‘Omics’ Data Analysis of Repurposed Drugs Entinostat and Tropicamide Against Dopamine Metabolism

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MASTER OF TECHNOLOGY

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CANDIDATE'S DECLARATION

I, Ambika Dubey, 2K17/BIO/01 student of M.Tech Bioinformatics, hereby declare that the project Dissertation titled **"Omics Data Analysis of Repurposed Drugs Entinostat and Tropicamide Against Dopamine Metabolism"** which is submitted by me to the department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Technology, is original and not copied from any source without paper citation. The work has not previously formed the basis for the award of any Degree, Diploma Associateship, Fellowship or other similar title or recognition.

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CERTIFICATE

I hereby certify that the Project Dissertation titled **"Omics Data Analysis of Repurposed Drugs Entinostat and Tropicamide Against Dopamine Metabolism"** which is submitted by Ambika Dubey, 2K17/BIO/01, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Technology, is a record of the project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part of full for any Degree or Diploma to this University or elsewhere.

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ABSTRACT

Background: Efficacy and effectiveness of the drugs in case of Alzheimer's disease (AD) as well as Parkinson's disease (PD) is quite challenging and rough path. The cost of manufacturing and approving a drug along with time makes the process of drug design and discovery intense, tiresome, non-profitable and extensive. After all these problems, when a drug finally reaches the clinical trials either it gets failed in the beginning itself otherwise eventually in the later phases which creates a huge economic burden to the manufacturers. All the approved drugs, aim at giving just the symptomatic-relief to the patients thus cannot eradicate the disorder completely during late onset/diagnosis and also have many side-effects. Therefore, it is inevitable to identify compounds aiming at disease-modification and not just relieving symptoms at an early stage. The best, profitable and less time-consuming process for the above is drug repositioning.

Methods: We generated a list of candidate drugs having the potential to cross blood-brain barrier for three overlapping gene targets extracted from different sources after functional annotation for both AD and PD, sorted by preprocessing of the original entrants. The final potentials were spotted through comparing gene-expression pattern of drugs with controls through Connectivity map (Cmap).

Results: The study highlighted two possible repurposed drugs entinostat and tropicamide to be used against three common targets of Alzheimer's and Parkinson's disease.

Keywords: Drug repositioning, Alzheimer's disease, Parkinson's disease, Connectivity map.

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LIST OF ABBREVATIONS

AD	Alzheimer's Disease
PD	Parkinson's Disease
Cmap	Connectivity Map
DEGs	Differentially Expressed Genes
NMDA	N- Methyl D-aspartate
Aβ	Beta-Amyloid
MAO	Mono-amine Oxidases
COMT	Catechol-*O*- methyltransferase
MPTP	1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine
GABA	Γ- aminobutyric acid
MAOA	Mono-amine oxidase form A
MAOB	Mono-amine oxidase form B
HPO	Human Phenotype Ontology
GWAS	Genome wide association studies
CTD	Comparative Toxicogenomics Database
HMDB	Human Metabolome Database
PSEA	Pathway-set Enrichment Analysis
BBB	Blood-Brain Barrier
ADME	Absorption Distribution Metabolism and Excretion
SVM	Support Vector Machine
DA	Dopamine
HDACi	Histone Deacetylase inhibitor

Chapter 1: Introduction

Today's medicine is tailored uniquely and categorically according to the stature of the patient. Because of new possibilities, emerging innovations and wearable technology this area of personalized medicine has become a hotspot for pharmacological research and economics. But, the burden of the cost of the processes, lengthy time and unexpected adverse events for predetermining drug is still a matter of concern and all these problems get multiplied when we talk about neurological disorders. A practical solution to combat these problems lies in the pipelines of pharmacological repositioning/repurposing. It is an escalator of strategic computational steps which help in repositioning the wheel of usage of an already approved drug. Thus, in order to improve productiveness and efficacy of modern drug discovery process drug personalizing and repositioning go hand in hand [1].

Neurological diseases have a wide impact not only on the patient and his care takers but also on the drug developers and the nation (economically). These diseases are multifaceted and age-related thus bound to get worsened slowly-slowly with the time. On the other hand, the drugs available up till now are just relieving from some of the symptoms, giving support for living life a little longer and not for complete eradication of the disease or its modification [2]. Neurological disorders are interlinked that means one symptom give rise to another sowing seeds for other type of dysfunctions to reside in sync. For example, Alzheimer's with Dementia or Parkinson's disease leading to cause Alzheimer's disease etc. There is an increase of 145% deaths due to Alzheimer's and related disorders. All these norms add up in increasing the difficulty level to treat the disease efficiently. Among all, Alzheimer's and Parkinson's diseases are most common and yet highly detrimental. Both the diseases have uncommon symptoms still if we highlight molecular pathogenesis both of them are vastly homogenous and have some mutual features relating to

mitochondrial dysfunction, response to oxidative stress, aging of brain, accumulation of proteins, nature of interactions etc. Due to these intricating similarities, it is of much importance that we study this crosstalk so that we can target specific, important or novel pathways and multiple-targets at once taken in a combination with a drug [3]. Experiments have proven the above fact as more than 90% of the differentially expressed genes (DEGs) have been known to occur concurrently in both the disorders with similar upstream/downstream regulators [4].

Looking at the current scenario of rapid failure and huge economic loss as over thousands of compounds identified as candidate drug have failed to prove their worth as defined through the studies conducted in the field of drug development and discovery, all the research scholars and scientists have been compelled to rethink and improvise on the type of process chosen and kind of methodology followed to derive a novel compound as an effective therapeutic molecule. A variety of inhibitors, monoclonal antibodies, enhancers etc. have been identified as potential therapeutics along with their different scoring and validating tools but all have constantly failed to give the exact said results in live. The chief reasons for the above failure could be many foremost being; targeting wrong candidates. Second being, failure of the proposed compound to show promising effects in long run clinical trials too. Thirdly, lack of reliable, accurate and precise instruments with good sensitivity and specificity and standardized tests. Fourth can be lack of precise steps taken from starting till the end of the discovery and developmental processes. Lastly, delayed treatment because of which the compound may not get enough time to work or bind with the targets. All these points can be the reason for the failure of the potential compounds in different phases of clinical trials [5].

In order to avoid all the aforesaid cons and risk, drug repositioning can be a promising approach in order to get a safe and efficient drug for medical needs that too early and light on the

pocket of developers. There are many advantages for using the repositioning approach, it eliminates the burden of selecting appropriate targets, drug's pharmacodynamics and pharmacokinetics properties, its toxicity and side-effects, testing on various models, patenting issues and lot more [6]. In this paper we have tried to reposition drugs computationally jotted from the databases towards some of the common identified targets of AD and PD and validated their effects through measuring their gene expression patterns with the ones already known.

Chapter 2: Review of Literature

There are more of symptomatic relieving drugs which have been approved, carrying some or the other side effects, variable response rates and tolerance but due to the lack of availability of significant medications, they are still being used. One class is of cholinesterase inhibitors in which Tacrine was first of them but causes liver toxicity. Next inhibitors discovered were Galantamine, Donepezil and Rivastigmine. Next and most popular one is a NMDA receptor blocker, Memantine which is normally well tolerated and have fewer side effects than others. These medicines are also prescribed in combination or alone depending upon its effects in treating mild to severe conditions of Alzheimer's disease. Other areas of the therapeutic remains anti-amyloid therapy in which beta-secretase and gamma-secretase enzymes are involved, candidates of which are still under clinical trials. Tarenflurbil, has shown to lessen the levels of beta-amyloid (Aβ) but failed to show results in demonstrations. Immunizations have failed to get approved in the trials as showed no progression. Monoclonal antibodies gave almost similar results bapineuzumab showed none, solanezumab showed some and aducanumab showed best promising results in clinical trials [7]. For the proper functioning and a healthy brain, a defect free lysosomal system is must. Animal model studies of rapamycin proved to be a double-edged sword. It can only prevent plaques and tangles accumulation in early AD brain and is used on people with delayed dementia [8].

Shaking palsy, after Alzheimer's is the second most prevailing disease in relation with age. More common in males, peak in ages more than 90 years and can coexists with dementia and depression. Levodopa remained the most effective therapeutic since 1960's for this disorder. It is characterized by Lewy bodies formation, SNCA gene's duplication or triplication, mutation in glucocerebrosidase 1 mutation and high nitrate and oxidative stress. Conventional dopamine precursors in case of PD treatment are levodopa or L-DOPA whereas cabergoline, apomorphine,

rotigotine, lisuride, pramipexol, bromocriptine, pergolide, amantadine are dopamine agonists. Selegiline and rasagiline are monoamine oxidase inhibitors. Entacapone and tolcapone are inhibitors for catechol-*O*- methyltransferase. These all are considered as anti-parkinsonian drugs. In terms of novel natural treatment for the disorder many compounds have been proposed which help in eliminating the risk of dopaminergic neurons as well as provide additional benefits of anti-inflammation, anti-oxidant and neuroprotective effects. Among them, atremorine is the strongest with many neuroprotective benefits. It protects against 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) induced neurodegeneration. Many drugs have been identified on the basis of the conventional ones but still somehow the problem has yet not been eradicated completely. Dopaminergic drugs have been seen to overstimulate the neurotransmitter inclining the danger towards blood vessels in brain and heart. Therefore new found drugs must consider dopaminergic protection for reducing early neurodegeneration [9].

Drugs proven to be efficacious among the studies fail to prove their aforementioned efficacy during clinical trials. For example, quetiapine is an antipsychotic used in PD psychosis, has failed to prove its efficacy in several randomized, double-blind clinical trials. Dementia remains non-responsive towards it. Pimavanserin another antipsychotic drug, it proved to be helpful among the diseased patients but discontinuation happened due to increase number of adverse events among the people like hallucinations, nausea, urinary tract infections etc. another drug clozapine although did not showed ill motor functions but made prone to fatal agranulocytosis because of which utmost care and monitoring was necessary for the patients because of this incommodious monitoring this medicine was given only when patients failed to response to the above ones [10].

Catechol-O-Methyltransferase (COMT), catalyzes transfer of methyl group from neurotransmitters resulting in their degeneration. It interferes with memory and decision-making. Being an independent risk enhancer for AD, COMT in prefrontal cortex it regulates dopamine levels, impairment in which can cause severe problems. Present on chromosome number 22q11.21, it has myriad allelic variations [11] [12] out of which one of the most found variation in COMT is at position 158, when valine substitute methionine which increases the rate of catabolism of DA up to four times specifically in asian population [13]. Patients with variations in DNA methylation or excessive mutations in PARK2 gene in dopaminergic neurons during late on-set of Parkinson's disease have been seen to have increased levels of membrane- bound COMT gene. This upregulation may cause reduced levels of dopamine release causing disturbance in movements and Parkinson's disease [14]. In astrocytes, MAOB synthesizes γ- aminobutyric acid (GABA) alteration in the levels of which causes memory decline in case of Alzheimer's disease signifying first Aβ independent target for AD. It also regulates Aβ production in AD brain through γ-secretase [15]. Monoamine oxidases are responsible for deamination of various neurotransmitters as well as xenobiotics varying their concentration in brain (mostly) and other tissues. MAOA's inhibitors have known to work against depression and anxiety whereas MAOB's inhibitors for AD and PD [16], [17]. The two forms of MAO's are based on their specificity towards substrate as well as inhibitors. Localization of MAOA is in catecholaminergic neurons whereas that of MAOB is in serotonergic neurons of glial cells. MAOB 's activity is age-related giving proofs of its relation with such disorders [18].

There are numerous methods of drug repurposing which can be used to find the best solution of our problems. First strategy, systematic drug repurposing, it uses computer-assisted approaches for integrating and analyzing large information drawn from literature, treatments and

trials. These approaches are classified into various sub-divisions like network-based techniques, bioinformatics, cheminformatics, signature-based techniques, 'omics' data mining and others. Second strategy is drug repurposing through cheminformatics which utilizes *in-silico* screening of the information from the already formed databases like DrugBank, these databases combine all the experimental and investigational research about a drug together, we can search about its mode of action, targets, similar compounds easily. Not only this it also provides validation status, type of drugs, pathways it is involved in and lot more. Third strategy of bioinformatics repositioning includes computer-aided linking of the drugs and proteins on the basis of similarity emphasizing on its binding sites and ligands. Different algorithms have been designed according to the need of the researcher in order to get best results. Fourth strategy is high-throughput literature analysis, automated literature mining is done in which large volumes of information is searched all together for validating the hypothesis made. Fifth strategy, is use of network-based approaches, simplifying query through analyzing relationships between compounds and targets on the basis of interactions, nodes and edges present at different levels. Sixth strategy, is signature-based repurposing, based on expression profiles of the genes sorted according to their scoring using various available tools like C-map. These scores are based on comparing of mRNA expression patterns or up/down regulation of the signatures etc. on different cell lines [19].

In order to establish similar method of causation among multiple diseases for treating them all with a similar type of drug can be made possible by identifying genetic profiles at phenotypic level using PheWAS data [20]. With the aim of repurposing drugs for rare diseases, Human Phenotype Ontology (HPO) is widely used for annotations of phenotypic aberrations, Monarch, another phenotypic resource helps in equating disease among species and self. CentoMD database links genotypes with phenotypes by using technique namely exome sequencing. Next Gen sequencing

data is now a hotspot for analyzing publicly accessible variations for rare diseases [21]. There are two types of repositioning approaches namely, drug-centric and disease-centric methods both of them helps in target-driven repurposing coming under the topic of 'strategic repurposing'. For fulfilling the urgent urge of an acceptable and accurate computational validation technique that can be applied before doing any wet-lab experiments, a database known as Drugs of New Indications has been made with old and newer indications of about 237 drugs, still under development for release [22]. The vast amount of data and its multifaceted analysis determines the success rate for identification of the drug repurposed therefore among all the available methods knowledge-based and signature-based methods (C-map) for recycling of old drugs have proved to give the best results but still there are some challenges faced in existing repositioning pipeline [23].

