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Nucleotide Relative Molecular Similarity within Anti-Psychotic Drug Structures

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Abstract

The development of antipsychotic drugs (APDs) over many years has brought about a shift in our comprehension of the critical cell receptors involved in schizophrenia and the classes of pharmaceuticals necessary for the control of symptoms. Phosphodiesterase inhibitors and β-arrestin agonists are now considered as medication along with conventional drugs acting at G protein-coupled receptors. A molecular modelling technique is used here to compare the chemical structures of past and current drugs of use in the treatment of schizophrenia. The data demonstrate that drug structures relate to ATP and cAMP nucleotide template structures. Phosphodiesterase inhibitors and third generation APDs relate better to cAMP nucleotide. The relative molecular similarity within APD, phosphodiesterase inhibitor and nucleotide structures is supportive of experimental evidence demonstrating interaction between these compounds and the primary role of adenine nucleotides in the pathogenesis and treatment of schizophrenia.

Keywords

Adenine Nucleotides, β-Arrestins, GPCR, Molecular Structure, Phosphodiesterases, Schizophrenia

1. Introduction

Medicinal chemists have formulated several generations of anti-psychotic drugs over the past 60 years to ameliorate the symptoms of schizophrenia, which are categorised as positive, negative and cognitive [1]. Anti-psychotic medication counterbalances a hyperdopaminergic state within the striatum [2]. Therapeutic effects derive from the antagonism/partial agonism of dopamine D2 receptors (D2R) on striatum spiny projection neurons endowed with two types of axonal projection pathways, direct and indirect [2] [3]. First generation APDs are D2R

antagonists whereas second generation drugs antagonise D2 and serotonin (5-HT) receptors [4]. More recent APDs with better clinical parameters demonstrate partial agonism at D2R/D3R with antagonism at 5-HT, α-adrenergic and histamine receptor sub-types [4]. The categorisation of APDs into typical, atypical and third generation drugs is not sufficient for matching drugs to patients, as there are substantial differences in their side effects [5]. The cognitive deficits of schizophrenia remain largely resistant to drug treatment [6].

The differential effects of APDs may partially relate to their disparate effects on cell kinase signalling pathways (cAMP-kinase, MAPK, GSK-3). However, no convincing abnormality in kinase activity is evident in postmortem brain samples from patients with schizophrenia [7]-[9]. Recent research trends also focus on the interaction of phosphodiesterases (PDEs) and β-arrestins with cellular pathways operating within the striatum and frontal cortex [10]. Activation of D2 and β-adrenergic receptors recruits the β-arrestin scaffold protein which inserts into the plasma membrane lipid bilayer to interact with other receptors by lateral diffusion [11] [12]. The binding of β-arrestin to phosphorylated GPCRs (G protein-coupled receptors) leads to the inhibition of cell signalling, internalisation, dephosphorylation and recycling of receptors within the plasma membrane [13]. Clinically effective APDs block D2R β-arrestin recruitment *in vitro* but do not reverse cortical related cognitive symptoms [13]. Recent comprehensive reviews on the structure, function and potential relevance of β-arrestins in schizophrenia are available [14] [15].

Phosphodiesterase enzymes by compartmentalising cAMP levels regulate cell function, to the extent that GPCR signalling may operate through independent cAMP nano domains [16] [17]. APDs alter PDE expression in the rat striatum and frontal cortex [18] [19], indicative of cyclic nucleotide regulation and supportive of the findings of nucleotide abnormalities in tissue samples and reduced striatal PDE10A in the brain scans of patients [18] [20]. In rats, cAMP supports the generation of cognitive processes by improving synaptic strength and neuron plasticity [21]. Small scale placebo controlled clinical studies on patients with schizophrenia identify improvements in verbal memory and cognitive-enhancement following treatment with a PDE4 inhibitor [21] [22]. Barbagallo *et al.* [23] review the current literature on the use of PDEs in preclinical and clinical studies of schizophrenia.

Evidence from the above experimental and clinical studies demonstrates that nucleotide, PDE and β-arrestin molecular species interact closely in the pathogenesis of schizophrenia. The current investigation aims to provide more information regarding this apparent molecular interdependency. Relative molecular similarity within the structures of APDs, adenine nucleotides, PDEs and β-arrestin is investigated with molecular modelling software.

