GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(RESEARCH ARTICLE)

In silico screening of drug Bank data base to PDE10: A drug repurposing approach

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GSC Biological and Pharmaceutical Sciences, 2023, 24(03), 010–021

Publication history: Received on 17 July 2023; revised on 25 August 2023; accepted on 28 August 2023

Article DOI: https://doi.org/10.30574/gscbps.2023.24.3.0350

Abstract

Drug repurposing has emerged as a promising strategy for expediting drug development by identifying new therapeutic applications for existing drugs. In this study employed *in silico* screening approach to explore the DrugBank database for potential phosphodiesterase 10 (PDE10) inhibitors with applications in neurological, psychiatric disorders and cancer treatment. PDE10 plays a crucial role in regulating cyclic nucleotide levels in the brain and has been implicated in various diseases, including schizophrenia, Parkinson's, Huntington's diseases, and certain types of cancer. Through molecular docking, we evaluated the interactions and energetics of 28 candidate inhibitors with PDE10. Notably, 17 candidates met all selection criteria, presenting excellent potential for further investigation. The theoretical inhibitors demonstrated favorable ADMETx properties, and their adverse effects were comparable or lower than controls. These findings indicate the viability of repurposing existing drugs, such as Nebivolol, Fluvastatin, Pioglitazone and others, for PDE10 inhibition in diverse pathologies. Validation of these candidates in preclinical studies may open new avenues for drug development and clinical applications, addressing unmet medical needs in various disorders and cancer treatment.

Keywords: PDE10; DrugBank; Drug repurposing; Molecular docking; ADMETx

1. Introduction

In recent years, drug repurposing has emerged as a promising approach to expedite drug development and reduce costs by identifying new therapeutic applications for existing drugs (1) (2). The use of *in silico* screening approaches has emerged as a powerful tool for identifying potential drug candidates by computationally analyzing large databases of known drugs and their targets. One promising target for drug repurposing is phosphodiesterase 10 (PDE10), an enzyme that plays a crucial role in regulating the levels of cyclic nucleotides in the brain. PDE10 dysregulation was implicated in various neurological and psychiatric disorders, including schizophrenia (3), Parkinson's (4), and Huntington's diseases (5); recently was implicated in lung and breast cancer (6). Studies have implicated PDE10 in certain types of cancer, like the one mentioned before, because dysregulation of the expression of the enzyme has been linked to altered intracellular signaling pathways involved in cell proliferation, survival, and angiogenesis. Some studies have suggested that PDE10 inhibitors are largely preclinical, conducted in cell lines or animal models, and focused on specific types of cancer, such as colorectal or prostate cancer (7),

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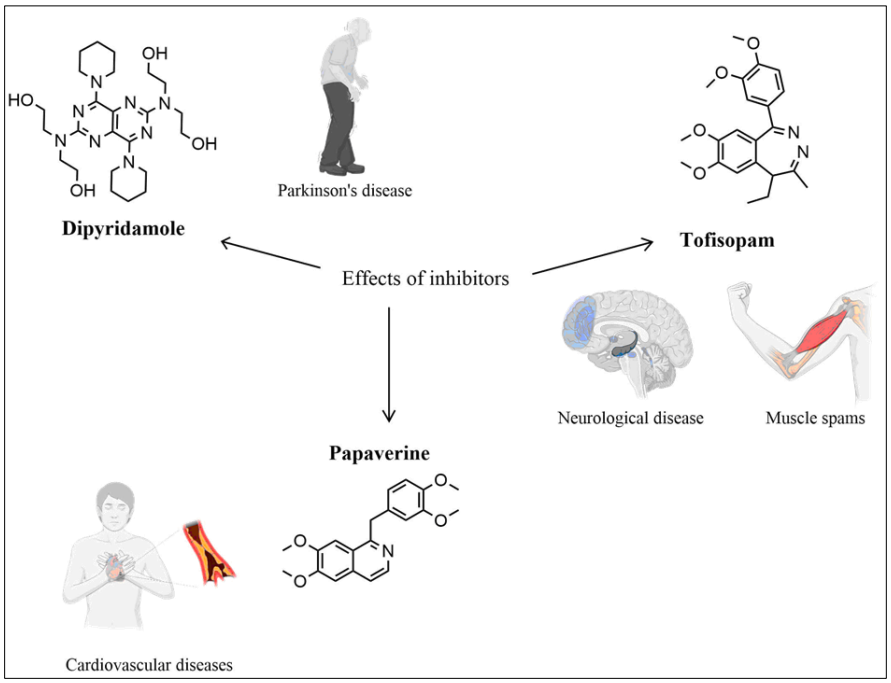