Chapter 3: Materials and Methodology

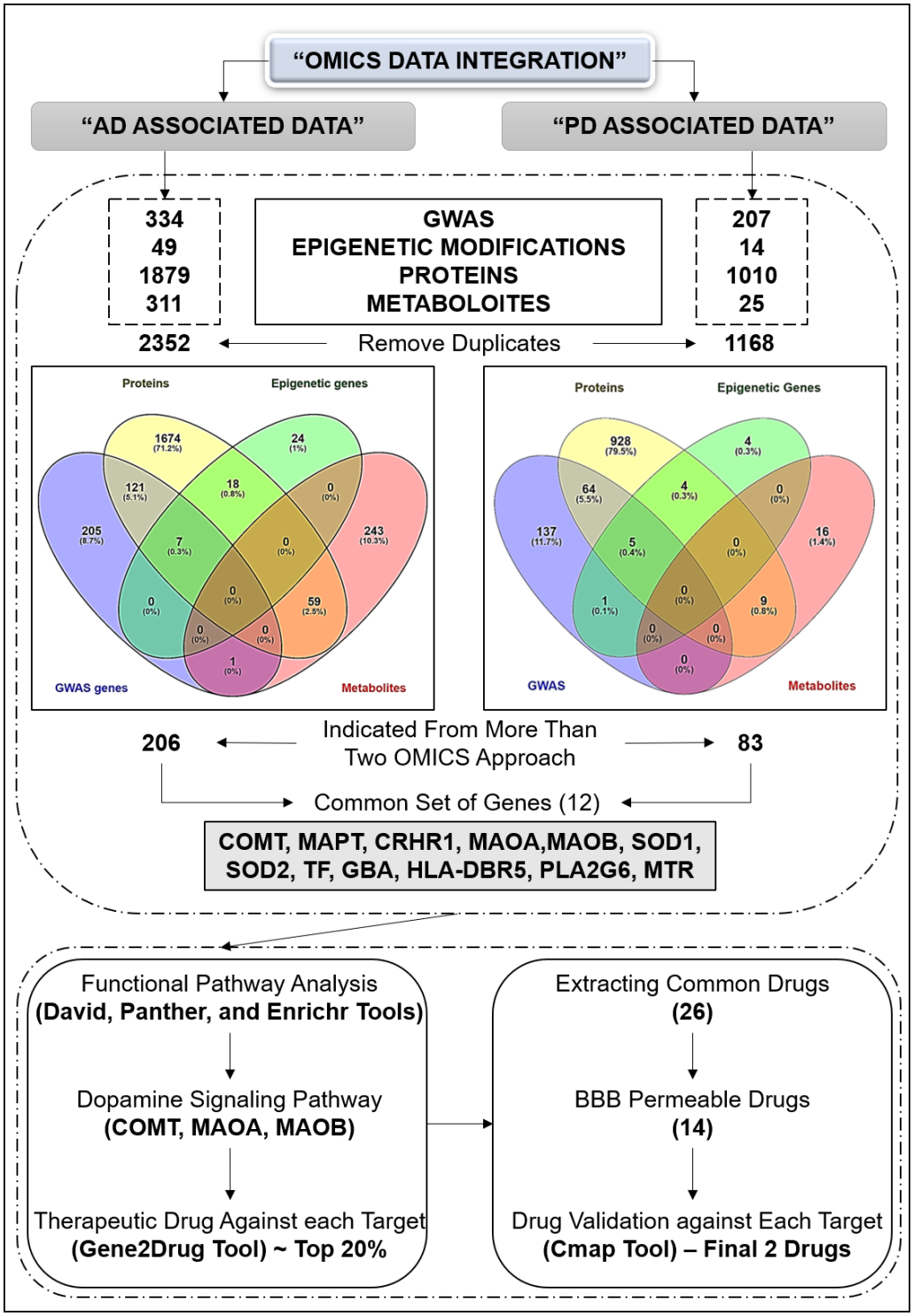

Figure 1: Workflow of drug repositioning through 'omics' data.

1. Searching for potential anti-AD and anti-PD targets:

To get potential anti-AD and anti-PD targets, we collected data from various sources. Data to be collected was sub-portioned in four forms that is genes, proteins, metabolites and epigenetic changes. In order to extract information related to AD and PD associated genetic variations, we explored genome wide association studies (GWAS) catalog (https://www.ebi.ac.uk/gwas). PubMed IDs, initial sample size, name of the gene, its position and region of presence, SNPs, p-value, odd-ratios or beta value etc. were jotted down [24]. To get possible information about the related proteins, we searched for them in comparative toxicogenomics database (CTD) (http://ctdbase.org/) [25]. Data was grouped among following headers, protein name, uniport id, gene name, protein class, scores etc. Facts related to epigenetics for both the was compiled through literature search under headings such as protein name, PubMed ID, epigenetic modification, its regulation, its source, location and method. For metabolites, we combed human metabolome database (HMDB) (http://www.hmdb.ca/) for data on metabolite's name, ID, source, its condition and concentration, age and sex [26]. All the above-mentioned data was gathered for both AD and PD which later on was filtered.

2. Data Filtration for accomplishing final set of targets:

Filtering of the targets was done according to the type of data we got from respective searches. Among them, only genes that were present in ≥ 2 metabolites, proteins and epigenetic variations were taken into final consideration. This work was done for both Alzheimer's and Parkinson's diseases disjointedly. Final genes were those that were common in both of these disorders.

3. Mapping gene-metabolites for AD and PD and visualizing the network:

Gene-metabolites related information was exported from HMDB database and Cytoscape software version 6.1 (https://cytoscape.org/) was used in order to construct the network for the same.

4. Pathway analysis and Functional Annotation:

In order to achieve precision amid the filtered data, the final common genes were then entered in Panther (http://pantherdb.org/); which contains information of about 15524 protein families and approximately 107627 distinct (function) subfamilies and Enrichr (https://amp.pharm.mssm.edu/Enrichr/) which contains 153 libraries, 302,225 terms and 19,977,890 lists analyzed [27]. Designed as an aid in high-throughput analysis, Panther classifies proteins and their genes. This classification is based on four fronts of families and sub-families, molecular function at biochemical level, biological processes at cell or organism level and last but not the least pathways specifying relations with neighboring interactome [28]. Functional annotation of the proposed targets was also done through DAVID (https://david.ncifcrf.gov/) tool giving p-value, false discovery rates differentiating all the targets amid all the biological processes [29].

5. Mapping core protein to existing drugs:

Taking advantage of the currently available genome-wide transcriptional data on Gene2drug (http://gene2drug.tigem.it/), helps in annotating pathways through assessing the effect of target gene through cellular mechanisms they are involved in thus, providing an essential and effective shortcut to drug discovery. It uses the method called as pathway-set enrichment analysis (PSEA). Gene expression profiles from connectivity map are converted to expression profiles and ranked according to their p-values of Kolmogorov-Smirnov statistic [30]. We entered our final filtered

core proteins in the dialog box and selected for all the biological pathways from the next one. The result page shows top 10% drugs prioritized by PSEA analysis. Enrichment score depicts the regulation that is "up or down" and p-value tells for extreme top and bottom ranks for the pathway. Smaller the rank, pathway is upregulated (at the top) whereas larger the rank, lower the profile and is down regulated. Files were exported for all of our target proteins and results were analysed. In order to cut-short the number of the drugs, we took top 10% drugs approximately 131 drugs according to their scores from all the targeted genes and found out the common ones amongst all.

6. Checking Blood-Brain permeability:

As the repurposed drugs are to be used for nervous system disorders blood-brain barrier (BBB) becomes a major concern. Therefore, we checked for this permeability through CBLigand (https://www.cbligand.org/CCGS/) tool. It aims at providing rapid identification of lead compounds and their targets, helps in drug discovery process, ADME profiling and lot more. It also contains an Alzheimer's disease related domain designed for its targets and pharmacology. The blood-brain barrier uses SVM and LiCABEDS algorithm [31]. Target Hunter identifies target molecules.

7. Mode of action of the drugs for repurposing:

For extraction of this knowledge we went to a unique database for bioinformatics and cheminformatics resource, Drug Bank. We got information on their ID, type (approved/ withdrawn/ investigational), their mode of action along with their enrichment scores and p-values from gene2drug.

8. Computational analysis of potential drug target and repositioned drugs:

In order to validate our candidate targets we used two tools namely ToppGene and ToppNet (https://toppgene.cchmc.org/). They prioritize the gene targets on the basis of functional similarity to training set and tropological features in protein-protein interaction networks respectively [32]. Among the training set we provided the high-risk well-known genes in AD and PD pathogenesis.

We also used Connectivity map (Cmap) tool (https://clue.io/cmap) in order to validate and analyze repurposed drugs. This tool uses transcriptional expression information to unravel relation between diseases, therapeutics and cells. Developed by Broad Institute, they used L1000 assay to generate expression profiles which are over 1 million. It can be used by biologists, chemist and pharmacologists in the areas of pathway analysis, structure-function relationship, drug discovery and many more [33] [17]. Here, with this tool we checked for the expression patterns of our filtered drugs with various sets of known drugs taken as control.

Chapter 4: Results

1. Mining of candidate AD and PD targets:

Extracting potential targets from four different sources made us analyze 344 GWAS genes for AD and 207 genes in case of Parkinson's disease. 1879 AD-related proteins and 1010 PD-related proteins from CTD database. 14 epigenetic (acetylation/ methylation) variations in brain in PD and 49 in case of AD among various regions in brain. 25 HMDB metabolites in case of Parkinson's and 311 that in Alzheimer's disease. After removing all the existing duplicates there were 2352 entries in case of AD and 1168 that in PD. 560 common targets were observed among the two diseases. Among all these genes/proteins, present in more than two AD/PD related metabolites when clubbed together came out to be 206 in Alzheimer's and 83 in Parkinson's disease. Among them common ones were sorted out and as a result we got 12 candidate genes for further studies. These genes were CRHR1, MAPT, MAOA, MAOB, TF, GBR, COMT, SOD1, SOD2, HLA-DBR5, PLA2G6 and MTR. Total 311 protein-metabolite interactions were indicated from the HMDB database. Yellow colored nodes indicate the proteins while the green colored nodes indicate the metabolites. Iron, Magnesium, Valine, L-dopa, Dihydroxybenzeneacetic acid were some of the AD-metabolites which interact with COMT, 1-methyl histamine was the one interacting with MAOB along with the zoomed-insert that shows metabolite dopamine (HMDB0000073) that interacts with all three targets of interest. While talking about PD, total of 25 protein-metabolite interactions were found in HMDB database. Out of which COMT interacted with Magnesium, S-Adenosylhomocysteine, 3-Methoxytyramine, Homovanillic acid and Vanylglycol whereas MAOA and MAOB were seen interacting with Serotonin, 1-phenylethylamine and 3-methoxytyramine (HMDB0000022) as common with COMT as shown in the zoomed-inset.

Fig. 2

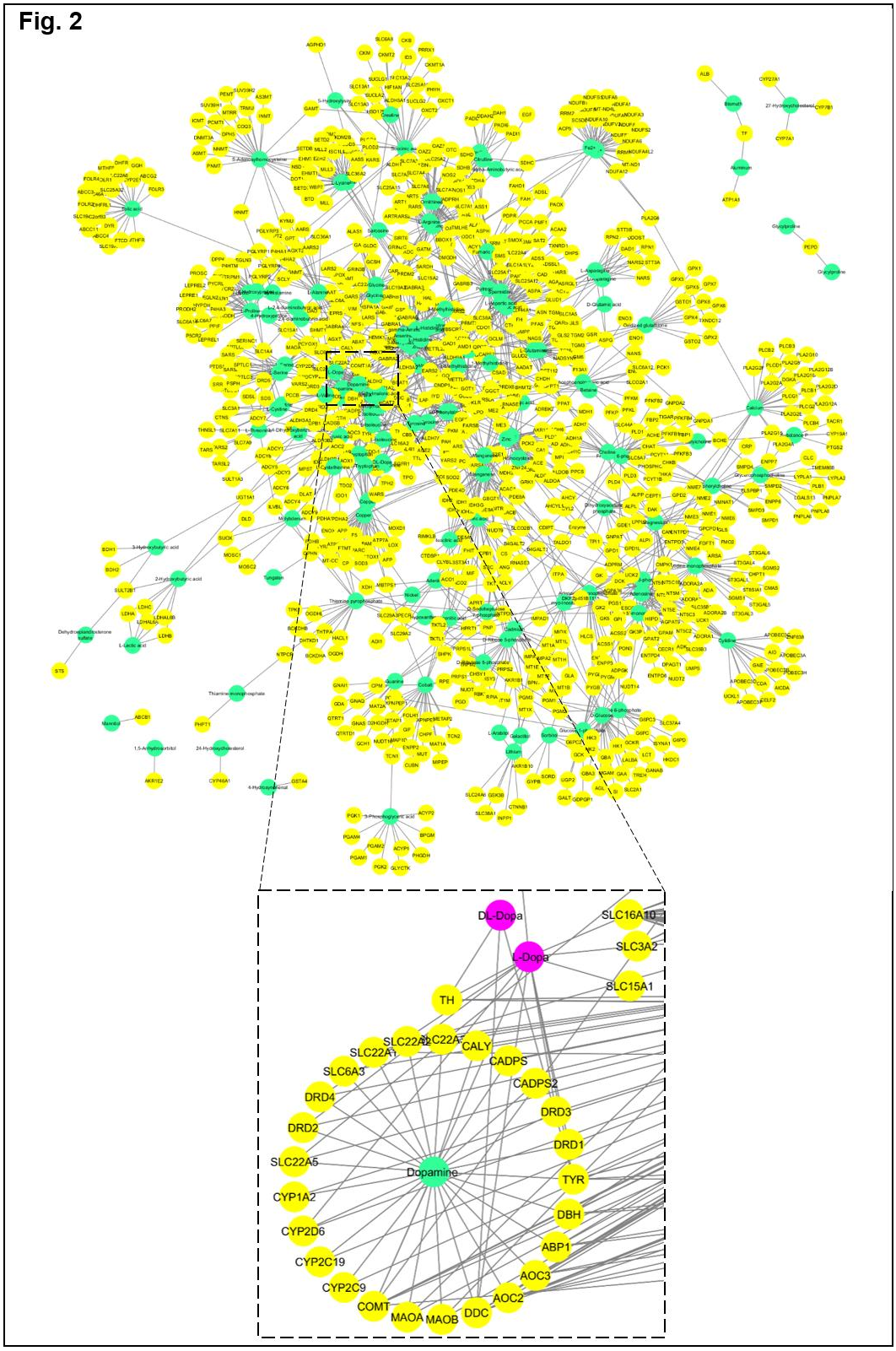

Figure 2: Gene-metabolite network of Alzheimer's disease.

