): 0.745/0.262 & (28): 0.613/0.443 is observed and the cytotoxicity prediction accuracy is 85.7% by biological assays. All of these phosphonates tested against human breast and colon cancer cell lines and compared with the standard drug, Adiramycin.

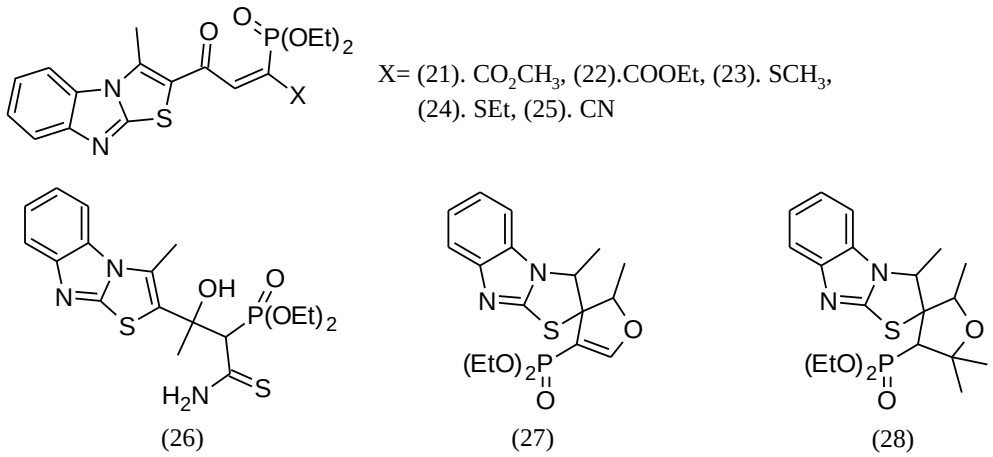

Fig. 12 Anticancer leads of Thiazolobenzimidazole (26-28) derivatives.

Yildirim et al[27] have reported the synthesis of new sulfanyl-2,3-disubstituted-1,4-naphthoquinones (29), substituted with trifluoromethyl methyl group at different positions of the phenyl group exhibited the activity for antibacterial and antifungal. The three analogues (30, 31 & 32) with probable activity score (31, Pa/Pi: 0.158/0.045 for antibacterial and 0.138/0.025 for antibiotic anthracycline-like) is calculated by PASS prediction and were tested against seven bacterial strains.

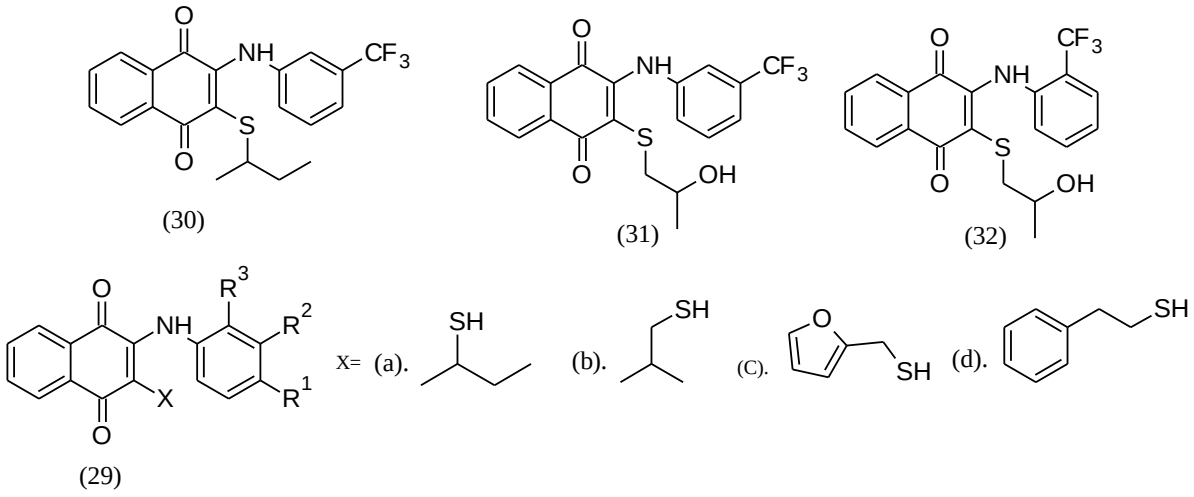

Fig. 13 Sulfanyl substituted 1,4-napthoquinones (30-32) as probes for antibacterial.

Derivatives of dithiocarbamates of 9,10-anthracenedione (33-35) is reported and found to exhibit anticancer activity whose pharmacological cytotoxicity evaluated against A549 (human lung), PC3 (prostate), HT29 (colon), MCF7 (human breast) cancer cell lines[28]. Staseevych et al found pyrrolidine (c) derivatives exhibit promising anticancer activity against human breast (MCF7) cell lines whose cytotoxicity GI_{50} values are 1.40 µM and 1.52 µM. PASS prdiction for the focal activity of all the derivatives compared with the standard drug, amethanthrone, mitoxanthrone and banoxanthrone and the best PASS score is observed for pyrrolidine derivatives (c).