2. Materials and Methods

The compound structures under investigation are representative of typical APDs (flupentixol, haloperidol, levomepromazine, periciazine, pimozide, trifluoperazine),

atypical APDs (amisulpride, clozapine, iloperidone, lumateperone, pimavanserin) and more recently developed structures (aripiprazole, cariprazine, lurasidone, xanomeline) [5] [24]. Other investigated compounds include PDE10A inhibitors and the β-arrestin agonist UNC9994. Compound structures are taken from Pubchem (https://pubchem.ncbi.nlm.nih.gov/) and the IUPHAR/BPS Guide to Pharmacology [25]. A full list of compounds is given in **Table 1**.

Table 1. Values for fitting compound structures to nucleotide templates.

Compounds	Fitting points	Interatomic distances (Å)	RM S (Å)
Amisulpride	N6C4C2	0.04, 0.06, 0.08	0.0048
Amisulpride	C1'N9N2	0.06, 0.08, 0.05	0.0098
Aripiprazole	N6C4C3	0.03, 0.06, 0.09	0.0126
Aripiprazole	N7C8O3	0.04, 0.07, 0.03	0.0039
Bromocriptine	N6C4C4'	0.03, 0.07, 0.06	0.0071
Cariprazine	N7C8N9	0.05, 0.08, 0.04	0.0201
Cariprazine	C6C4C2'	0.04, 0.07, 0.04	0.0145
Clozapine	C4N9C2'	0.04, 0.04, 0.04	0.0095
Clozapine	C6C4C2	0.02, 0.06, 0.07	0.0119
Clozapine	C6N7C5	0.07, 0.09, 0.10	0.0202
Flupentixol-cis	C6C4C2	0.02, 0.07, 0.07	0.0125
Flupentixol-cis	C3C6C4'	0.03, 0.03, 0.00	0.0010
Haloperidol	N6C4C2	0.02, 0.06, 0.07	0.0196
Haloperidol	C6C2C4'	0.06, 0.03, 0.07	0.0014
Iloperidone	C6C5N7	0.05, 0.11, 0.07	0.0182
Iloperidone	C5C4C1'	0.04, 0.09, 0.10	0.0119
JNJ-42314415	C2'C1'N6	0.06, 0.08, 0.04	0.0018
Levomempromazine	N6C4C2	0.03, 0.07, 0.08	0.0191
Levomempromazine	C4C1'C2'	0.08, 0.06, 0.09	0.0116
Lumateperone	C5C2N9	0.06, 0.07, 0.11	0.0052
Lumateperone	C8N9C4'	0.04, 0.07, 0.04	0.0018
Lurasidone	C8N9N3	0.04, 0.08, 0.07	0.0140
Lurasidone	N1C2O3	0.05, 0.05, 0.03	0.0046
MK-8189	C3'C2'C4'	0.11, 0.09, 0.04	0.0151
MP-10	N3C4C2'	0.03, 0.02, 0.03	0.0022
Periciazine	C6C4C2	0.02, 0.06, 0.07	0.0130
Periciazine	C4C1'C2'	0.09, 0.07, 0.09	0.0107
Pimavanserin	C1'N3N6	0.08, 0.09, 0.01	0.0027
Pimavanserin	C1'N9C8	0.04, 0.05, 0.04	0.0064
Pimozide	N6C4C2	0.02, 0.06, 0.07	0.0178

Continued

Pimozide	C4'C2'C6	0.03, 0.05, 0.06	0.0059
PQ-10	O3N1C6	0.02, 0.09, 0.08	0.0070
Sumanirole	C5N9C2	0.01, 0.02, 0.03	0.0007
TAK-063	N6C6C4'	0.02, 0.05, 0.07	0.0010
Trifluoperazine	C5N9C2	0.11, 0.11, 0.05	0.0070
Trifluoperazine	C4C1'C2'	0.08, 0.07, 0.09	0.0119
UNC9994	C3'C2C5	0.03, 0.05, 0.07	0.0047
Xanomeline	C4C5N6	0.11, 0.04, 0.09	0.0138
Xanomeline	O3O5N9	0.05, 0.04, 0.04	0.0014

Compound structures are built from the contents of the Nemesis software program fragment file (Oxford Molecular version 2.1) and minimised by conformational analysis. The molecular structures used for fitting are minimum energy conformers in an uncharged form. The conformation of the ATP structure is described by the torsion angle (bond angle described by 4 adjacent atoms) C8N9C1'O9 −38˚ (Figure 1). The Nemesis program fits paired molecular structures on a three-point basis. Fitting-points, comprised of atoms of similar type and partial charge within compound and nucleotide structures, are identified in the text and table with respect to the nucleotide labels. Colour-coded atoms in the figures identify ligand fitting-points: carbon-green, nitrogen-blue, oxygen-red, sulphur-yellow, fluorine-purple. Bond order within the molecular structures is not shown to improve on presentation. Likewise, the triphosphate chain of ATP is cropped if not relevant to the fitted drug structure. The Nemesis program computes goodness-of-fit values, in respect of inter-atomic distance at each fitting-point and root mean square (RMS) value. The sequence of fitting points (given in Table 1, left to right) provides the fit with the lowest RMS value.