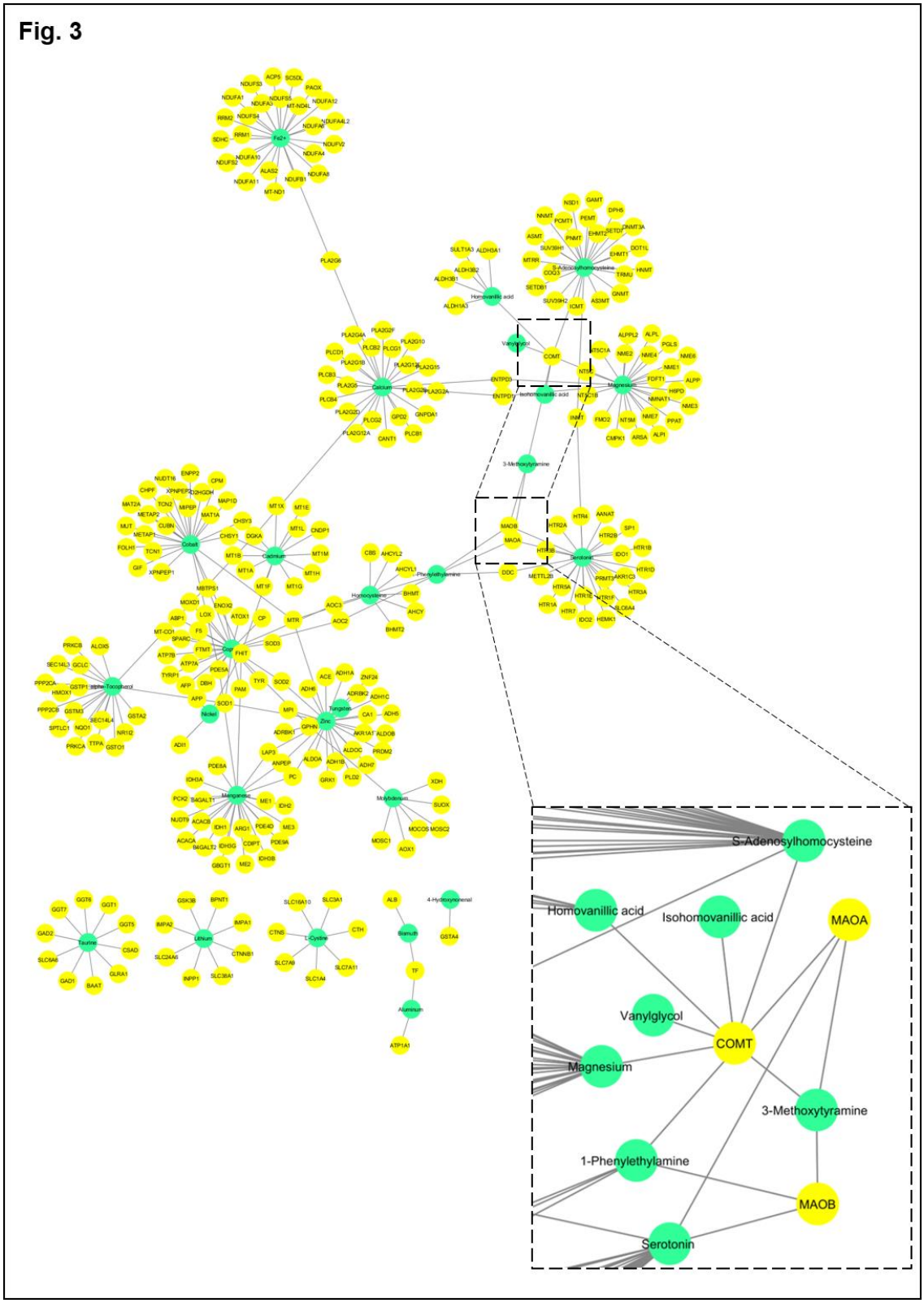

Figure 3: Gene-metabolite network in case of Parkinson's disease.

2. Identification of main candidate genes through enrichment analysis using DAVID and PANTHER:

These 12 gene targets went through pathway analysis through panther which provided the information on the pathways in which our query genes are involved in. 3 genes, COMT, MAOB and MAOA were pinned to be in two pathways that are dopamine receptor mediated signaling pathway and adrenaline and non-adrenaline biosynthesis pathway; rest of the genes remained unidentified in terms of common targeted pathways. DAVID tool was used for doing functional enrichment annotation of same 12 target genes. This tool gave information of pathways in which these genes are present based on the fold enrichment score, Benjamini and FDR values. False discovery rates ≤ 0.5 are considered important and the results have shown that only GO:0042420~dopamine catabolic process having three genes are significant are thus taken for further studies.

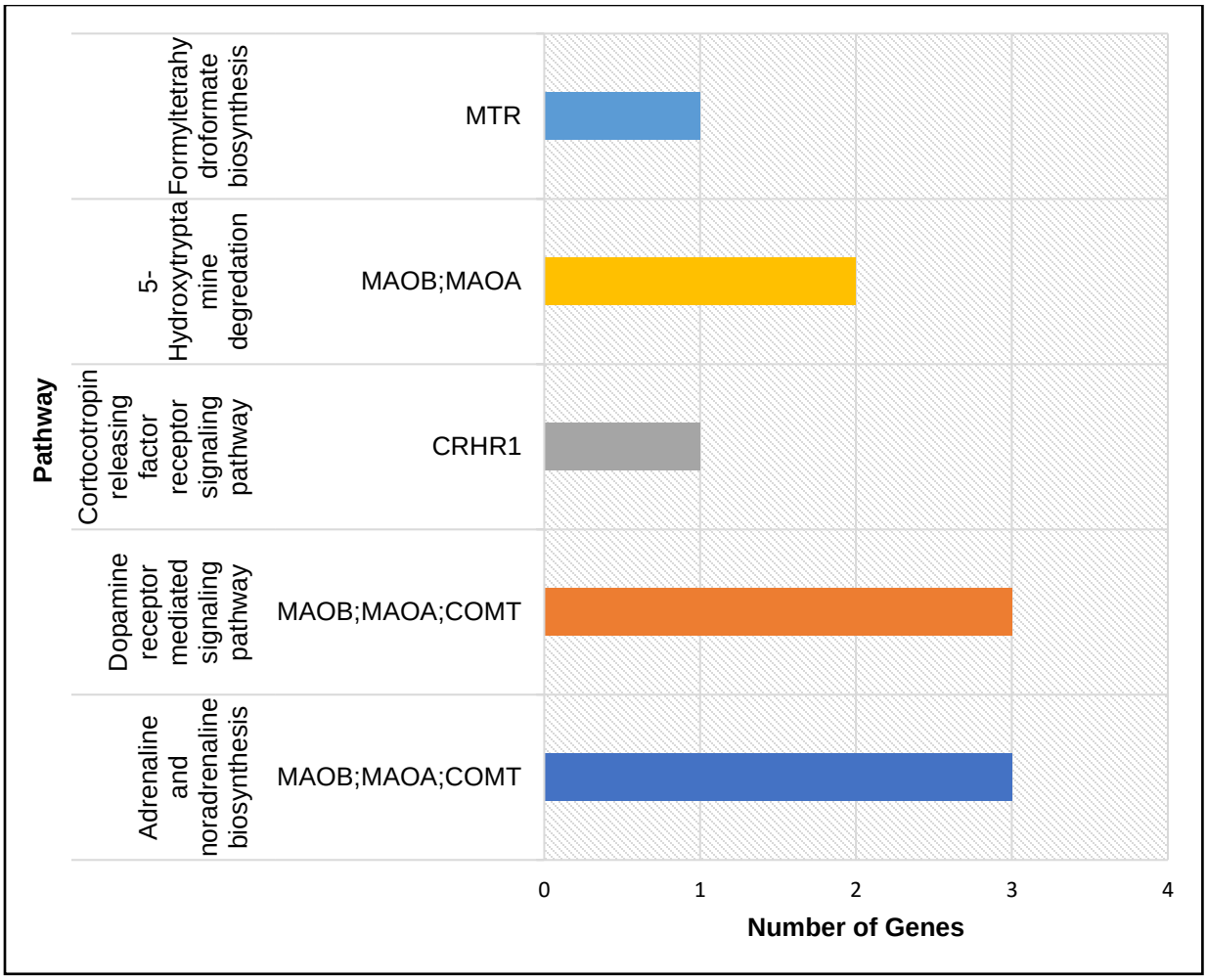

Figure 4: Graph showing important pathways from pathway analysis with the targets involved.

Table 1: Functional enrichment analysis of 12 candidate genes using DAVID.

Term	Count	P-Value	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Bonferroni	Benjamini	FDR
GO:0042420~dopamine catabolic process	3	3.90E-06	MAOA, MAOB, COMT	12	5	16792	839.6	9.39E-04	9.39E-04	0.00503345
GO:0042135~neurotransmitter catabolic process	3	1.09E-05	MAOA, MAOB, COMT	12	8	16792	524.75	0.00262355	0.00131264	0.01407798
GO:0050665~hydrogen peroxide biosynthetic process	3	1.40E-05	MAOB, SOD1, SOD2	12	9	16792	466.444444	0.00337067	0.00112482	0.01809345
GO:0048678~response to axon injury	3	1.36E-04	MTR, SOD1, SOD2	12	27	16792	155.481481	0.03218126	0.00814427	0.1751528

GO:0042493~response to drug	4	8.70E-04	MAOB, COMT, SOD1, SOD2	12	304	16792	18.4122807	0.18928792	0.04109998	1.11831532
GO:0000303~response to superoxide	2	0.0032715	SOD1, SOD2	12	5	16792	559.733333	0.54602663	0.12332546	4.14404363
GO:0032496~response to lipopolysaccharide	3	0.0049212	MAOB, COMT, SOD2	12	164	16792	25.597561	0.69545405	0.15620661	6.17313222
GO:0010269~response to selenium ion	2	0.0052297	MAOB, SOD2	12	8	16792	349.833333	0.71738217	0.1461139	6.54814241
GO:0055114~oxidation-reduction process	4	0.0058205	MAOA, MAOB, SOD1, SOD2	12	592	16792	9.45495495	0.75508199	0.14470996	7.26246113
GO:0019430~removal of superoxide radicals	2	0.0078352	SOD1, SOD2	12	12	16792	233.222222	0.84978919	0.17268648	9.66071508
GO:0042554~superoxide anion generation	2	0.0091356	SOD1, SOD2	12	14	16792	199.904762	0.89049663	0.18214705	11.1781759
GO:0006801~superoxide metabolic process	2	0.0130276	SOD1, SOD2	12	20	16792	139.933333	0.95758611	0.2315322	15.580351
GO:0051881~regulation of mitochondrial membrane potential	2	0.0181953	SOD1, SOD2	12	28	16792	99.952381	0.98803114	0.28852784	21.1146442
GO:0035774~positive regulation of insulin secretion involved in cellular response to glucose stimulus	2	0.0188395	HLA-DRB5, PLA2G6	12	29	16792	96.5057471	0.98978231	0.27920645	21.7805953
GO:0055072~iron ion homeostasis	2	0.0194834	TF, SOD2	12	30	16792	93.2888889	0.99127736	0.27102964	22.4409637
GO:0000302~response to reactive oxygen species	2	0.0252607	SOD1, SOD2	12	39	16792	71.7606838	0.99790046	0.31980612	28.1405989
GO:0001895~retina homeostasis	2	0.0259007	TF, SOD1	12	40	16792	69.9666667	0.99820783	0.31065917	28.7476336
GO:0006879~cellular iron ion homeostasis	2	0.0284569	TF, SOD1	12	44	16792	63.6060606	0.99904862	0.32059171	31.1252733
GO:0042542~response to hydrogen peroxide	2	0.0329157	SOD1, SOD2	12	51	16792	54.875817	0.99968602	0.34592631	35.098093
GO:0006749~glutathione metabolic process	2	0.0360891	SOD1, SOD2	12	56	16792	49.9761905	0.9998578	0.35783801	37.7956808
GO:0008217~regulation of blood pressure	2	0.0417774	SOD1, SOD2	12	65	16792	43.0564103	0.99996585	0.38721935	42.3737707
GO:0032259~methylation	2	0.046808	MTR, COMT	12	73	16792	38.3378995	0.9999904	0.40853298	46.1613965
GO:0007626~locomotory behavior	2	0.0536859	SOD1, SOD2	12	84	16792	33.3174603	0.99999832	0.43909206	50.9688725

GO:0007565~female pregnancy	2	0.056797 3	CRHR1, COMT	12	89	16792	31.4456929	0.99999924	0.44410578	53.0107 479
GO:0002576~platelet degranulation	2	0.065459 8	TF, SOD1	12	103	16792	27.171521	0.99999992	0.47932744	58.2896 613
GO:0045471~response to ethanol	2	0.066691 4	MAOB, SOD1	12	105	16792	26.6539683	0.99999994	0.47257891	58.9940 738
GO:0043524~negative regulation of neuron apoptotic process	2	0.083173 8	SOD1, SOD2	12	132	16792	21.2020202	1	0.53934408	67.4239 054

3. Identifying top rank genes amidst our potential targets:

The ToppNet scores of the genes in both the diseases prioritized COMT as the top ranked target based on interactions and enrichment score values. However, based on tropological features in protein-protein interaction networks it uses k-step Markov method for generating the scores.