Figure 1 PDE10 inhibitors and their clinical uses

The current state of research in the field of PDE10 inhibitors (Figure 1) is characterized by a growing body of literature that highlights the therapeutic potential of targeting this enzyme. However, the limited number of approved PDE10 inhibitors for clinical use indicates the need for further exploration and discovery of new drug candidates. Controversial and diverging hypotheses exist regarding the specific mechanisms underlying PDE10 inhibition and its potential therapeutic applications. There are three commercial inhibitors of PDE10, those are: Papaverine, Tofisopam and Dipyridamole. In papaverine, regarding neurodegenerative diseases, such as Alzheimer's disease (8) or Parkinson's disease (9), it has not been specifically investigated or recognized as a potential therapeutic agent for these conditions. However, some studies suggest that papaverine as PDE10 inhibitor primarily breaks down cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) in cells (10). A study suggests that Tofisopam could modulate cellular processes involved in neurodegeneration and amyloid-beta accumulation (11). And finally, dipyridamole has been investigated for its potential neuroprotective effects in various neurodegenerative diseases. As it has shown promise in experimental studies by modulating inflammatory responses, reducing oxidative stress, and promoting neuronal survival (12). Also, it has been found to have anti-cancer properties through multiple mechanism. However, further research is needed to understand the underlying mechanisms and explore their clinical utility in cancer treatment (13).

An *in silico* screening approach to explore the DrugBank database, a comprehensive collection of approved and investigational drugs, in search of potential PDE10 inhibitors. By utilizing computational methods, we aimed to identify existing drugs that have the potential to target PDE10 and repurpose them for the treatment of neurological and psychiatric disorders, and different types of cancer.

2. Material and methods

2.1. DrugBank Data Base Prepared.

All drugs in the DrugBank database (14) were prepared in LigPrep (15) under physiological conditions of pH 7.4 and stable protonation and tautomer states at this condition (16).

2.2. PDE10 enzyme prepared.

For the preparation of the study protein, the crystal with code 6IJH (17) from the protein data bank was used, cleaned of co-crystallized molecules and modeled at physiological conditions of pH=7.4 in Protein Preparation Wizard (18) according to the previously established protocol (16).

2.3. Docking Molecular

The validation of the crystal used was carried out with its co-crystal, obtaining an RMSD of 0.75 A. The database was studied by molecular docking by Glide (19) with standard precision and flexibility in the catalytic site with the movement of Ser, Thr and Try residues, as well as the formation of disulfide bridge bonds, according to the protocol previously reported (16).

2.4. ADMETx

ADME values were obtained from the DrugBank database and those not available were predicted with Schrodinger's QikProp (20). The toxicological data were obtained from the DrugBank database (14) and from bibliographic reports in medical records described in the table below.

3. Results and discussion

The PDE10 enzyme is responsible for the hydrolysis of cAMP and cGMP, the inhibitors work by blocking the catalytic site of this process to prevent hydrolysis. Given the diverse role of this enzyme, drugs are used for pathologies, however, they are not used based on their efficacy as a PDE10 inhibitor. Through molecular coupling we can observe the energy of each inhibitor with the PDE10, in Table 1 we can observe these inhibitors as well as the interactions of each one with the enzyme, finding those key residues of interaction as well as the energetic limits for selection of new candidates.