3. Results

Figures 1-3 provide the respective fitting patterns of atypical, typical and third generation APD structures. Figure 1 also includes the template structures of ATP, cAMP, the fitted structures of dopamine, sumanirole (D2 agonist) and DOI (5-HT_{2A} agonist). The atypical APD structures (Figure 1) are superimposed on ATP (6, 9, 11, 13, 15) and cAMP (8, 10, 12, 14, 16) templates. The fits of dopamine and the dopamine agonist sumanirole focus on the pyrimidine-like moiety of the purine ring and differ in their respective fitting-points at N6 and N9. The fit of dopamine is not altered by the use of the N6 or C6 fitting-point. The amisulpride structure (11) reproduces the dopamine fit. Clozapine (6) does not provide a good fit with the chlorine atom at N6 or with the fitting-points of sumanirole. The fitting-points of DOI are on the indole-like moiety of the purine ring. Clozapine (7) pimavanserin (9), lumateperone (13), and iloperidone (15) structures relate better to the DOI fit. The superimposed and fitted structures on the cAMP template align along the

length of the nucleotide and differ in their fitting-points.

In Figure 2, the structures of the typical APD compounds give dopamine-like fits on the ATP template (1, 3, 5, 7, 9, 11). The substituted benzene rings of haloperidol, pimozide and levomepromazine structures fit to the amino-pyrimidine moiety of the purine ring with fluorine and oxygen atoms providing a good fitting-point at N6. The N6 fitting-point provides a good fit for levomepromazine but not for the other tricyclic APDs. The tricyclic APD structures differ in the distances between the side-chain amine nitrogen and the connecting atom on the tricyclic ring; distances range from 3.8 Å (periciazine) to 5.0 Å (levomepromazine). In common with the atypical APDs, the typical APD structures (2, 4, 6, 8, 10, 12) superimpose along the length of the cyclic nucleotide template.