Table 2: Top prioritized gene in both AD and PD.

	Rank	ID	Name	Interactant Count	Score		Rank	ID	Name	Interactant Count	Score
PD	1	1312	COMT	36	3.52E-05	**AD**	1	1312	COMT	36	2.95E-05
	2	4128	MAOA	6	6.46E-06		2	4128	MAOA	6	4.29E-06
	3	4129	MAOB	5	6.10E-06		3	4129	MAOB	5	3.65E-06

4. Mapping of potential drugs with our candidate targets:

Different drugs popped up ranked according to their e-scores and p-value from gene2drug, in order to be precise with our work we only took top 10% drugs approximately and ran-down the filter to search for the common drugs among all the three targets. Results showed us 26 main drugs common in all of our extracted genes. Information on which were gathered from drug bank, chEMBL and PubChem on their mode of action and their current status of approval.

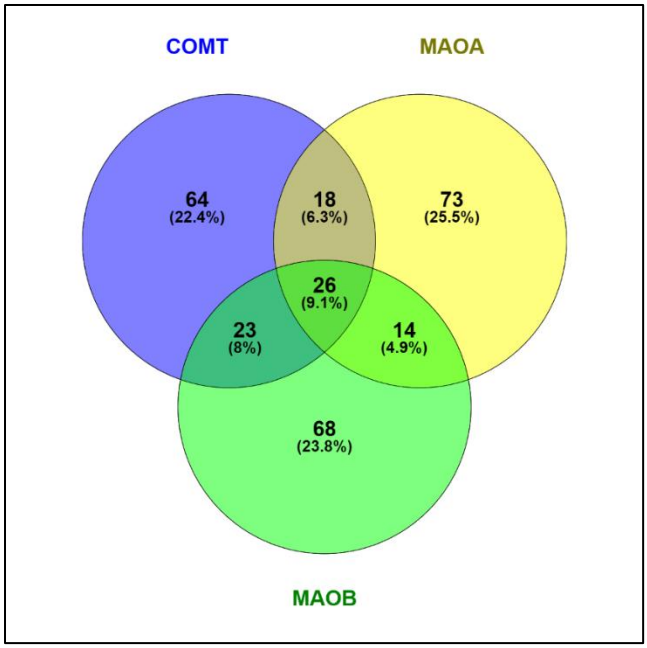

Figure 5: Statistics of mapped drugs and the commons ones of main targets.

Table 3: All common drugs amid three targets with their e-scores and p-values along with their status as approved (yellow), experimental (brown), withdrawn (red), not given (green).

DRUGS	COMT		MAOA		MAOB		Status	Role
	E-Score	P-Value	E-Score	P-Value	E-Score	P-Value		
5109870	0.6	3.97E-05	0.59	1.43E-02	0.59	1.43E-02		NA
Azacitidine	0.77	3.38E-08	0.87	5.63E-05	0.79	3.05E-05		antineoplastic agent
Tyrphostin AG825	0.72	3.31E-07	0.6	1.32E-02	0.61	2.27E-03		ErbB2 inhibitor
Camptothecin	0.65	5.64E-06	0.8	2.58E-04	0.7	2.75E-04		Antitumor
Alsterpaullone	0.64	8.72E-06	0.85	7.45E-05	0.67	5.88E-04		NA
Trifluridine	0.64	1.13E-05	0.6	1.34E-02	0.69	4.11E-04		Herpes simplex virus type 1 and 2
GW-8510	0.63	1.51E-05	0.76	6.72E-04	0.65	9.87E-04		CDK2 inhibitor
Apigenin	0.61	2.78E-05	0.85	8.82E-05	0.56	7.14E-03		NA

Luteolin	0.61	3.56E-05	0.7	2.21E-03	0.58	4.34E-03		Anti-inflammatory agent
H-7	0.59	5.77E-05	0.8	2.55E-04	0.61	2.58E-03		Protein Kinase Inhibitor
Irinotecan	0.58	8.15E-05	0.78	3.68E-04	0.56	6.88E-03		colateral cancer
Tropicamide	0.57	1.25E-04	0.59	1.44E-02	0.57	6.25E-03		Muscarinic
Doxorubicin	0.55	2.58E-04	0.81	1.93E-04	0.71	2.18E-04		anthracycline antibiotic
Clemizole	0.52	6.87E-04	0.57	2.30E-02	0.53	1.41E-02		H1 antagonist
Daunorubicin	0.51	9.25E-04	0.78	4.12E-04	0.8	2.01E-05		antineoplastic agent
Sulfanilamide	0.51	9.73E-04	0.58	1.76E-02	0.52	1.54E-02		Antibacterial
MS-275	0.5	1.09E-03	0.63	8.06E-03	0.58	5.01E-03		Anticancer
Levothyroxine Sodium	0.5	1.19E-03	0.75	7.45E-04	0.53	1.31E-02		Thyroid
Pirenzepine	0.49	1.50E-03	0.67	3.91E-03	0.6	3.20E-03		Muscarinic acetylcholine receptor M1
Etamivan	0.48	1.85E-03	0.6	1.42E-02	0.55	8.67E-03		NA
Norcyclobenzaprine	0.48	2.00E-03	0.69	2.54E-03	0.57	5.95E-03		muscle relaxant
Nomifensine	0.48	2.06E-03	0.6	1.39E-02	0.54	1.06E-02		Antidepressive Agents
Iohexol	-0.47	2.69E-03	-0.69	2.60E-03	-0.67	6.28E-04		radiographic procedures
Thioguanosine	0.46	4.07E-03	0.58	1.86E-02	0.55	7.95E-03		Antimetabolite
Canrenoic Acid	0.45	4.63E-03	0.67	3.78E-03	0.72	1.65E-04		aldosterone antagonist
Mitoxantrone	0.44	5.44E-03	0.85	8.26E-05	0.85	8.26E-05		antineoplastic agent

5. Checking for permeability in brain:

Blood-Brain barrier permeability was checked on CBLigand and threshold was set on 0.02 and scores were noted on the basis of which positive and negatively permeable were separated. Sulfanilamide with permeability score 0.277, GW-8510 with score 0.146, H-7 with score 0.12, Pirenzepine with score 0.106, Tropicamide with score 0.094, Alsterpaullone score 0.087, Norcyclobenzaprine with score 0.085, Nomifensine score 0.08, Tyrphostin AG825 and MS-

275 (MS-275 is the external ID used by companies for the product) or Entinostat with score 0.066, Clemizole with score 0.057, Etamivan score 0.049, Canrenoic Acid with score 0.033 and lastly with a score of 0.022 Apigenin were the positive ones.

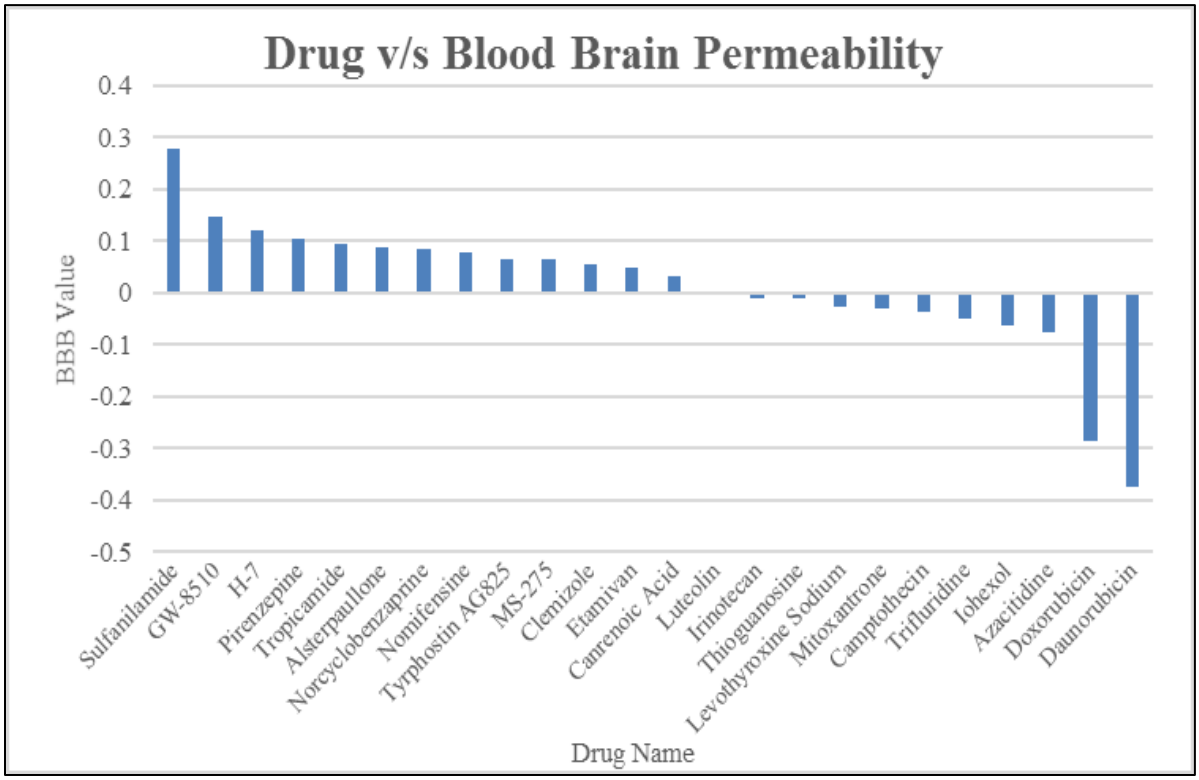

Figure 6: Blood-brain barrier permeability scores of the drugs.

6. Computational analysis of repurposed drugs:

In order to analyze the above permeable drugs, we evaluated gene expression patterns of these signature drugs against different types of drugs taken as control. We gauged our drugs with two different sets of control, one control was according to the disease like memantine (Z score = -1.02 COMT, 0.45 MAOA, -0.38 MAOB) and galantamine (Z score = -0.27 COMT, -0.1 MAOA, 1.15 MAOB) for Alzheimer's disease, pramipexole (Z score = 0.82 COMT, 0.5 MAOA, -2.2 MAOB) and amantadine (Z score = -0.13 COMT, -1.14 MAOA, -0.2 MAOB) for Parkinson's disease. Second set was taken specific to the targets like tolcapone (Z score =

-0.29) and entacapone (Z score = -0.02) for COMT and selegiline (Z score = -0.46 MAOA, -0.19 MAOB) for MAOs. Out of all our available permeable candidates entinostat (MS-275) (Z score = -1.37 COMT, -1.02 MAOA, -0.95 MAOB) showed the significant downregulation of these genes better than the controls. Although, another drug tropicamide (Z score = -1.05 MAOA, -1.15 MAOB) gave better results for both mono-amine oxidases.

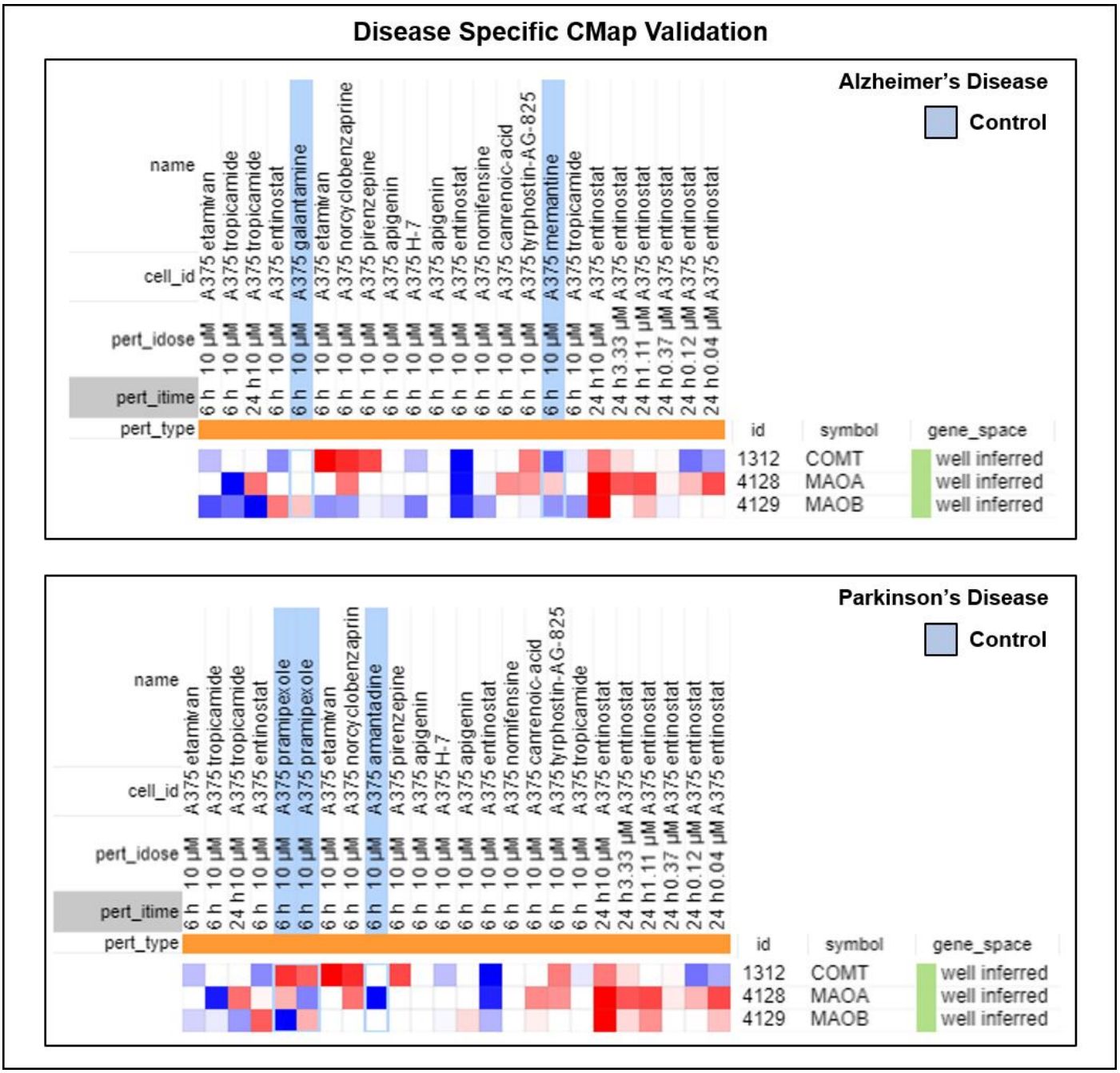

Figure 7: Gene expression pattern of candidate targets with disease-specific controls.