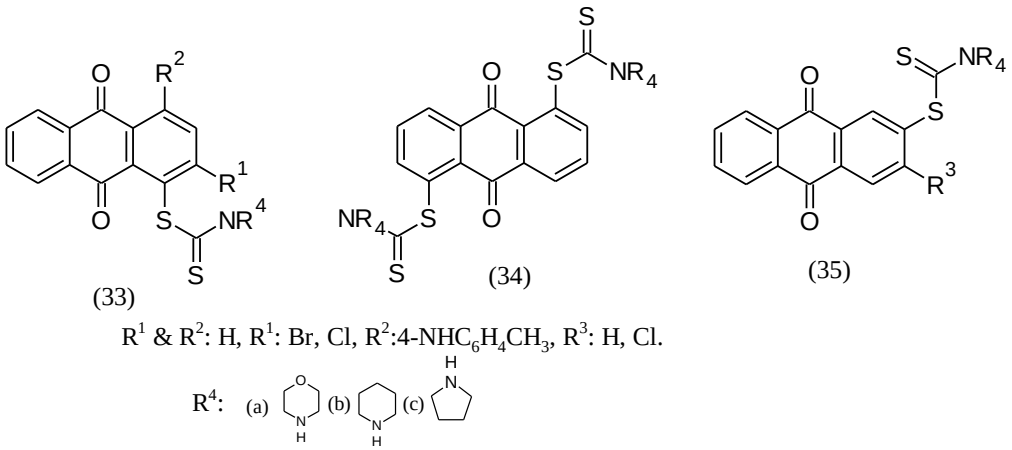

Fig. 14 Human Breast cancer leads of 9,10-anthracenedione (33-35) derivatives.

Poroikovet al[29] have recently described for the PASS prediction along with case study of kinease inhibitors which provide us good meaningful into the topic of virtual screening for the beginers and researchers who actively involved in the drug discovery research and development.

2.2 CASE STUDY: PASS ACTIVITY SPECTRA FORARIPIPRAZOLE:

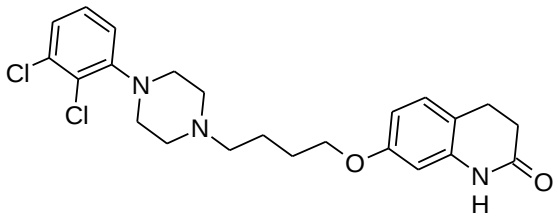

Fig. 15 Aripiprazole-atypical antipsychotic drug.

Smiles Notation: Clc4cccc(N3CCN(CCCCOc1ccc2CCC(=O)Nc2c1)CC3)c4Cl

Chemical Name: 7-(4-(4-(2,3-dichlorophenyl)-1-piperazinyl)butyloxy)-3,4-dihydro-2(1H)-quinolinone

Molecular Formula: $C_{23}H_{27}Cl_2N_3O_2$; Molecular weight: 448.388; Commercial Name (Medical terms): Abilify, Abillitat, OPC-14597; Pubchem ID: 60795

Aripiprazole is well known drug for the treatment of Schizophrenia and Bipolar disorder. It was developed by OTSUKA Pharmaceuticals, Japan. The pharmacological activities were proven already for arippiprazole as CYP2D6 and CYP3A4 substrate, Bipolar disorders treatment, 5-HT antagonist and Dopamine partial agonist. We drawn the chemical structure of Aripiprazole in ACD ChemSketch and obtained smiles notation. The smiles notation is uploaded in the PASS online prediction System[30].

The focal biological activity spectra (Table 2) is obtained with in a minute and listed with descending order of probable active (P_a) and inactive (P_i). The Pa/Pi score is highlighted in Bold which corresponds to the biological activity of aripirazole as we could found more similarity with pharmacological actions which is clinically already explained for this atypical antipsychotic drug.

Table 3: Prediction Activity spectra for Aripiprazole by PASS online System.

Entry	P_a	P_i	Activity Name
1	**0.909**	**0.004**	**Antineurotic**
2	0.751	0.013	Acute neurologic disorders treatment
3	**0.675**	**0.010**	**CYP2D6 substrate**
4	**0.654**	**0.011**	**CYP2D substrate**
5	0.663	0.035	Antiischemic, cerebral
6	0.602	0.007	5 Hydroxytryptamine antagonist
7	0.601	0.040	CYP3A4 substrate
8	0.557	0.004	Alpha 1 adrenoreceptor antagonist
9.	0.525	0.005	Alpha 1 adrenoreceptor antagonist
10	0.531	0.023	CYP2C19 substrate
11	0.525	0.039	Vasodilator, peripheral
12	0.490	0.006	Antialcoholic
13	0.514	0.056	CYP3A substrate
14	0.477	0.029	Sigma receptor agonist
15	0.480	0.040	Anticonvulsant
16	**0.427**	**0.003**	**Bipolar disorders treatment**
17	0.450	0.028	Prostate disorders treatment
18	0.416	0.010	Calcium channel activator
19	**0.414**	**0.009**	**Alpha adrenoreceptor antagonist**
20	**0.389**	**0.009**	**5 Hydroxytryptamine 1 antagonist**
21	**0.375**	**0.008**	**5 Hydroxytryptamine 1A antagonist**
22	**0.361**	**0.003**	**Dopamine D2S antagonist**
23	0.383	0.035	Antipsychotic

3. CONCLUSION

This review article is more helpful for the research scholars and scientists as one could easily find out the past work carried out on the new chemical substances followed by their biological activity prediction by the PASS system. All the past work which we represented in this article explained with chemical structures to give an immediate access and hence one can design his own rsearch to find out new chemical entities for the future drug.

4. Coflicts of Interest

There are no conflicts to declare.

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