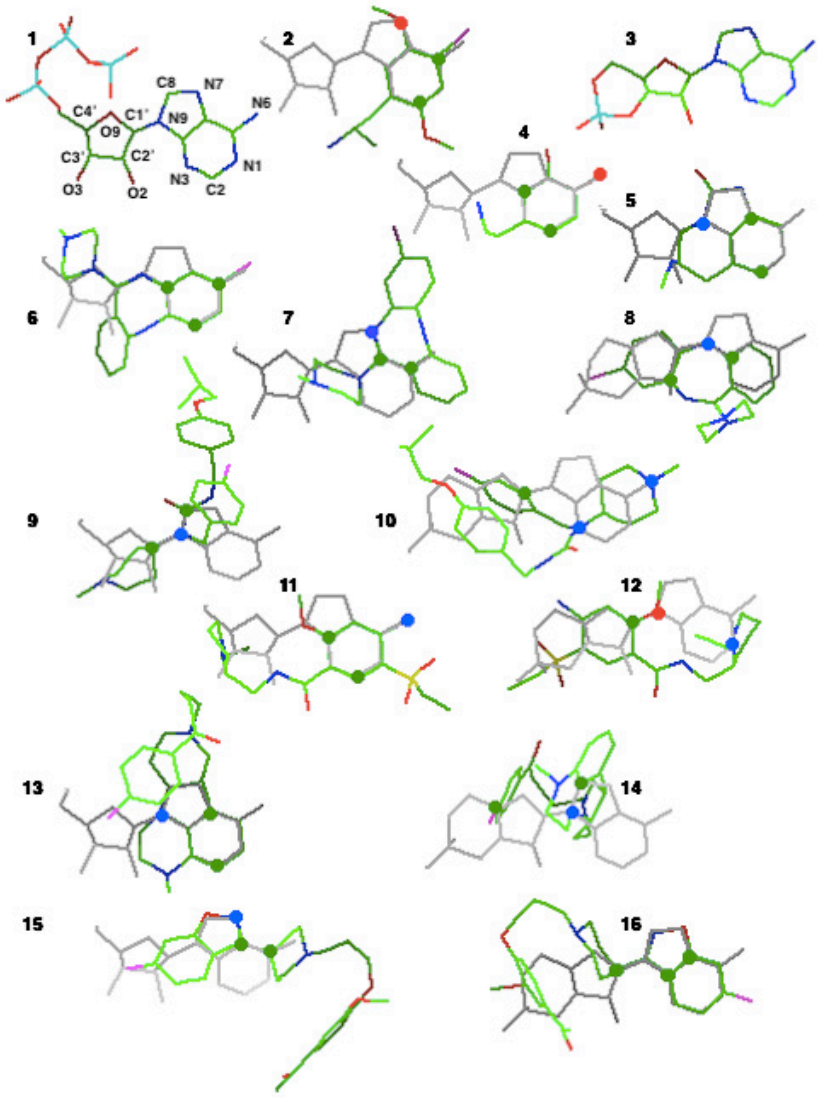

Figure 1. Fits of atypical anti-psychotic drug structures to ATP and cAMP templates (grey): 1 ATP, 2 DOI, 3 cAMP, 4 dopamine, 5 sumanirole, 6 clozapine, 7 clozapine, 8 clozapine, 9 pimavanserin, 10 pimavanserin, 11 amisulpride, 12 amisulpride, 13 lumateperone, 14 lumateperone, 15 iloperidone, 16 iloperidone.

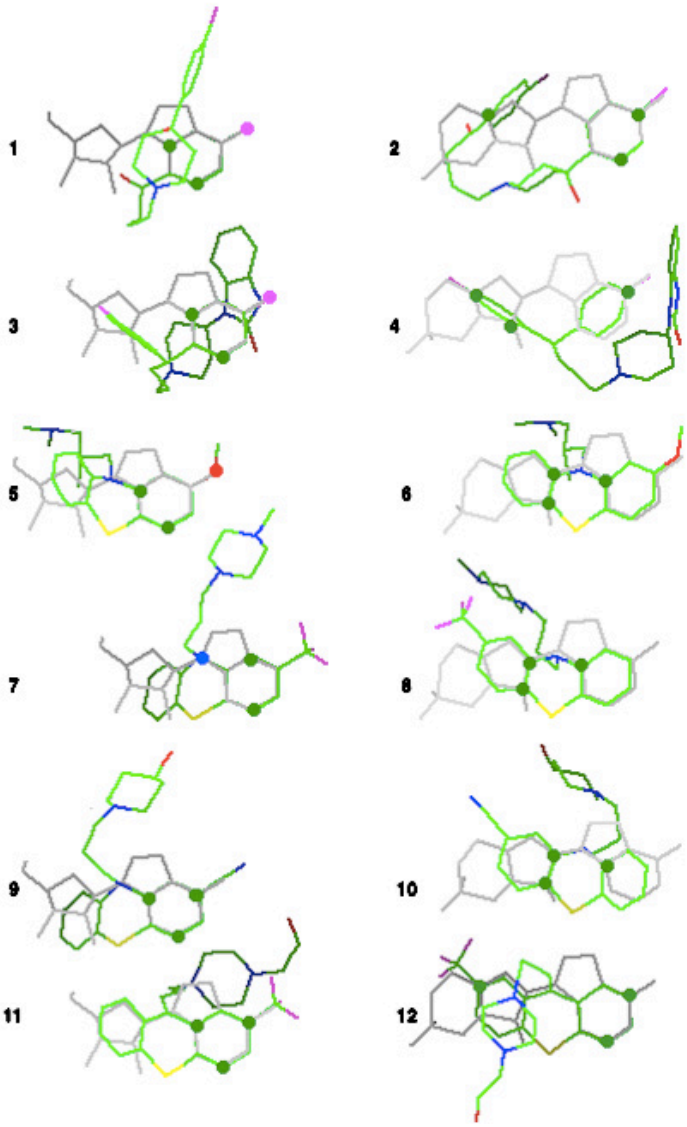

Figure 2. Fits of typical anti-psychotic drug structures to ATP and cAMP templates (grey): 1 haloperidol, 2 haloperidol, 3 pimozide, 4 pimozide, 5 levomepromazine, 6 levomepromazine, 7 trifluoperazine, 8 trifluoperazine, 9 periciazine, 10 periciazine, 11 flupentixol-cis, 12 flupentixol-cis.