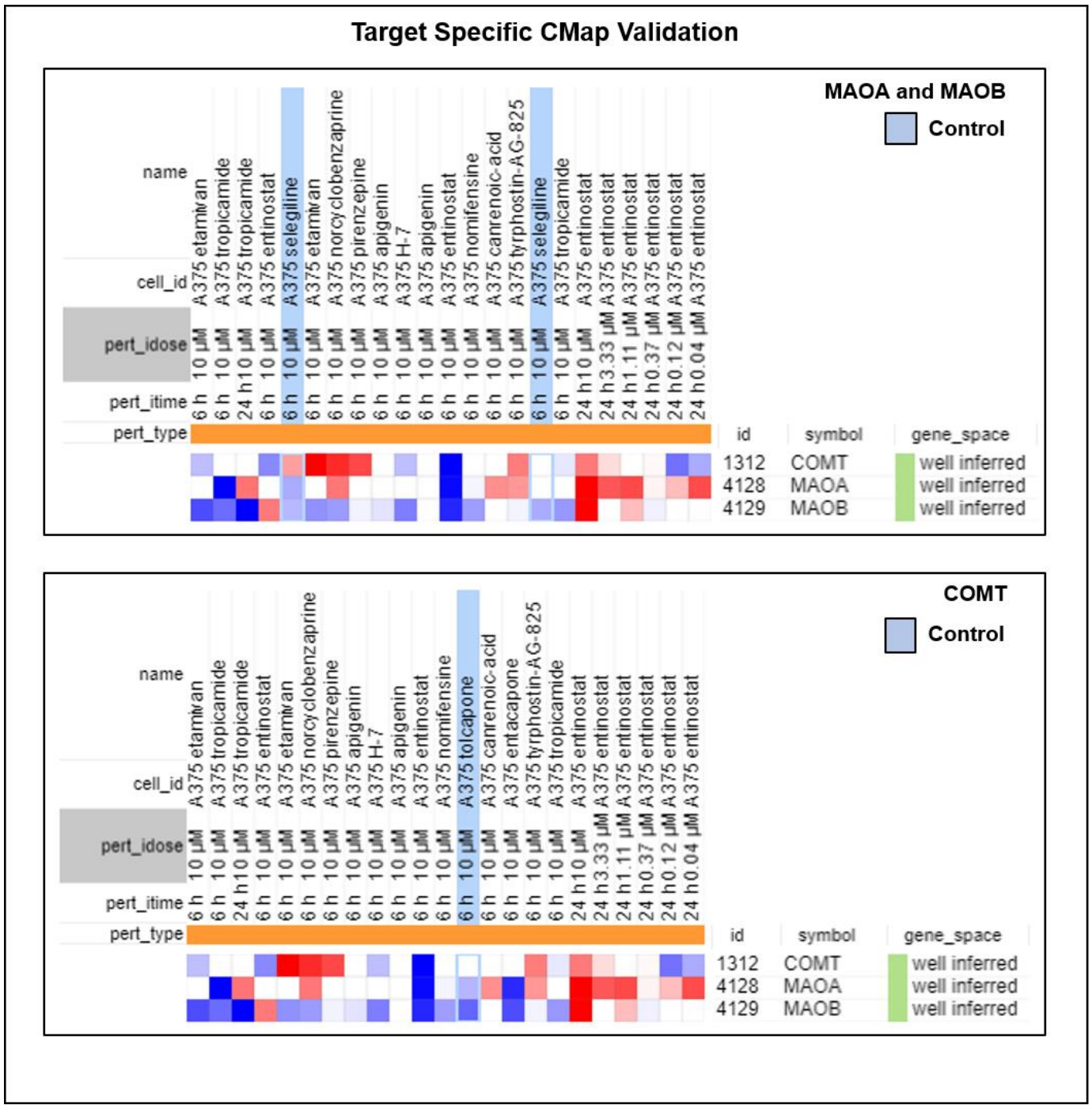

Figure 8: Gene expression pattern of candidate drugs with target-specific controls.

7. Determining Mode of Action of the Drugs:

Entinostat being an orally administered lipophilic mediator has been known to have variable pharmacokinetic properties with longer half-life of around 100hrs. Known for its part contrary to breast cancer, it is well-sustainable. It induces hyperacetylation among histones in specific gene sets, setting a break point in proliferation and differentiation of these cells finally leading them towards apoptosis [34] this unique mode of action of the drug gave an opportunity to look and make the most to discover and exploit area of its clinical activity. Even in case of estrogen-receptor positive breast cancer patients entinostat have shown well tolerated and safe results [35]. It targets specifically HDAC 1 and HDAC 3, this specific selectivity of targets makes it better drug than the broad-spectrum inhibitors and along with other targeted therapies it has shown boosted synergistic activity [36]. HDAC 3 has been known to regulate long term memory related activity negatively [37]. In Lung cancer studies, Entinostat has been connected to more sensitive response against high expression of SALL4 gene [38]. On the other hand, Tropicamide which is an antagonist for muscles in the eyes (muscarinic) and antisialorrheic [39] is proved to be efficient in Parkinson's disease with no major safety issues [40]. It dilates the pupil of the eye by blocking the receptor (M4 in brain) and thus prevents cycloplegia (near vision). It modulates potassium channels, inhibits adenylate cyclase [41]. Evidences suggests deposition of Aβ in eye leads to late onset of Alzheimer's disease progression in brain [42]. Another mechanism of action of tropicamide relates with parasympathetic and sympathetic nervous system symbolizing its working like an anticholinergic agent. Studies done shows that tropicamide inhibits parasympathetic promoting sympathetic or (adrenergic and non-adrenergic) drive making pupil to dilate. It acts similar to atropine which is an CNS stimulator [43].

Chapter 5: Discussion and Conclusion:

In current study, we have determined our candidate targets against whom drugs are to be repurposed. Epigenetic modifications, specifically methylation are well connected with Alzheimer's and Parkinson's diseases and these genetic variations can prove to control aging through modulating these epigenetic variations [44], [45], [46]. The approach of repurposing drugs has been seen to treat resistant disease well provide temporary diminution of disease or pain [47].

Overall, we had 3520 targets in both the diseases out of which only 560 are the common ones and overall 12 targets which are common as well as present in more than two studies in amid all the databases. Pathway analysis showed the occurrence of these targets in different pathways they follow. Among our targets, only 3 of them, COMT, MAOB, MAOA were involved in two pathways one being dopamine receptor mediated signaling pathway and another is adrenaline and non-adrenaline biosynthesis pathway as provided by panther pathway analysis. On the other hand, DAVID and Enrichr tool also validated the same results prioritizing dopamine signaling pathway as the foremost process in AD, PD overlap. Dopamine is a dominant component of neurobiology. It regulates basic learning and performing of various tasks in day to day life. Among neuronal diseases, like Parkinson's disease the loss or reduction in dopamine levels results in impair motor function and increment in severity of the disease. Increasing DA transmission somehow within neurons is the basic treatment strategy for such diseases [48]. The ToppNet tool lined up the foremost target among them using tropological features of targets in PPI network. COMT had highest interaction count as well as score than the other two genes. This signifies that COMT gene combine more with the other proteins in PPI network as compared with MAO's which interacts more with each other, which along with COMT help in DA catabolism with aldehyde dehydrogenase [13].

The drugs sorted for these targets were ranked according to their p-value and enrichment scores which were top 10% approximately 131 drugs among which we had 26 common drugs for all three targets together which can be repurposed against them. As we are talking to identify a drug for brain related disorders blood-brain permeability remains an unneglected factor for which when we checked, conclude with 14 drugs which are permeable in brain and thus can be used for treating brain-related disorders. Out of them, Sulfanilamide used as an anti-bacterial drug showed the highest permeability to cross the brain-barrier on the other hand Canrenoic acid and Apigenin were the ones which can poorly cross the blood-brain barrier. Both Sulfanilamide and Canrenoic acid are approved drugs with their role as an anti-bacterial and aldosterone antagonist respectively but apigenin is still an experimental drug with an unspecified role.

Gene Expression profiling data analysis gave two important drugs with their repurposed role in treating aberrations in dopamine levels. Entinostat was favorable for all the three targets but in case of mono-amine oxidases, Tropicamide showed better results than that of Entinostat with time. Entinostat is a histone deacetylase inhibitor (HDACi) which is benzamide derivative and an anti-cancer drug with oral bioavailability, having property to cross blood-brain barrier and showing better results than the controls with a dose of 10μm in six hours. This HDACi have been seen in improving behavioral adversities in case of AD in mouse models [49]. Adverse reactions depends on the dosage given [34]. In a study on Alzheimer's diseases, cerebral amyloidosis animal model MS-257 showed significant improvement in microglial activation, refined Aβ deposition and enhanced social behavior thus signifying the reach of the drug's activity in neurodegeneration [50]. It has been studied for increasing neuronal cell life by avoiding the formation of HDAC3 and REST complex at promoter region and enhancing the expression of sodium-calcium exchange during deprived milieus [37]. The combination of dopamine and entinostat have been seen in

refining behavior based on exposure and fear-inhibitory memory [51]. In case of tropicamide, an antimuscarinic antagonist [41] showed better results for mono-amine oxidases when seen over 24hrs. It is safe to use but have been seen causing blurred vision, hallucinations, headache, vomiting, nausea etc. as mentioned earlier about its role in enhancing sympathetic nervous system which is also known as adrenergic and non-adrenergic activity which relates to fear-flight and fight again the two pathways as shown by functional annotation of our main targets. . Entinostat is believed to lower down dopamine metabolism by downregulating COMT which is responsible for metabolizing dopamine present in circulation whereas Tropicamide showed better results with mono-anime oxidases which metabolize dopamine in mitochondria which if not corrected may lead to the formation of reactive oxygen species leading to increase in oxidative stress leading to mitochondrial dysfunction and apoptosis and also in increased protein misfolding and neuronal toxicity ultimately showing signs of Alzheimer's and Parkinson's disease [52], [53].

In conclusion, systemic analysis of 'Omics-data' revealed three targeted overlapping genes COMT, MAOA and MAOB in AD and PD involved in dopamine signaling pathway, which have to be downregulated by our repurposed drug in order to fight against cognitive impairments of these diseases. On the basis of their permeability into the brain, final 14 candidates were listed whose expression pattern were checked against both disease specific and target specific controls from which we got our final two drugs (Entinostat and Tropicamide) which shows their links to disturbances in dopamine metabolism through the approach of 'Omics' data usage in through the approach of drug repositioning.

