Polypharmacology – a challenge for current drug design approaches

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Abstract

Drug design process faces many challenges, and the most important ones are connected with side effects. Finding compounds that possess affinity towards target of interest is relatively simple; however, an approach one disease-one target is now making space for the search of polypharmacological ligands, where activity towards several proteins is considered at one time. Such proteins are not always the target ones, but very often such panels include also anti-targets, interaction with which is not desired, due to the side effects that may occur upon such contact. In the study, we examined ligands of four G protein-coupled receptors, forming antipsychotic profile: dopamine receptor D_2, serotonin receptors 5-HT_{2A}, 5-HT_{2C} (anti-target), and 5-HT_6. Number of ligands belonging to particular activity groups, as well as the selected compound structures are examined in detail. Also compound similarity between sets of different activity groups is analysed, giving a picture of difficulty of constructing molecular modeling methodologies that can help in the search of compounds with desired activity profile.

Keywords: G protein-coupled receptors, polypharmacology, serotonin receptors, dopamine receptors, antipsychotic profile, ligands

Introduction

Polypharmacology paradigm is now ruling the drug design process. It is not only connected with the fact that in order to fight a disease it is not sufficient to modulate activity of just one protein, but also with side effects that are caused by undesired interaction of ligands with particular proteins. The side effects are the main reason of compounds failures in clinical trials. However, the design of polypharmacological ligands is very difficult and requires a lot of knowledge and experience, often supported by a little bit of luck [1–4].

Serotonin and dopamine receptors are representatives of G protein-coupled receptors (GPCRs) – the largest and most diverse group of proteins in the human genome. They control the great variety of physiological functions in organism and malfunctioning in signal transduction within this group of targets is related with many diseases. In the study, we consider psychotic disorders, and the selected profile is the antipsychotic one and is composed of the following targets: D_2, 5-HT_{2A}, 5-HT_6, and anti-target: 5-HT_{2C} [5–7].

Central nervous system disorders are one of the biggest problems of societies in developed countries and are predicted to be still a growing problem. The drugs currently used to treat disorders such as depression and anxiety possess long list of drawbacks, such as delay in the therapeutic effect (not mentioning the treatment-resistant patients), and adverse effects such as headache, weight gain, nausea, diarrhea, fatigue, sweating, dizziness, tremor, and dry mouth. Moreover, despite the extensive research programs carried out on mental diseases, the knowledge about the pathophysiology and mechanisms of the great number of them is still limited. The need for search of new drugs is not only present in the field of depression and anxiety, but disorders such as Alzheimer's disease and schizophrenia are also still waiting for their more effective treatment. For example, in schizophrenia, the currently used treatment strategies are quite effective in the controlling of the positive symptoms of this disorder, whereas the negative symptoms, such as cognitive disorders, and memory problems are not sufficiently treated by the neuroleptics used, although they are extremely important aspects from the social point of view, enabling patients coming back to professional activities and proper functioning in the society. This makes the desire for the search for antipsychotics with precognitive properties leading to better treatment of this serious, nowadays incurable disease [8, 9].

In the study, we analysed ligands of receptors included in the considered activity profile and estimated difficulty of constructing predictive models that can be used in the search for new antipsychotic compounds.

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Materials and Methods

The respective sets of compounds were prepared on the basis of the ChEMBL database [10] data (only human-based assays and activities expressed in K_i values were considered). The division into the set of active and inactive compounds was performed via imposing the respective threshold for activity parameter: 100 nM and 1000 nM for active and inactive sets, respectively [11]. Ligand structures were compared manually and automatically using InstantJChem [12] and ligand overlap was checked using Venn Diagrams tool [13].

Example compound was docked to crystal structures of D_2 and 5-HT_{2A} (the respective PDB codes are as follows: 6CM4 [14], and 6A93 [15]). Three-dimensional conformation and protonation state in pH = 7.4 was generated in LigPrep [16], and the docking was performed in Schrödinger's Glide in standard precision mode [17] with grid centered at D3x32 (according to GPCRdb numbering [18]).

Results and Discussion

The total numbers of ligands belonging to particular activity groups are presented in Table 1.

The overlap of structures between particular target protein and the anti-target 5-HT_{2C}R was presented with the use of Venn diagrams (Figure 1).

The performed analysis show that there is relatively small overlap of ligands between the considered target and anti-target, especially for compounds inactive towards 5-HT_{2C} – only several compounds are the same, as for other compound groups (most often it is just one molecule). This might lead to great difficulties in constructing molecular modeling approaches enabling selection of compounds, selectively active towards one of the considered targets, and at the same time inactive towards 5-HT_{2C}.