Table 1 Binding coupling energy and interaction by Reference PDE10 inhibitors

Name	BCE	Charged (-)	Polar	Apolar	Gly	HB	Pi-pi staking
Papaverine	-7.867	Asp-674 Asp-634 Glu-592 Glu-699 Glu-695	Ser-677 Ser-573 Ser-571 Asn-572 Gln-726 Thr-685 Hie-567 His-525	Leu-675 Leu-635 Val-678 Tyr-730 Tyr-693 Try-524 Phe-729 Phe-639 Phe-570 Ile-692 Trp-762 Ala-689 Ala-636 Met-713 Met-714	Gly-725	Gln-726	Phe-729 Phe-696
Tofisopam	-6.029	Asp-674 Asp-634 Glu-592 Glu-699 Glu-695	His-525 Hie-567 Ser-677 Ser-589 Ser-571 Ser-573 Asn-572 Gln-726	Tyr-524 Tyr-693 Val-678 Val-733 Phe-696 Phe-729 Phe-639 Phe-570 Leu-675 Leu-635 Ile-692 Ile-711 Met-714 Met-713 Met-591 Ala-636	Gly-569 Gly-725	Asn-572 Gln-592	Phe-696
Dipyridamole	-5.929	Asp-634 Asp-674 Glu-592	Gln-726 Ser-589 Ser-573 Ser-571 Ser-677 Thr-633 Asn-572 His-525 Hie-567	Phe-729 Phe-639 Phe-696 Met-713 Ile-711 Ile-692 Ala-732 Ala-636 Val-733 Leu-635 Leu-675 Tyr-524 Tyr-693	Gly-728 Gly-725	Gly-725 Asp-634 Asp-674	

These inhibitors that are in phase/clinical use present a large number of adverse effects, mainly nausea, vomiting, dizziness, drowsiness, and low blood pressure, given this, new inhibition alternatives are constantly sought, from the database by means of molecular coupling by Schrodinger, a total of 9823 drug interactions with PDE10, however, only 1225 were better than Dipyridamole (reference lower energy inhibitor), and only 176 better than Papaverine (best inhibitor found *in silico*), giving excellent candidates for study in a model *in vitro* or *in vivo*, considering that there are already toxicity studies of these as well as safety and effectiveness window studies. However, depending on the application that is sought to be given, there are other selection criteria, that is, if the application is towards the Central Nervous System (CNS), it must be able to reach it, as well as a minimally invasive administration, since they are long-term treatments; while for associations in cancer, the aim is to contrast the adverse effects of the drug against those of the same pathology. Table 2 shows the selected candidates with higher energy than the selected inhibitor, as well as their clinical use and route of administration, which also met the Lipinsky, Ghose and Veber criteria, resulting in 17 candidates and 9 candidates that do not meet all the criteria but do have high energy.

Table 2 DrugBank Inhibitors PDE10 candidates with traditional clinical use and administration route