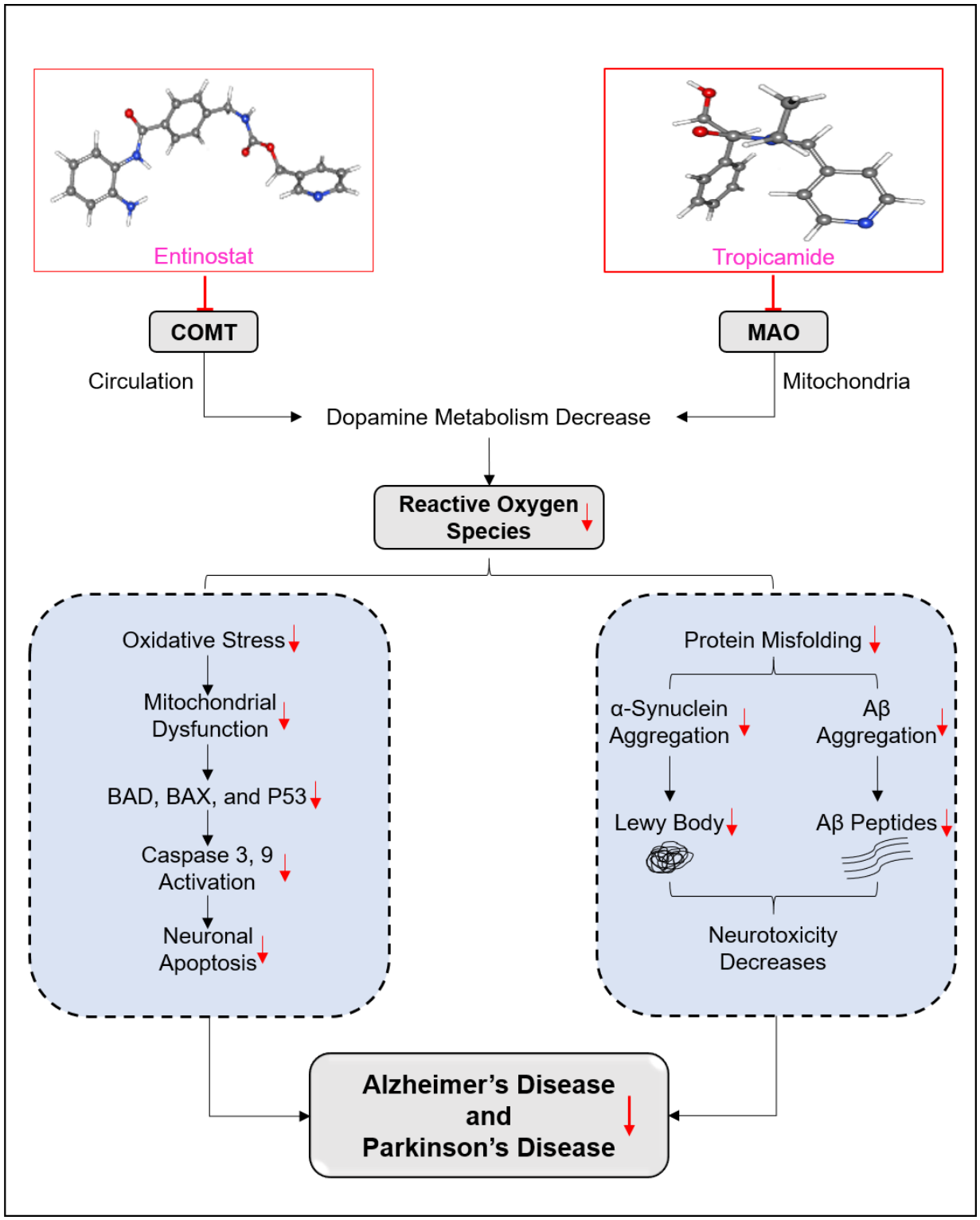

Figure 9: Possible signaling mechanism of the two resulting repurposed drugs Entinostat and Tropicamide in case of AD and PD.

Appendix

Table T1: Genes for Alzheimer's disease present in more than two studies:

NAME	GWAS	GENES	EPIGENETIC GENES	METABOLITES
CDH1				
TIMP2				
COL25A1				
TFEB				
HDAC9				
SHANK2				
APOE				
TOMM40				
MTHFD1L				
PCDH11X				
FBXL7				
IL6				
PRRC2C				
FMN2				
CTNNA2				
MOBP				
STK32B				
AFF1				
ANKRD55				
CAMK4				
DMXL1				
MEGF10				
NKAIN2				
PDE7B				
BZW2				
EXOC4				
CSMD1				
ST18				
NCS1				
SPON1				
ARHGAP20				
SLC4A8				
CRADD				
ANO4				
GPC6				
MYO16				
CLMN				
GABRG3				
LIPC				
VAT1L				
SP6				

CACNA1G				
BCAS3				
TGM6				
PARVB				
BCAM				
EXOC3L2				
BCL3				
APOC1				
MS4A3				
FANCD2				
IL19				
GAB2				
OSBPL6				
PTPRG				
NR3C2				
SH3RF1				
FAT1				
KCNN2				
CDKAL1				
DST				
GRIN3A				
FARP1				
DCHS2				
VLDLR				
ST6GAL1				
CLU				
ZNF292				
ABCA1				
BIRC3				
GRIN2B				
TREM2				
PPP1R3B				
MMP3				
CR1				
PPP1R37				
SUCLG2				
SORL1				
GLIS3				
GRIN3B				
SLC2A9				
VSNL1				
ECHDC3				
NFIC				
FRMD4A				
IRF6				
TMEM106B				
CDC42SE2				
RAPGEF6				

FNIP1				
ACSL6				
EPHA1				
TAS2R62P				
MS4A6E				
MS4A4A				
MS4A6A				
SLC24A4				
CRHR1				
MAPT				
PTK2B				
MS4A4E				
CD2AP				
CD33				
ABI3				
PLCG2				
BSG				
ATM				
HS3ST1				
SQSTM1				
TREML2				
NDUFAF6				
AP2A2				
SPPL2A				
TRIP4				
SCIMP				
ACE				
NME8				
ZCWPW1				
FERMT2				
CASS4				
HLA-DRB5				
HLA-DRB1				
AOX1				
BDNF				
ARC				
SERPINF1				
CDK5				
COX2				
SYP				
EGR1				
ANK1				
SPG7				
CRTC1				
FOS				
SERPINF2				
SLC2A1				
IGFBP7				

RPL13				
SYT1				
HOMER1				
DUSP22				
ACHE				
BCHE				
CYP2D6				
MPO				
NOS3				
MAOB				
SOD2				
TF				
CHAT				
SOD1				
NOS2				
GSR				
COMT				
MAOA				
NOS1				
PKLR				
SDS				
ALDH2				
PLA2G4A				
TH				
PLA2G6				
PDE5A				
APRT				
CBS				
DBH				
DRD4				
GLUL				
TAT				
ACO1				
DLD				
DRD1				
GAD1				
GBA				
ODC1				
PLD2				
PRDX6				
EHMT1				
ACO2				
AMD1				
AOC2				
ARG2				
DRD2				
DRD3				
GPI				

HDC				
HK1				
LDHA				
MPI				
MTR				
PNP				
OTC				
PC				
AOC3				
GPHN				
SLC7A9				
PADI4				
GDE1				
SRR				
NT5C1A				
BIN1				
PICALM				
ABCA7				
INPP5D				
MEF2C				
CELF1				
RIN3				

Table T2: Genes for Parkinson's disease present in more than two studies:

NAME	GWAS	GENES	EPIGENETIC GENES	METABOLITE
TCIM				
GBA				
MAPT				
MCCC1				
LAMP3				
SCARB2				
GAK				
SREBF1				
RAI1				
SLC41A1				
RIT2				
PRDM2				
PDE10A				
CRHR1				
HLA-DRB5				
STK39				
GCH1				
NUCKS1				
FAM47E				
BST1				
CCDC62				
SH3GL2				
NDUFAF2				
HLA-DRA				
SYT11				
ACMSD				
HIP1R				
DLG2				
SEMA5A				
DGKQ				
LHFPL2				
KLHDC1				
TPM1				
SLC45A3				
PM20D1				
SIPA1L2				
TMEM163				
TMEM175				

MIR4697				
TMEM229B				
VPS13C				
STH				
SPPL2C				
KANSL1				
DDRGK1				
ITPKB				
STAB1				
BAP1				
CTSB				
BIN3				
SLC2A13				
WNT3				
TCEANC2				
MX2				
ZP3				
HTR2A				
LINC02210				
NSF				
CYP17A1				
CNNM2				
BORCS7				
ITGA8				
MMRN1				
STBD1				
INPP5F				
BCKDK				
PARK7				
PPARGC1A				
PRKAR2A				
TNKS2				
DDC				
MAOB				
MAOA				
SOD1				
SOD2				
PLA2G6				
COMT				
MTR				
TF				

LRRK2				
SNCA				
PARK16				
GPNMB				
STX1B				
FGF20				

Table T3: Drugs mapped for COMT gene:

Rank	Name	E-Score	P-Value
1	azacitidine	0.77	3.38E-08
2	cyanocobalamin	0.73	2.50E-07
3	tyrphostin_AG-825	0.72	3.31E-07
4	camptothecin	0.65	5.64E-06
5	antimycin_A	0.65	6.91E-06
6	alsterpaullone	0.64	8.72E-06
7	trifluridine	0.64	1.13E-05
8	GW-8510	0.63	1.51E-05
9	apigenin	0.61	2.78E-05
10	luteolin	0.61	3.56E-05
11	5109870	0.6	3.97E-05
12	H-7	0.59	5.77E-05
13	ursolic_acid	0.59	5.93E-05
14	ketoconazole	0.59	6.23E-05
15	strophanthidin	0.58	7.64E-05
16	irinotecan	0.58	8.15E-05
17	primaquine	0.57	1.16E-04
18	scopolamine	0.57	1.19E-04
19	trifluprom azine	0.57	1.20E-04
20	tropicamide	0.57	1.25E-04
21	0175029-0000	0.56	1.53E-04
22	CP-319743	0.56	1.65E-04
23	propantheline bromide	0.56	1.79E-04
24	ginkgolide_A	0.56	1.91E-04
25	aminophenazone	0.55	2.37E-04
26	doxorubicin	0.55	2.58E-04
27	fluocinonide	0.55	2.60E-04
28	mianserin	0.55	2.67E-04
29	prilocaine	0.54	3.16E-04
30	cantharidin	0.54	3.30E-04
31	thioperamide	-0.54	3.33E-04
32	15(S)-15-methylprostaglandin_E2	0.54	3.47E-04
33	spectinomycin	0.54	3.52E-04
34	chenodeoxycholic_acid	0.54	3.59E-04
35	zomepirac	0.53	4.00E-04

36	Prestwick-1100	0.53	4.30E-04
37	pseudopelletierine	0.53	5.30E-04
38	5149715	0.52	5.72E-04
39	primidone	-0.52	6.30E-04
40	digoxin	0.52	6.39E-04
41	clemizole	0.52	6.87E-04
42	deferoxamine	0.51	7.45E-04
43	acetylsalicylic_acid	0.51	7.73E-04
44	cefotaxime	0.51	8.10E-04
45	8-azaguanine	0.51	9.03E-04
46	procyclidine	0.51	9.08E-04
47	daunorubicin	0.51	9.25E-04
48	16,16-dimethylprostaglandin_E2	0.51	9.55E-04
49	ciclopirox	0.51	9.55E-04
50	sulfanilamide	0.51	9.73E-04
51	moroxydine	0.5	1.01E-03
52	naringin	0.5	1.08E-03
53	MS-275	0.5	1.09E-03
54	bucladesine	0.5	1.11E-03
55	nisoxetine	0.5	1.13E-03
56	alpha-estradiol	0.5	1.16E-03
57	levothyroxine_sodium	0.5	1.19E-03
58	fludroxycortide	0.5	1.19E-03
59	quinethazone	0.5	1.24E-03
60	gefitinib	0.49	1.39E-03
61	medrysone	0.49	1.39E-03
62	sulconazole	0.49	1.42E-03
63	isocarboxazid	0.49	1.44E-03
64	midodrine	0.49	1.50E-03
65	trimethoprim	0.49	1.50E-03
66	pirenzepine	0.49	1.50E-03
67	epivincamine	0.49	1.65E-03
68	pheneticillin	-0.49	1.70E-03
69	lynestrenol	0.49	1.73E-03
70	etamivan	0.48	1.85E-03
71	yohimbic_acid	-0.48	1.86E-03
72	dexverapamil	0.48	1.92E-03
73	chlorhexidine	0.48	1.93E-03
74	cytochalasin_B	0.48	1.99E-03

75	norcyclobenzaprine	0.48	2.00E-03
76	nicergoline	0.48	2.03E-03
77	azacyclonol	0.48	2.06E-03
78	nomifensine	0.48	2.06E-03
79	cisapride	0.48	2.18E-03
80	mephenytoin	0.48	2.31E-03
81	BCB000039	0.47	2.38E-03
82	ceforanide	0.47	2.46E-03
83	alpha-ergocryptine	-0.47	2.49E-03
84	cefadroxil	0.47	2.57E-03
85	5114445	0.47	2.65E-03
86	iohexol	-0.47	2.69E-03
87	naringenin	0.47	2.72E-03
88	STOCK1N-28457	0.47	2.83E-03
89	prednisolone	-0.47	2.97E-03
90	nadolol	-0.47	3.05E-03
91	U0125	-0.47	3.08E-03
92	rescinnamine	0.47	3.13E-03
93	dienestrol	0.46	3.27E-03
94	deptropine	0.46	3.27E-03
95	salbutamol	0.46	3.42E-03
96	tiapride	0.46	3.53E-03
97	flunisolide	0.46	3.65E-03
98	famotidine	0.46	3.73E-03
99	minoxidil	0.46	3.90E-03
100	oxaprozin	0.46	3.92E-03
101	niclosamide	0.46	3.94E-03
102	citiolone	0.46	3.99E-03
103	bendroflumethiazide	0.46	4.04E-03
104	thioguanosine	0.46	4.07E-03
105	hydrocotarnine	0.46	4.11E-03
106	amrinone	0.45	4.31E-03
107	pirenperone	-0.45	4.33E-03
108	urapidil	0.45	4.41E-03
109	simvastatin	0.45	4.45E-03
110	canrenoic_acid	0.45	4.63E-03
111	gliclazide	0.45	4.68E-03
112	metixene	0.45	4.71E-03
113	acepromazine	0.45	4.75E-03

114	syrosingopine	0.45	4.81E-03
115	cyclopentolate	0.45	5.08E-03
116	gelsemine	-0.45	5.31E-03
117	alpha-yohimbine	-0.45	5.40E-03
118	ergocalciferol	0.44	5.42E-03
119	mitoxantrone	0.44	5.44E-03
120	flupentixol	0.44	5.69E-03
121	salsolinol	0.44	5.80E-03
122	dilazep	0.44	5.81E-03
123	maprotiline	-0.44	5.85E-03
124	latamoxef	0.44	5.87E-03
125	astemizole	0.44	5.88E-03
126	haloperidol	0.44	5.90E-03
127	tanespimycin	0.44	5.97E-03
128	5248896	0.44	6.22E-03
129	debrisoquine	-0.44	6.27E-03
130	etifenin	0.44	6.30E-03
131	tolnaftate	-0.44	6.35E-03

Table T4: Drugs mapped for MAOA gene:

Rank	Name	E-Score	P-Value
1	azacitidine	0.87	5.63E-05
2	alsterpaullone	0.85	7.45E-05
3	mitoxantrone	0.85	8.26E-05
4	apigenin	0.85	8.82E-05
5	doxorubicin	0.81	1.93E-04
6	H-7	0.8	2.55E-04
7	camptothecin	0.8	2.58E-04
8	irinotecan	0.78	3.68E-04
9	daunorubicin	0.78	4.12E-04
10	N-acetylmuramic_acid	0.77	5.24E-04
11	thioperamide	-0.76	6.46E-04
12	GW-8510	0.76	6.72E-04
13	levothyroxine_sodium	0.75	7.45E-04
14	moroxydine	0.75	7.69E-04
15	latamoxef	0.75	8.05E-04
16	metacycline	0.74	9.15E-04
17	BCB000039	0.73	1.24E-03
18	procarbazine	-0.72	1.35E-03
19	bacampicillin	0.72	1.45E-03
20	alpha-yohimbine	-0.71	1.71E-03
21	antimycin_A	0.71	1.77E-03
22	lymecycline	0.71	1.77E-03
23	1,4-chrysenequinone	0.7	2.06E-03
24	equilin	0.7	2.06E-03
25	etofenamate	0.7	2.15E-03
26	luteolin	0.7	2.21E-03
27	estriol	0.7	2.29E-03
28	oxaprozin	0.7	2.34E-03
29	tolnaftate	-0.69	2.36E-03
30	cefaclor	-0.69	2.39E-03
31	norcyclobenzaprine	0.69	2.54E-03
32	iohexol	-0.69	2.60E-03
33	bromperidol	0.69	2.79E-03
34	16-phenyltetranorprostaglandin_E2	0.69	2.81E-03
35	Prestwick-981	-0.68	2.89E-03
36	pirenperone	-0.68	3.19E-03
37	picrotoxinin	0.67	3.46E-03

38	isocorydine	-0.67	3.52E-03
39	quinpirole	-0.67	3.52E-03
40	canrenoic_acid	0.67	3.78E-03
41	cefapirin	0.67	3.80E-03
42	dilazep	0.67	3.86E-03
43	pirenzepine	0.67	3.91E-03
44	cefmetazole	-0.67	3.93E-03
45	naproxen	0.66	4.24E-03
46	homosalate	0.66	4.26E-03
47	lobelanidine	-0.66	4.26E-03
48	famotidine	0.66	4.41E-03
49	mefexamide	-0.66	4.59E-03
50	parthenolide	0.65	5.22E-03
51	etidronic_acid	0.65	5.31E-03
52	5707885	0.65	5.49E-03
53	homochlorcyclizine	-0.64	6.20E-03
54	betonicine	-0.64	6.27E-03
55	ginkgolide_A	0.64	6.31E-03
56	monastrol	0.64	6.63E-03
57	morantel	0.64	6.70E-03
58	finasteride	-0.64	7.04E-03
59	benzamil	-0.63	7.23E-03
60	liothyronine	0.63	7.27E-03
61	acetazolamide	0.63	7.43E-03
62	dipyridamole	0.63	7.55E-03
63	mycophenolic_acid	0.63	7.72E-03
64	chlorambucil	0.63	7.76E-03
65	lorglumide	0.63	7.76E-03
66	diloxanide	-0.63	7.89E-03
67	scriptaid	0.63	7.89E-03
68	MS-275	0.63	8.06E-03
69	pergolide	-0.63	8.15E-03
70	levomepromazine	-0.63	8.41E-03
71	thiostrepton	0.63	8.41E-03
72	etilefrine	-0.62	8.60E-03
73	biperiden	-0.62	8.88E-03
74	rolitetracycline	0.62	9.02E-03
75	sitosterol	0.62	9.26E-03
76	cycloserine	0.62	9.41E-03

77	zomepirac	0.62	9.41E-03
78	pancuronium_bromide	0.62	9.56E-03
79	phenindione	0.61	1.14E-02
80	reserpine	0.61	1.19E-02
81	8-azaguanine	0.6	1.21E-02
82	bisacodyl	0.6	1.23E-02
83	quinethazone	0.6	1.25E-02
84	droperidol	0.6	1.26E-02
85	metyrapone	0.6	1.29E-02
86	tyrphostin_AG-825	0.6	1.32E-02
87	trifluridine	0.6	1.34E-02
88	procainamide	0.6	1.36E-02
89	nomifensine	0.6	1.39E-02
90	etamivan	0.6	1.42E-02
91	5109870	0.59	1.43E-02
92	tropicamide	0.59	1.44E-02
93	napelline	0.59	1.44E-02
94	cefsulodin	0.59	1.45E-02
95	dimethadione	0.59	1.47E-02
96	hydrastinine	0.59	1.56E-02
97	5194442	0.59	1.56E-02
98	methacholine_chloride	0.59	1.56E-02
99	piromidic_acid	0.59	1.57E-02
100	spectinomycin	0.59	1.65E-02
101	omeprazole	0.59	1.66E-02
102	triamterene	-0.58	1.68E-02
103	Prestwick-864	0.58	1.69E-02
104	fludroxycortide	0.58	1.70E-02
105	etoposide	0.58	1.75E-02
106	chlorpropamide	-0.58	1.76E-02
107	sulfanilamide	0.58	1.76E-02
108	thioguanosine	0.58	1.86E-02
109	isometheptene	-0.58	1.88E-02
110	etacrynic_acid	0.58	1.89E-02
111	fisetin	0.58	1.89E-02
112	chlorcyclizine	-0.58	1.90E-02
113	tyrphostin_AG-1478	-0.58	1.90E-02
114	Prestwick-857	-0.58	1.92E-02
115	nafcillin	0.58	1.94E-02

116	amylocaine	0.58	1.97E-02
117	demecarium_bromide	-0.57	2.01E-02
118	labetalol	0.57	2.04E-02
119	betamethasone	-0.57	2.13E-02
120	altretamine	-0.57	2.16E-02
121	STOCK1N-35215	0.57	2.18E-02
122	timolol	-0.57	2.19E-02
123	heptaminol	-0.57	2.22E-02
124	butoconazole	0.57	2.27E-02
125	clemizole	0.57	2.30E-02
126	Prestwick-1084	0.56	2.34E-02
127	cephaeline	-0.56	2.38E-02
128	Y-27632	-0.56	2.44E-02
129	memantine	-0.56	2.45E-02
130	15-delta_prostaglandin_J2	0.56	2.50E-02
131	scopolamine	0.56	2.51E-02

Table T5: Drugs mapped for MAOB gene:

Rank	Name	E-Score	P-Value
1	C-75	0.92	4.83E-07
2	daunorubicin	0.8	2.01E-05
3	azacitidine	0.79	3.05E-05
4	urapidil	0.76	5.81E-05
5	meropenem	0.75	7.70E-05
6	dienestrol	0.73	1.39E-04
7	trimethoprim	0.73	1.40E-04
8	talampicillin	0.72	1.62E-04
9	canrenoic_acid	0.72	1.65E-04
10	simvastatin	0.72	2.01E-04
11	doxorubicin	0.71	2.18E-04
12	camptothecin	0.7	2.75E-04
13	0175029-0000	0.7	3.35E-04
14	5253409	0.69	3.56E-04
15	chlortalidone	-0.69	4.11E-04
16	trifluridine	0.69	4.11E-04
17	citiolone	0.68	5.18E-04
18	flunisolide	0.68	5.18E-04
19	etiocholanolone	-0.68	5.32E-04
20	alsterpaullone	0.67	5.88E-04
21	iohexol	-0.67	6.28E-04
22	omeprazole	0.67	6.38E-04
23	prasterone	0.67	7.10E-04
24	aciclovir	-0.66	7.80E-04
25	remoxipride	0.66	8.71E-04
26	5109870	0.65	9.26E-04
27	fenbufen	0.65	9.39E-04
28	flupentixol	0.65	9.66E-04
29	GW-8510	0.65	9.87E-04
30	letrozole	0.65	9.95E-04
31	propylthiouracil	0.65	1.04E-03
32	ciclopirox	0.65	1.09E-03
33	F0447-0125	0.65	1.11E-03
34	emetine	-0.65	1.12E-03
35	picrotoxinin	0.64	1.30E-03
36	quipazine	-0.64	1.31E-03
37	alpha-estradiol	0.63	1.77E-03
38	finasteride	-0.63	1.79E-03
39	pararosaniline	0.62	2.08E-03
40	ebselen	0.62	2.11E-03
41	3-acetylcoumarin	0.62	2.13E-03
42	tyrphostin_AG-825	0.61	2.27E-03
43	flavoxate	0.61	2.29E-03
44	1,4-chrysenequinone	0.61	2.41E-03
45	ganciclovir	0.61	2.52E-03

46	H-7	0.61	2.58E-03
47	dexverapamil	0.61	2.68E-03
48	Prestwick-1080	0.6	2.92E-03
49	hexylcaine	0.6	3.05E-03
50	STOCK1N-35215	0.6	3.07E-03
51	moxonidine	0.6	3.07E-03
52	oxamic_acid	0.6	3.14E-03
53	pirenzepine	0.6	3.20E-03
54	propantheline_bromide	0.6	3.27E-03
55	hydrocotarnine	0.6	3.31E-03
56	quercetin	0.6	3.47E-03
57	ciprofibrate	0.59	3.53E-03
58	cyanocobalamin	0.59	3.56E-03
59	droperidol	0.59	3.57E-03
60	cephaeline	-0.59	3.80E-03
61	sulfamonomethoxine	-0.59	3.83E-03
62	decitabine	0.59	4.14E-03
63	luteolin	0.58	4.34E-03
64	diphenhydramine	-0.58	4.54E-03
65	atropine_methonitrate	-0.58	4.67E-03
66	ellipticine	0.58	4.73E-03
67	mitoxantrone	0.85	8.26E-05
68	MS-275	0.58	5.01E-03
69	tiratricol	0.57	5.44E-03
70	CP-645525-01	0.57	5.83E-03
71	norcyclobenzaprine	0.57	5.95E-03
72	acepromazine	0.57	6.17E-03
73	tropicamide	0.57	6.25E-03
74	syrosingopine	0.57	6.27E-03
75	tolfenamic_acid	0.57	6.42E-03
76	corticosterone	0.57	6.46E-03
77	bucladesine	-0.56	6.53E-03
78	irinotecan	0.56	6.88E-03
79	oxamniquine	-0.56	6.88E-03
80	apigenin	0.56	7.14E-03
81	pizotifen	-0.56	7.19E-03
82	natamycin	0.56	7.62E-03
83	eldeline	0.56	7.69E-03
84	thioguanosine	0.55	7.95E-03
85	primidone	-0.55	8.20E-03
86	dexpropranolol	0.55	8.63E-03
87	etamivan	0.55	8.67E-03
88	calmidazolium	0.55	8.69E-03
89	azathioprine	0.55	8.88E-03
90	pentolonium	0.55	9.07E-03
91	benzamil	-0.55	9.20E-03
92	Y-27632	-0.55	9.32E-03
93	rolitetracycline	0.55	9.35E-03

94	butoconazole	0.55	9.37E-03
95	phenoxybenzamine	0.55	9.63E-03
96	pempidine	0.54	9.93E-03
97	AG-012559	-0.54	9.98E-03
98	trifluoperazine	0.54	1.02E-02
99	bisoprolol	0.54	1.04E-02
100	carbenoxolone	0.54	1.04E-02
101	mepacrine	0.54	1.05E-02
102	nomifensine	0.54	1.06E-02
103	pipenzolate_bromide	0.54	1.09E-02
104	aminophenazone	0.54	1.12E-02
105	cinchonidine	0.54	1.12E-02
106	oxytetracycline	0.54	1.12E-02
107	piromidic_acid	0.54	1.13E-02
108	nocodazole	-0.54	1.15E-02
109	cisapride	0.54	1.15E-02
110	0297417-0002B	0.54	1.16E-02
111	paromomycin	-0.53	1.18E-02
112	ribostamycin	0.53	1.21E-02
113	trichlormethiazide	0.53	1.23E-02
114	acetylsalicylic_acid	0.53	1.29E-02
115	fasudil	0.53	1.31E-02
116	levothyroxine_sodium	0.53	1.31E-02
117	iobenguane	-0.53	1.35E-02
118	trimipramine	0.53	1.35E-02
119	rifabutin	0.53	1.41E-02
120	clemizole	0.53	1.41E-02
121	5707885	0.53	1.42E-02
122	strophanthidin	0.53	1.42E-02
123	trihexyphenidyl	-0.52	1.43E-02
124	mycophenolic_acid	0.52	1.44E-02
125	3-nitropropionic_acid	0.52	1.47E-02
126	5149715	0.52	1.48E-02
127	biotin	0.52	1.53E-02
128	sulfanilamide	0.52	1.54E-02
129	cefazolin	0.52	1.54E-02
130	verteporfin	0.52	1.55E-02
131	felbinac	-0.52	1.55E-02

Table T6: Common mapped drugs sorted by their permeability scores:

DRUGS	BBB
Sulfanilamide	0.277
GW-8510	0.146
H-7	0.12
Pirenzepine	0.106
Tropicamide	0.094
Alsterpaullone	0.087
Norcyclobenzaprine	0.085
Nomifensine	0.08
Tyrphostin AG825	0.066
MS-275	0.066
Clemizole	0.057
Etamivan	0.049
Canrenoic Acid	0.033
Apigenin	0.022
Luteolin	0.003
Irinotecan	-0.011
Thioguanosine	-0.011
Levothyroxine Sodium	-0.027
Mitoxantrone	-0.029
Camptothecin	-0.037
Trifluridine	-0.051
Iohexol	-0.064
Azacitidine	-0.074
Doxorubicin	-0.287
Daunorubicin	-0.374

Table T7: Gene expression values of three targets with 14 candidate drugs with Alzheimer's-specific controls