As the total number of known datapoints for all receptors considered is relatively high, a solution to this problem is a construction of separate predictive models evaluating activity towards particular protein, and then combining such prediction into one final answer about the activity profile of assessed compounds.

As an additional analysis, examples of compound structures for which activity towards receptors included in the anti-psychotic panel is provided were gathered. However, no compounds were found, for which activity towards all proteins considered was reported, only 10 compounds with 5-HT_{2A}, D_2, and 5-HT_{2C} components examined were available (Figure 2).

Table 1. Number of compounds belonging to particular activity groups

Target/ Group of compounds	5-HT_{2A}	5-HT_{2C}	5-HT_6	D_2
Actives	1837	968	2020	2473
Inactives	713	595	364	1839

From both activity groups considered, the highest number of ligands occurred for D_2R, whereas the lowest for 5-HT_{2C}R. Interestingly, despite relatively high number of compounds active towards 5-HT_6R (2020), the set of compounds inactive towards 5-HT_6R is quite narrow and includes only 364 structures, which can influence predictive models constructed for this target, due to high class imbalance occurring in the starting dataset.

The conducted analysis show that despite relatively low number of structures for which required activity data is available, the provided examples are promising in terms of possibilities of designing new ligands of such a type, as majority of them display quite strong activity towards targets (with K_i values even below 10 nM) and very strong inactivity towards 5-HT_{2C} at the same time (e.g., K_i = 10 000 nM).

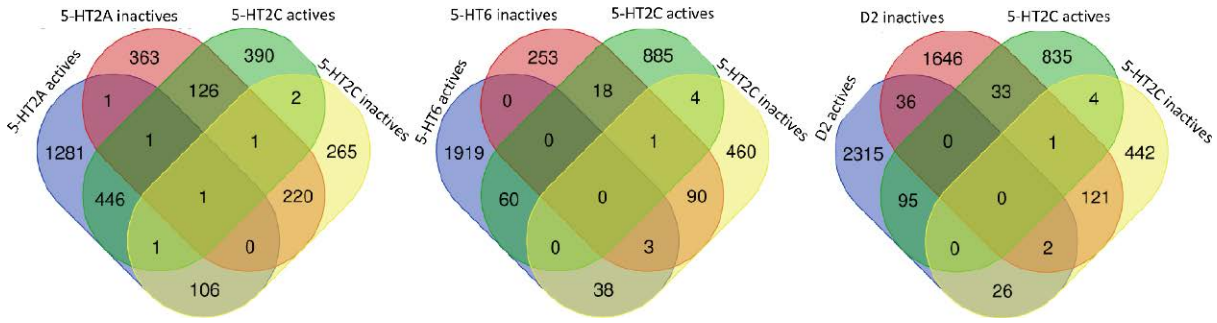

Figure 1. Venn diagrams of the number of ligands overlapping between particular activity groups