Drug Candidate or Candidate repurposing	DrugBank ID	BCE	Clinical Use	Administration Route	L/G/V
Raltitrexed	DB00293	-10.195	Advanced colorectal cancer. (21)	Intravenous	1/1/1
Tedizolid phosphate	DB09042	-9.137	Bacterial infections of the skin and soft tissues. (22)	Intravenous/ Oral	1/1/1
Vilazodone	DB06684	-8.997	Antidepressant for major depressive disorder in adults. (23)	Oral	1/1/1
Nebivolol	DB04861	-8.823	High blood pressure and chronic heart failure. (24) (25)	Oral	1/1/1
Fluvastatin	DB01095	-8.751	Hypercholestemia and preventing cardiovascular diseases. (26)	Oral	1/1/1
Pitavastatin	DB08860	-8.687	Hypercholestemia and preventing cardiovascular diseases. (27)	Oral	1/1/1
Bepotastine	DB04890	-8.491	Symptoms of allergic conjunctivitis. (28)	Ophthalmic	1/1/1
Mirabegron	DB08893	-8.155	Overactive bladder. (29)	Oral	1/1/1
Prucalopride	DB06480	-8.150	chronic constipation in adults. (30)	Oral	1/1/1
Pioglitazone	DB01132	-8.101	Type 2 diabetes, Alzheimer's and multiple sclerosis. (31)	Oral	1/1/1
Drotaverine	DB06751	-8.070	Relieves pain and muscle spasms for biliary and renal colic. (32)	Oral	1/1/1
Protokylol	DB06814	-7.992	-	Respiratory	1/1/1
Olodaterol	DB09080	-7.979	Prolonged bronchodilator for EPOC. (33)	Respiratory	1/1/1
Floctafenine	DB08976	-7.939	Analgesic and anti-inflammatory for moderate to severe pain. (34)	Oral	1/1/1
Erlotinib	DB00530	-7.926	Metastatic non-small cell lung cancer and advanced pancreatic cancer. (35)	Oral	1/1/1
Rosiglitazone	DB00412	-7.885	Type 2 Diabetes and Breast Cancer (Clinical Trial). (36)	Oral	1/1/1
Tiagabine	DB00906	-7.873	Epilepsy and seizure disorders. (37)	Oral	1/1/1
Pralatrexate	DB06813	-11.094	Treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL). (38)	Intravenous	0/1/1
Dipyrithione	DB11327	-10.334	Pyrithione derivatives are used for the treatment of dandruff and seborrheic dermatitis. (39)	Topical	1/1/0
Light green SF yellowish	DB11183	-11.118	Histological stain used for the examination of tissues and cells. (40)	Ophtalmic	0/0/1

Leucovorin	DB00650	-10.910	Used as rescue treatment to counteract the toxic effects in cancer chemotherapy. (41)	Intramuscular/intravenous	0/0/1
Lanreotide	DB06791	-10.875	Treats acromegaly. (42)	Subcutaneous	0/0/1
Indium In-111 pentetreotide	DB11835	-10.842	Used in the diagnosis of neuroendocrine tumors. (43)	Intravenous	0/0/1
Levoleucovorin	DB11596	-10.719	Used as rescue treatment to counteract the toxic effects in cancer chemotherapy. (44)	Intravenous	0/0/1
Gonadorelin	DB00644	-10.219	It test the functionality of the pituitary gland and hypothalamus: Also used to treat certain hormone-related conditions. (45)	Intravenous/subcutaneous	0/0/1
Methotrexate	DB00563	-10.216	Treatment of various types of cancer and autoimmune diseases. (46)	Oral	0/0/1
Papaverine	DB01113	-7.867	Vascular spasms as a vasodilator. (47) (48)	intravenous/ Intramuscular	1/1/1
Tofisopam	DB08811	-6.029	Used as an anxiolytic agent in anxiety disorders. (49)	Oral	1/1/0
Dipyridamole	DB00975	-5.929	Used as antiplatelet therapy. It increases blood flow to the heart. (50)	Intravenous/oral	0/0/0

Table 2 shows the 28 candidates for repositioning. However, Protokylol has no direct use and Indium In-111 pentetreotide and Light green SF yellowish are used as contrast dye, so they are not suitable for pathology treatments associated with PDE10. The rest of the candidates are viable a priori due to their current uses, including some that are already being used against pathologies related to PDE10, such as Nebivolol, Fluvastatin, Pioglitazone and Rosiglitazone used in cardiac pathologies and diabetes. While Raltitrexed, Erlotinib, Rosiglitazone and Pralatrexate are used against cancer, which allows us to infer that these drugs may have more than one molecular target. The remaining 25 candidates were selected based on the pathology on which they could act, according to the ADMETx properties (Table 3). For a drug directed at the CNS it is necessary that it have a good bioavailability, therefore a good adsorption by blood brain barrier (BBB) and also that it has an effect on the CNS, the latter predicted by QikProp, as a value -2 idodeno and -1 good for new drugs on the CNS, resulting in 6 candidates for this type of treatment, Fluvastatin, Pitavastatin, Mirabegron, Pioglitazone, Vilazodone and Plalatrexate, however, these last two have a very low Jm value indicating a high probability of bioaccumulation which rules them out as drugs for CNS, given the type of adverse effects that could present, therefore; 4 candidates would remain.