ID	Name	Dose	Time	1312	4128	4129
Gene Symbol				COMT	MAOA	MAOB
Gene Space				well inferred	well inferred	well inferred
CPC004_A375_6H:BRD-K38055836-001-13-8:10	etamivan	10 µM	6 h	-0.66	0.11	-0.75
CPC005_A375_6H:BRD-A79672927-001-10-8:10	tropicamide	10 µM	6 h	0.05	-1.05	-0.58
CPC005_A375_24H:BRD-A79672927-001-10-8:10	tropicamide	10 µM	24 h	-0.32	0.74	-1.15
CPC013_A375_6H:BRD-K77908580-001-04-7:10	entinostat	10 µM	6 h	-0.85	0.26	1.54
CPC011_A375_6H:BRD-K49481516-004-14-2:10	galantamine	10 µM	6 h	-0.27	-0.1	1.15
CPC015_A375_6H:BRD-K38055836-001-13-8:10	etamivan	10 µM	6 h	1.01	-0.01	-0.39
CPC016_A375_6H:BRD-K63165456-001-03-3:10	norcyclobenzaprine	10 µM	6 h	0.85	0.73	-0.34
CPC015_A375_6H:BRD-K89375097-300-06-2:10	pirenzepine	10 µM	6 h	0.74	0.18	0.12
CPC014_A375_6H:BRD-K01493881-001-19-5:10	744	10 µM	6 h	244	0.17	0.04
CPC014_A375_6H:BRD-A55756846-001-16-2:10	H-7	10 µM	6 h	-0.65	0.17	-0.49
CPC014_A375_6H:BRD-K01493881-001-20-3:10	apigenin	10 µM	6 h	-0.32	0.07	0.67
CPC014_A375_6H:BRD-K77908580-001-05-4:10	entinostat	10 µM	6 h	-1.37	-1.02	-0.95
CPC020_A375_6H:BRD-A29644307-001-01-7:10	nomifensine	10 µM	6 h	-0.14	-0.21	-0.33
CPC018_A375_6H:BRD-K46556543-237-03-0:10	canrenoic-acid	10 µM	6 h	-0.37	0.64	0.53
CPC018_A375_6H:BRD-K87919739-001-03-4:10	tyrphostin-AG-825	10 µM	6 h	0.55	0.62	0.12
CPC020_A375_6H:BRD-A79803969-003-13-8:10	memantine	10 µM	6 h	-1.02	0.45	-0.38
CPC020_A375_6H:BRD-A79672927-001-15-7:10	tropicamide	10 µM	6 h	-0.5	0.22	-0.36
PCLB003_A375_24H:BRD-K77908580-001-04-7:10	entinostat	10 µM	24 h	0.55	1.14	2.18
PCLB003_A375_24H:BRD-K77908580-001-04-7:3.33	entinostat	3.33 µM	24 h	0.19	0.84	0.69
PCLB003_A375_24H:BRD-K77908580-001-04-7:1.11	entinostat	1.11 µM	24 h	-0.24	0.89	1.19
PCLB003_A375_24H:BRD-K77908580-001-04-7:0.37	entinostat	0.37 µM	24 h	0.08	0.3	0.11
PCLB003_A375_24H:BRD-K77908580-001-04-7:0.12	entinostat	0.12 µM	24 h	-0.94	0.49	0.44
PCLB003_A375_24H:BRD-K77908580-001-04-7:0.04	entinostat	0.04 µM	24 h	-0.73	0.88	0.85

Table T8: Gene expression values of three targets with 14 candidate drugs with Parkinson's-specific controls

ID	Name	Dose	Time	1312	4128	4129
Gene Symbol				COMT	MAOA	MAOB
Gene Space				well inferred	well inferred	well inferred
CPC004_A375_6H:BRD-K38055836-001-13-8:10	etamivan	10 µM	6 h	-0.66	0.11	-0.75
CPC005_A375_6H:BRD-A79672927-001-10-8:10	tropicamide	10 µM	6 h	0.05	-1.05	-0.58
CPC005_A375_24H:BRD-A79672927-001-10-8:10	tropicamide	10 µM	24 h	-0.32	0.74	-1.15
CPC013_A375_6H:BRD-K77908580-001-04-7:10	entinostat	10 µM	6 h	-0.85	0.26	1.54
CPC011_A375_6H:BRD-K06388322-001-05-8:10	pramipexole	10 µM	6 h	0.82	0.5	-2.2
CPC011_A375_6H:BRD-K06388322-003-07-0:10	pramipexole	10 µM	6 h	0.65	-0.67	0.96
CPC015_A375_6H:BRD-K38055836-001-13-8:10	etamivan	10 µM	6 h	1.01	-0.01	-0.39
CPC016_A375_6H:BRD-K63165456-001-03-3:10	norcyclobenzaprine	10 µM	6 h	0.85	0.73	-0.34
CPC015_A375_6H:BRD-K70330367-003-03-8:10	amantadine	10 µM	6 h	-0.13	-1.14	-0.2
CPC015_A375_6H:BRD-K89375097-300-06-2:10	pirenzepine	10 µM	6 h	0.74	0.18	0.12
CPC014_A375_6H:BRD-K01493881-001-19-5:10	apigenin	10 µM	6 h	-0.36	0.17	0.04
CPC014_A375_6H:BRD-A55756846-001-16-2:10	H-7	10 µM	6 h	-0.65	0.17	-0.49
CPC014_A375_6H:BRD-K01493881-001-20-3:10	apigenin	10 µM	6 h	-0.32	0.07	0.67
CPC014_A375_6H:BRD-K77908580-001-05-4:10	entinostat	10 µM	6 h	-1.37	-1.02	-0.95
CPC020_A375_6H:BRD-A29644307-001-01-7:10	nomifensine	10 µM	6 h	-0.14	-0.21	-0.33
CPC018_A375_6H:BRD-K46556543-237-03-0:10	canrenoic-acid	10 µM	6 h	-0.37	0.64	0.53
CPC018_A375_6H:BRD-K87919739-001-03-4:10	tyrphostin-AG-825	10 µM	6 h	0.55	0.62	0.12
CPC020_A375_6H:BRD-A79672927-001-15-7:10	tropicamide	10 µM	6 h	-0.5	0.22	-0.36
PCLB003_A375_24H:BRD-K77908580-001-04-7:10	entinostat	10 µM	24 h	0.55	1.14	2.18
PCLB003_A375_24H:BRD-K77908580-001-04-7:3.33	entinostat	3.33 µM	24 h	0.19	0.84	0.69
PCLB003_A375_24H:BRD-K77908580-001-04-7:1.11	entinostat	1.11 µM	2.23536 E+11	-0.24	0.89	1.19

PCLB003_A375_24H:BRD-K77908580-001-04-7:0.37	entinostat	0.37 µM	24 h	0.08	0.3	0.11
PCLB003_A375_24H:BRD-K77908580-001-04-7:0.12	entinostat	0.12 µM	24 h	-0.94	0.49	0.44
PCLB003_A375_24H:BRD-K77908580-001-04-7:0.04	entinostat	0.04 µM	24 h	-0.73	0.88	0.85

Table T9: Gene expression values of three targets with 14 candidate drugs with COMT-specific controls

ID	Name	Dose	Time	1312	4128	4129
Gene symbol				COMT	MAOA	MAOB
Gene space				well inferred	well inferred	well inferred
CPC004_A375_6H:BRD-K38055836-001-13-8:10	etamivan	10 µM	6 h	-0.66	0.11	-0.75
CPC005_A375_6H:BRD-A79672927-001-10-8:10	tropicamide	10 µM	6 h	0.05	-1.05	-0.58
CPC005_A375_24H:BRD-A79672927-001-10-8:10	tropicamide	10 µM	24 h	-0.32	0.74	-1.15
CPC013_A375_6H:BRD-K77908580-001-04-7:10	entinostat	10 µM	6 h	-0.85	0.26	1.54
CPC015_A375_6H:BRD-K38055836-001-13-8:10	etamivan	10 µM	6 h	1.01	-0.01	-0.39
CPC016_A375_6H:BRD-K63165456-001-03-3:10	norcyclobenzaprine	10 µM	6 h	0.85	0.73	-0.34
CPC015_A375_6H:BRD-K89375097-300-06-2:10	pirenzepine	10 µM	6 h	0.74	0.18	0.12
CPC014_A375_6H:BRD-K01493881-001-19-5:10	apigenin	10 µM	6 h	-0.36	0.17	0.04
CPC014_A375_6H:BRD-A55756846-001-16-2:10	H-7	10 µM	6 h	-0.65	0.17	-0.49
CPC014_A375_6H:BRD-K01493881-001-20-3:10	apigenin	10 µM	6 h	-0.32	0.07	0.67
CPC014_A375_6H:BRD-K77908580-001-05-4:10	entinostat	10 µM	6 h	-1.37	-1.02	-0.95
CPC020_A375_6H:BRD-A29644307-001-01-7:10	nomifensine	10 µM	6 h	-0.14	-0.21	-0.33
CPC020_A375_6H:BRD-K10852020-001-01-1:10	tolcapone	10 µM	6 h	-0.29	-0.42	-0.62
CPC018_A375_6H:BRD-K46556543-237-03-0:10	canrenoic-acid	10 µM	6 h	-0.37	0.64	0.53
CPC020_A375_6H:BRD-K83636919-001-01-4:10	entacapone	10 µM	6 h	-0.02	-0.9	-0.74
CPC018_A375_6H:BRD-K87919739-001-03-4:10	tyrphostin-AG-825	10 µM	6 h	0.55	0.62	0.12
CPC020_A375_6H:BRD-A79672927-001-15-7:10	tropicamide	10 µM	6 h	-0.5	0.22	-0.36
PCLB003_A375_24H:BRD-K77908580-001-04-7:10	entinostat	10 µM	24 h	0.55	1.14	2.18
PCLB003_A375_24H:BRD-K77908580-001-04-7:3.33	entinostat	3.33 µM	24 h	0.19	0.84	0.69
PCLB003_A375_24H:BRD-K77908580-001-04-7:1.11	entinostat	1.11 µM	24 h	-0.24	0.89	1.19
PCLB003_A375_24H:BRD-K77908580-001-04-7:0.37	entinostat	0.37 µM	24 h	0.08	0.3	0.11

PCLB003_A375_24H:BRD-K77908580-001-04-7:0.12	entinostat	0.12 µM	24 h	-0.94	0.49	0.44
PCLB003_A375_24H:BRD-K77908580-001-04-7:0.04	entinostat	0.04 µM	24 h	-0.73	0.88	0.85

Table T10: Gene expression values of three targets with 14 candidate drugs with MAO-specific controls

Id	Name	Dose	Time	1312	4128	4129
Gene symbol				COMT	MAOA	MAOB
Gene space				well inferred	well inferred	well inferred
CPC004_A375_6H:BRD-K38055836-001-13-8:10	etamivan	10 µM	6 h	-0.66	0.11	-0.75
CPC005_A375_6H:BRD-A79672927-001-10-8:10	tropicamide	10 µM	6 h	0.05	-1.05	-0.58
CPC005_A375_24H:BRD-A79672927-001-10-8:10	tropicamide	10 µM	24 h	-0.32	0.74	-1.15
CPC013_A375_6H:BRD-K77908580-001-04-7:10	entinostat	10 µM	6 h	-0.85	0.26	1.54
CPC011_A375_6H:BRD-K86434416-003-13-0:10	selegiline	10 µM	6 h	0.42	-0.46	-0.19
CPC015_A375_6H:BRD-K38055836-001-13-8:10	etamivan	10 µM	6 h	1.01	-0.01	-0.39
CPC016_A375_6H:BRD-K63165456-001-03-3:10	norcyclobenzaprine	10 µM	6 h	0.85	0.73	-0.34
CPC015_A375_6H:BRD-K89375097-300-06-2:10	pirenzepine	10 µM	6 h	0.74	0.18	0.12
CPC014_A375_6H:BRD-K01493881-001-19-5:10	apigenin	10 µM	6 h	-0.36	0.17	0.04
CPC014_A375_6H:BRD-A55756846-001-16-2:10	H-7	10 µM	6 h	-0.65	0.17	-0.49
CPC014_A375_6H:BRD-K01493881-001-20-3:10	apigenin	10 µM	6 h	-0.32	0.07	0.67
CPC014_A375_6H:BRD-K77908580-001-05-4:10	entinostat	10 µM	6 h	-1.37	-1.02	-0.95
CPC020_A375_6H:BRD-A29644307-001-01-7:10	nomifensine	10 µM	6 h	-0.14	-0.21	-0.33
CPC018_A375_6H:BRD-K46556543-237-03-0:10	canrenoic-acid	10 µM	6 h	-0.37	0.64	0.53
CPC018_A375_6H:BRD-K87919739-001-03-4:10	tyrphostin-AG-825	10 µM	6 h	0.55	0.62	0.12
CPC020_A375_6H:BRD-K86434416-003-14-8:10	selegiline	10 µM	6 h	-0.07	0.05	-0.25
CPC020_A375_6H:BRD-A79672927-001-15-7:10	tropicamide	10 µM	6 h	-0.5	0.22	-0.36
PCLB003_A375_24H:BRD-K77908580-001-04-7:10	entinostat	10 µM	24 h	0.55	1.14	2.18
PCLB003_A375_24H:BRD-K77908580-001-04-7:3.33	entinostat	3.33 µM	24 h	0.19	0.84	0.69
PCLB003_A375_24H:BRD-K77908580-001-04-7:1.11	entinostat	1.11 µM	24 h	-0.24	0.89	1.19

PCLB003_A375_24H:BRD-K77908580-001-04-7:0.37	entinostat	0.37 µM	24 h	0.08	0.3	0.11
PCLB003_A375_24H:BRD-K77908580-001-04-7:0.12	entinostat	0.12 µM	24 h	-0.94	0.49	0.44
PCLB003_A375_24H:BRD-K77908580-001-04-7:0.04	entinostat	0.04 µM	24 h	-0.73	0.88	0.85

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