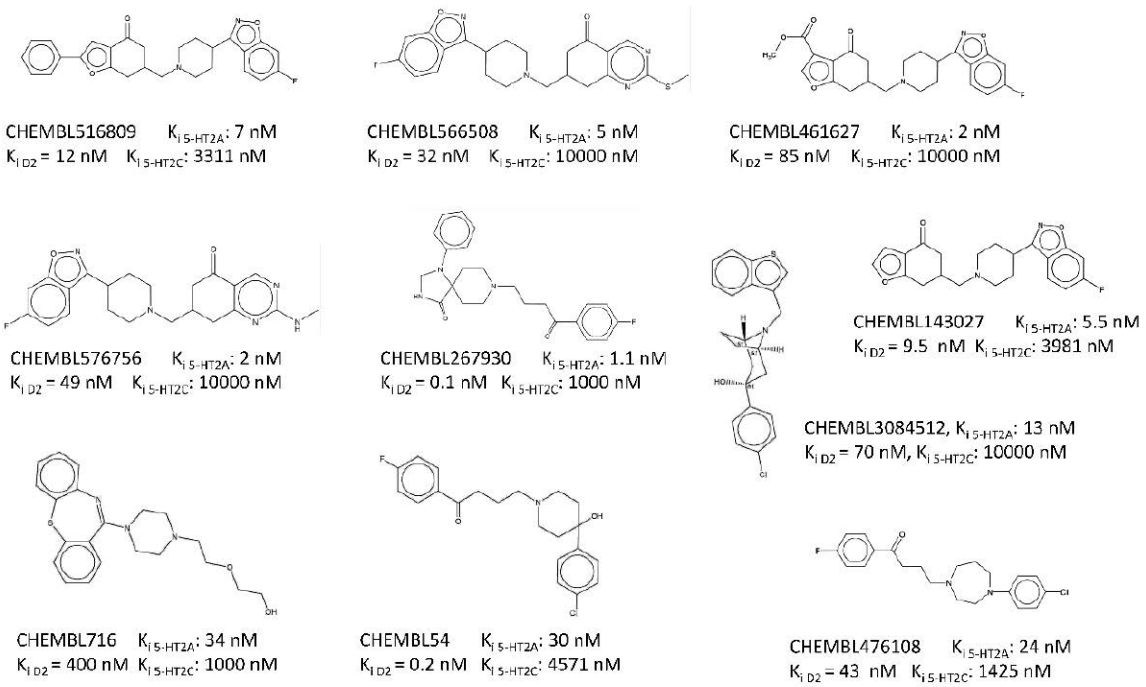

Figure 2. Structures of compounds active towards 5-HT_{2A} and D_2 receptors and inactive towards 5-HT_{2C}

As one of the compound, CHEMBL576756, possessed chemical structure very similar to one of very popular atypical antipsychotics, risperidone (the compounds share the same scaffold), the compound was docked to crystal structures of dopamine receptor D_2 and serotonin receptor 5-HT_{2A} (Figure 3). The docking results indicate that CHEMBL576756 occupy the same region of the binding site as risperidone and their docking poses are very similar. In the case of both 5-HT_{2A}, and D_2, the compounds interact with amino acids reported as the most important ones for activity within these groups of receptors (W 3x28, D 3x32, S 5x461, F 6x51, and F 6x52).

Finally, analysis of similarity between different datasets was carried out with the use of ECFP fingerprint [20] and Tanimoto coefficient [21] as similarity measure. They were all carried out with reference to 5-HT_{2C} – separately for the sets of active and inactive compounds, and the results were presented in the form of histograms (Figure 4).

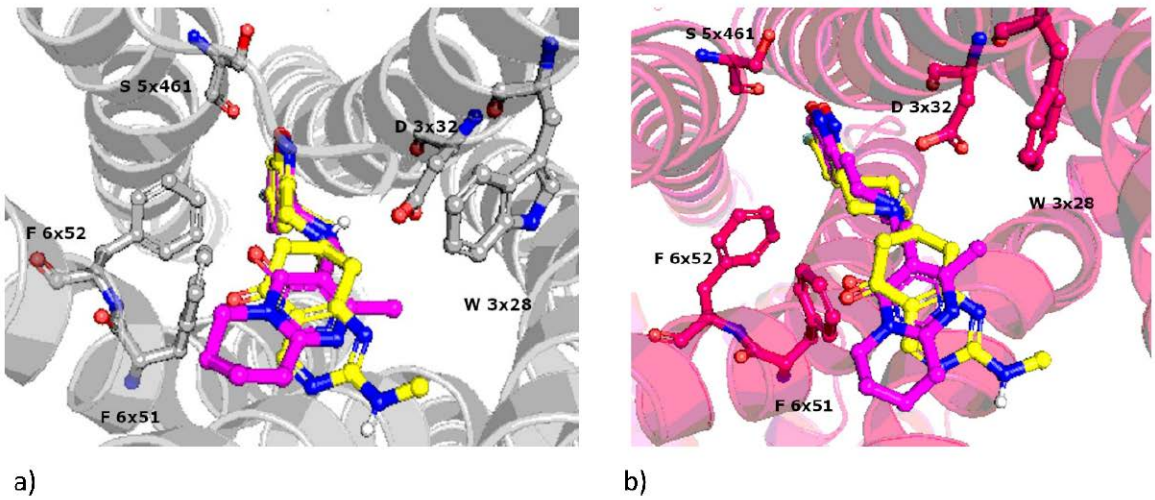

Figure 3. Comparison of docking poses of CHEMBL576756 (magenta) and co-crystallized risperidone (yellow) for a) 5HT_{2A}, and b) D_2 receptors. Picture generated in Pymol [19]