Table 3 ADMETx Properties of DrugBank PDE10 inhibitors candidates

Drug Candidate or Candidate repurposing	ATC code	BBB	CNS	LogP	TPSA	Physiological Charge	Jm
Raltitrexed	L01BA03	No	-2	1.650	148.400	-2	0.000002
Tedizolid phosphate	J01XX11	-	-2	0.820	152.790	-2	0.000205
Vilazodone	N06AX24	Yes	-2	4.210	102.290	1	0.000000
Nebivolol	C07FB12	Yes	0	2.440	70.950	1	0.010653
Fluvastatin	C10AA04	Yes	-2	3.690	82.690	-1	0.001694
Pitavastatin	C10AA08	Yes	-2	3.750	90.650	-1	0.000355
Bepotastine	V	No	0	3.640	62.660	0	0.000795
Mirabegron	G04BD12	Yes	-2	2.200	100.270	1	0.003659
Prucalopride	A06AX05	-	0	2.090	76.820	1	0.012296
Pioglitazone	A10BD09	Yes	-1	3.170	68.290	-1	0.017562
Drotaverine	A03AD02	Yes	0	5.350	48.950	1	0.007690
Protokylol	V	-	-2	1.290	91.180	1	0.066532
Olodaterol	R03AL06	-	-2	2.020	100.050	1	0.000798
Floctafenine	N02BG04	-	-2	3.050	91.680	0	0.014529
Erlotinib	L01EB02	Yes	0	3.130	74.730	0	2.145554
Rosiglitazone	A10BD04	Yes	0	2.950	71.530	-1	0.041677
Tiagabine	N03AG06	Yes	0	4.980	40.540	0	0.000060
Pralatrexate	L01BA05	Yes	-2	0.1	207.3	-2	0.000003
Dipyrithione	-	-	0	0.5	53.88	0	0.811216
Light green SF yellowish	-	-	-	2.08	177.85	-2	
Leucovorin	-	No	-2	-0.46	215.55	-2	0.000000
Lanreotide	H01CB03	-	-2	1.87	355.08	2	0.002634
Indium In-111 pentetreotide	V09IB01	-	-2	1.24	530.22	-2	0.113416
Levoleucovorin	-	-	-2	-1.1	215.55	-2	0.000000
Gonadorelin	V04CM01	No	-2	-0.09	476.63	1	0.000013
Methotrexate	L04AX03	No	-2	-0.05	205.92	-2	0.000000
Papaverine	N03AG06	Yes	1	4.190	49.810	0	2.512056
Tofisopam	N05BA23	Yes	1	4.29	61.64	0	0.079666
Dipyridamole	B01AC07	No	-2	1.52	145.44	0	0.002332

BBB “blood brain barrier”, CNS “Central nervous system”, LogP “octanol/water partition coefficient”, TPSA “surface area polar topology”, Jm “Epidermal transfer coefficient”

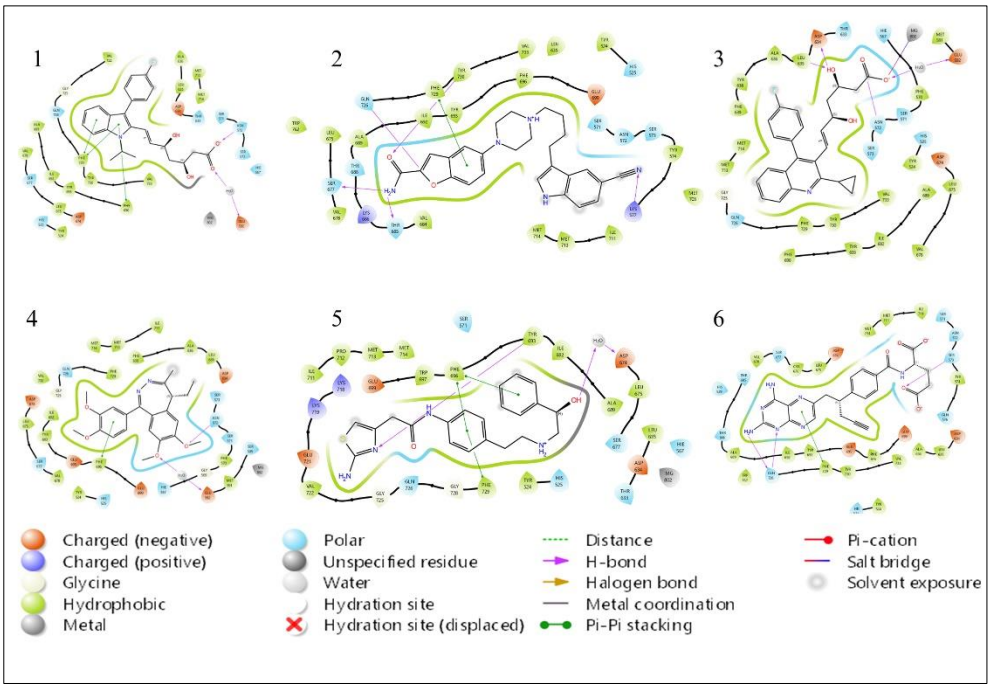

Figure 2 Interaction DrugBank inhibitors PDE10 drug candidates for CNS diseases use. (1. Fluvastatin, 2. Vilazodone, 3. Pitavastatin, 4. Tofisopam, 5. Mirabegron, 6. Pralatrexate)

For candidates for repositioning for use against cardiovascular diseases and diabetes, it is necessary that they be adsorbed in blood, but it is preferable that they do not pass or influence CNS, so with the data in Table 3, resulting in 5 new candidates, Nebivolol, Drotaverine, Erlotinib, Rosiglitazone and Tiaganine, as well as Tofisopam, whose inhibitory effect on PDE10 is already known. Analyzing your Jm, Drotavarine, Rosiglitazone or Tagabine would not be recommended given their high predisposition to biocumulation resulting in Nebivolol and Erlotinib as new as well as Tofisopam as known.