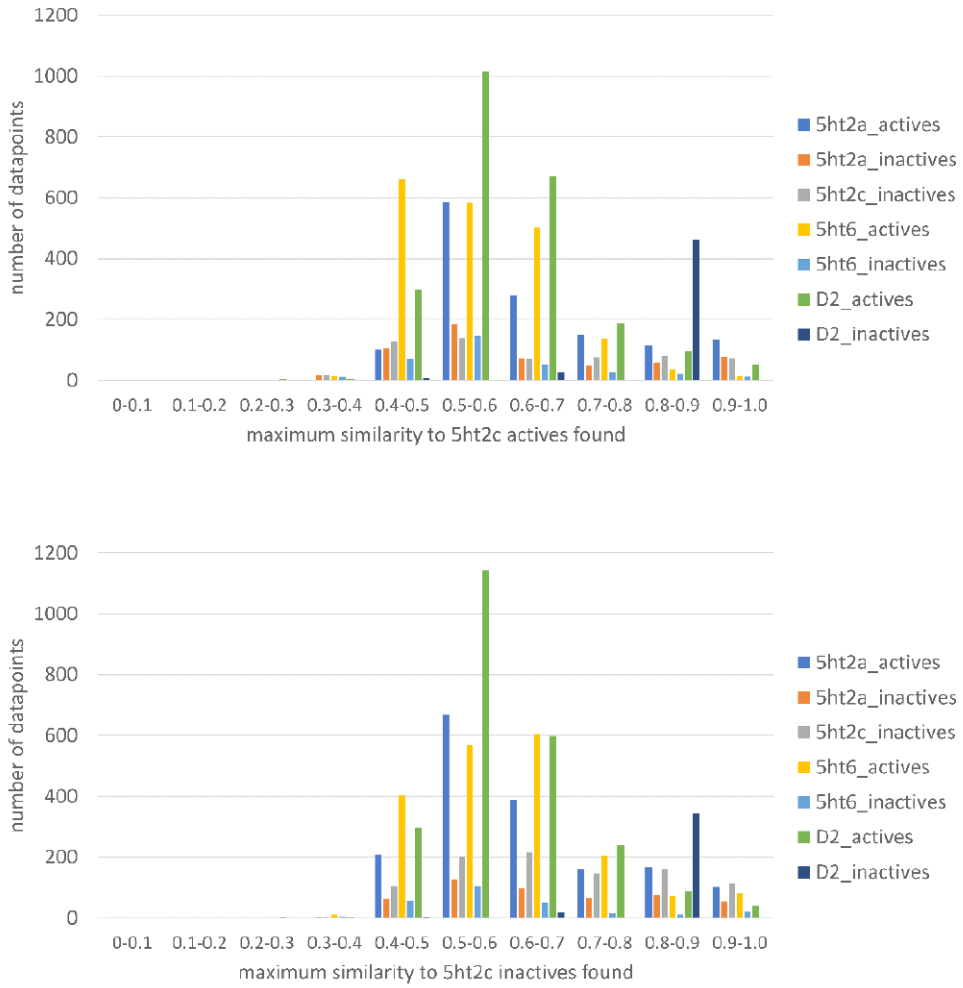

Figure 4. Distribution of similarity coefficients (maximum values) to 5-HT_{2C} ligands (active and inactive compounds, respectively)

The analysis of distribution of similarity coefficients to compounds examined towards 5-HT_{2C} (both active and inactive compounds) revealed that the similarity rate is similar for all targets considered with peaks between 0.4-0.7 values (Tanimoto coefficient was used as a similarity measure). Only for compounds with K_i values above 1000 nM towards D_2R (considered as inactive towards this receptor), there was a significant fraction of compounds with similarity values between 0.8 and 0.9, which is inconsistent with findings for other compound sets and should be considered when using this data for construction of predictive models regarding this pair of proteins (D_2, 5-HT_{2C}).

Conclusions

The concept of polypharmacology now rules the process of new drug design, increasing the probability of new active compound found to be introduced into the market. It is connected not only with targeting more than one receptor during compound evaluation, but also with consideration of anti-target interaction with which can lead to serious side effects. On the other hand, taking into account several aspects simultaneously, it makes the whole process of searching for new ligands more difficult and complicated. In the study, we analysed ligands of receptors included in the anti-psychotic profile, taking into account their numbers and structures similarity. By analysing these factors, we assessed the difficulty of developing and applying molecular modeling approaches for searching new compounds characterized by anti-psychotic properties. In addition, the compound example compound was docked to crystal structures of selected receptors and the obtained poses were similar to the orientation adopted by co-crystallized ligand (risperidone, known for its antipsychotic properties). It confirms that docking can also be used for searching of new compounds of the considered activity profile.

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