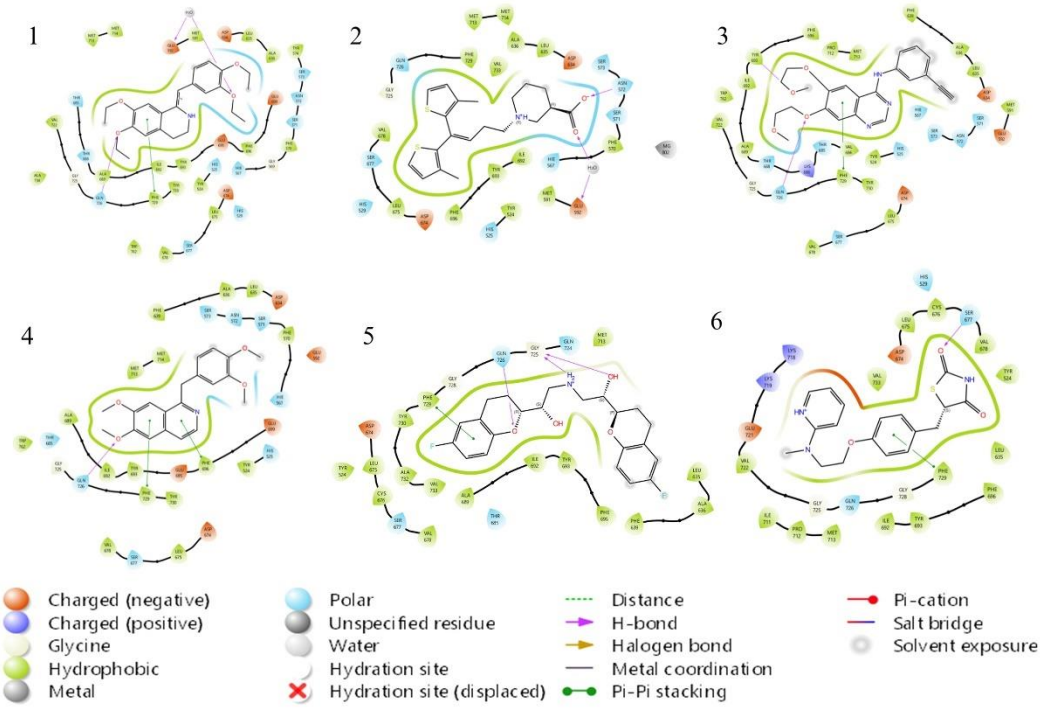

Figure 3 Interaction DrugBank inhibitors PDE10 drug candidates for diabetes and cardiovascular diseases use. (1. Drotaverine, 2. Tiagabine, 3. Erlotinib, 4. Papaverine, 5. Nebivolol)

For the selection of candidates against Cancer, it is difficult to limit the candidates, given the aggressive nature of the pathology, however a low bioaccumulation and null effect on CNS is convenient, resulting in 6, Nebivolol, Prucalopride, Drotaverine, Erlotinib, Rosiglitazone and Dipyrithione, of which Erlotinib and Dipyrithione are already used against some types of cancer, and even Nebivolol, Drotaverine, Erlotinib and Rosiglitazone, were previously candidates against cardiovascular pathologies.

For the selection of candidates against cancer, it is convenient not to limit their selection given the aggressiveness of the pathology, however, it is important to consider a low bioaccumulation and no effect on the CNS. Our analysis yielded 6 candidates: Nebivolol, Prucalopride, Drotaverine, Erlotinib, Rosiglitazone and Dipyrithione, of which Erlotinib and Dipyrithione are currently used for some types of cancer and Nebivolol, Drotaverine, Erlotinib and Rosiglitazone were previously candidates against cardiovascular pathologies.

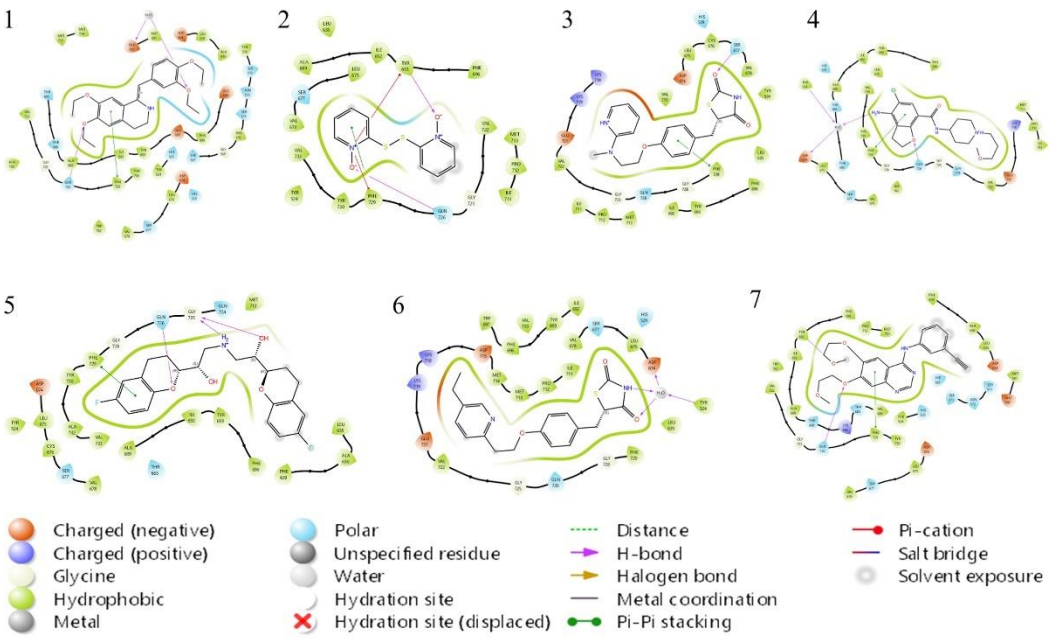

Figure 4 Interaction DrugBank inhibitors PDE10 drug candidates for cancer use. (1. Drotaverine, 2. Dipyrithione, 3. Rosiglitazone, 4. Prucalopride, 5. Nebivolol, 6. Pioglitazone, 7. Erlotinib)

At the level of adverse effect in table 4 we can see that these are at the same level or lower than the controls, several of these adverse effects can even be explained by PDE10 inhibition, such as a drop in blood pressure, giving an overview of largest application of these compounds for further *in vitro* and *in vivo* studies.

Table 4 Adverse effects of Drug Candidates repositioning by PDE10

Drug Candidate repurposing	**Adverse effects**	**Diseases**
Vilazodone	Nauseas, diarrea, vómitos, insomnio, cefalea, mareos (51) Nausea, diarrea, vomiting, insomnio, headache, dizziness	CNS
Nebivolol	Fatigue, dizziness, headache, nausea, headache. (52)	Cardiovascular disease, Cancer
Fluvastatin	Muscle pain, headache, abdominal pain, nausea. (53)	CNS
Pitavastatin	Muscle pain, headache, abdominal pain, nausea. (54)	CNS
Mirabegron	Increased blood pressure, headache, swelling of nose and throat, diarrhea (55)	CNS

Prucalopride	Headache, nausea, diarrhea, vomiting, abdominal pain (56)	Cancer
Pioglitazone	Weight gain, edema, headache, hypoglycemia, (57)	Cardiovascular disease, Cancer
Drotaverine	Dizziness, drowsiness, dry mouth, blurred vision, nausea, (58)	Cardiovascular disease, Cancer
Erlotinib	Skin rash, diarrhea, nausea, vomiting, loss of appetite (59)	Cardiovascular disease, Cancer
Rosiglitazone	Edema, weight gain, headache, pain in the extremities, hypoglycemia (60)	Cardiovascular disease, Cancer
Tiagabine	Dizziness, drowsiness, trembling, nervousness, nausea (61)	Cardiovascular disease
Pralatrexate	Nausea, vomiting, diarrhea, anemia, hepatitis, fibrosis, alopecia. (62)	CNS
Dipyrithione	Skin irritation, dryness or flakiness, allergic reactions (63)	Cancer
Papaverine	Nausea, vomiting, dizziness, drowsiness, low blood pressure. (64)	N/A
Tofisopam	Nausea, vomiting, diarrhea, stomach discomfort, drowsiness, skin rash or itching, headaches, dizziness. (65)	Cardiovascular disease
Dipyridamole	Diarrhea, abdominal discomfort, dizziness, drop in blood pressure (66)	N/A

4. Conclusion

The potential of *in silico* screening for drug repurposing to identify PDE10 inhibitors whit therapeutic applications in neurological and psychiatric disorders, as well as cancer treatment. The analysis of DrugBank database led to the discovery of 28 promising candidates, 17 of which fully met the selection criteria. These candidates showed favorable interactions with PDE10 and exhibited acceptable ADMETx properties, suggesting their viability for further investigation. Moving forward, further *in vitro* and *in vivo* studies are essentials to validate the efficacy and safety of these PDE10 inhibitors. If successful, these candidates could open new avenues for the treatment of a wide range of disorders, thereby improving patient outcomes and addressing unmet medical needs. Overall, the study contributes to the growing field of drug repurposing and highlights the importance of computational approaches in expediting drug discovery and development.

Compliance with ethical standards

Acknowledgments

CONACYT Pronaces-317580 Project for access to the Schrödinger License by Jesus Sandoval Ramirez.

Disclosure of conflict of interest

There is no conflict of interest between the authors on this manuscript.

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