Third generation APD structures (Figure 3) demonstrate a mix of fits to the ATP template with respect to dopamine and DOI. The template fit of aripiprazole (7) relates to the dopamine fit, in contrast to the DOI-like fits of lurasidone (1) and cariprazine (3). In comparison to the typical APDs the superimposition of most atypical and third generation drug structures along the length of the cAMP structure is more extensive, and this is even more apparent for the PDE10A inhibitor structures in Figure 4 (1 - 5). The structure of bromocriptine (6), a D2 agonist and PDE2 modulator, is included for comparison. UNC9994 (7), a β-arrestin2 agonist, also demonstrates molecular similarity with the same fitting values for ATP and cAMP templates. The range of fitting-point and RMS goodness-of-fit values for the structures in Table 1 are respectively 0.00 - 0.11 Å and 0.0010 - 0.0202 Å.

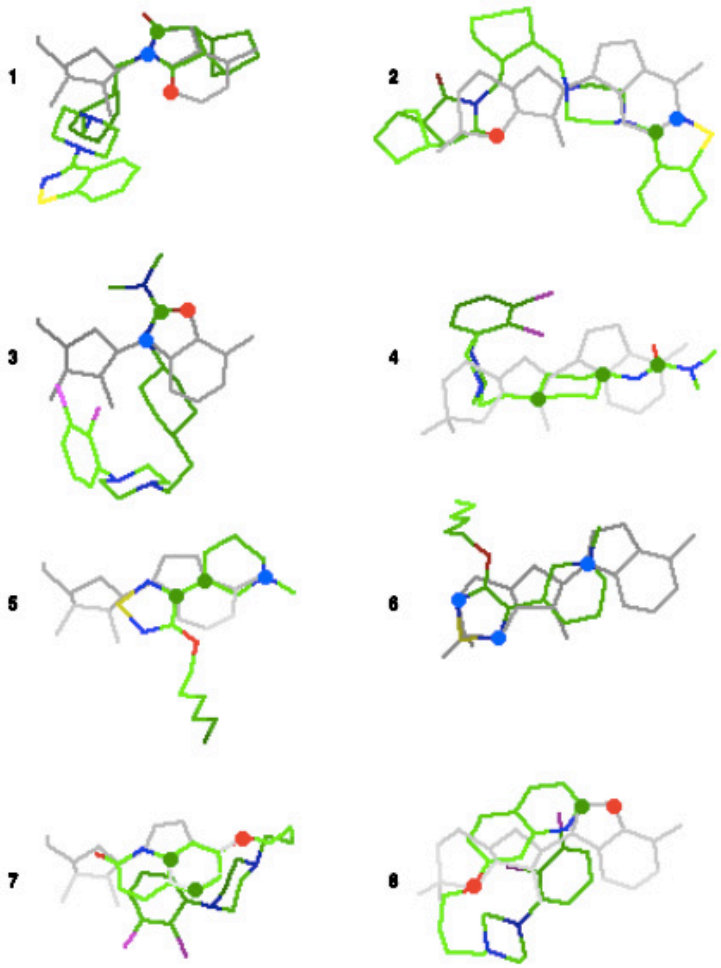

Figure 3. Fits of third-generation anti-psychotic drug structures to ATP and cAMP templates (grey): 1 lurasidone, 2 lurasidone, 3 cariprazine, 4 cariprazine, 5 xanomeline, 6 xanomeline, 7 aripiprazole, 8 aripiprazole.

4. Discussion

The results demonstrate that APD and PDE inhibitor structures share relative molecular similarity with adenine nucleotide structures. The nucleotide and drug structures are of a similar molecular size and share a considerable degree of planarity, permitting good fits of the minimum energy drug conformers. Drug structures from different pharmacological receptor classes provide fitting patterns that may influence nucleotide function and therapeutic effects. Notwithstanding the simplicity of the pharmacophore for fitting dopamine structures (N6C4C2/C6C4C2), this may direct the nucleotide antagonistic properties of the APD structures. In agreement with the current APD categorisation, typical APD structures demonstrate a dopamine-like fit, whereas atypical and third generation drugs show a mixed pattern with respect to dopamine and 5-HT. Xanomeline blocks dopamine receptor agonists despite lacking dopamine receptor affinity [26]. The fitted typical APD structures, in comparison to third generation drugs, demonstrate foreshortening in relation to the length of the cAMP structure. The foreshortening is

especially evident in comparison to the fits of PDE10A inhibitor structures, which incorporate molecular side chains or substantial substituent groups for inhibiting PDE activity.

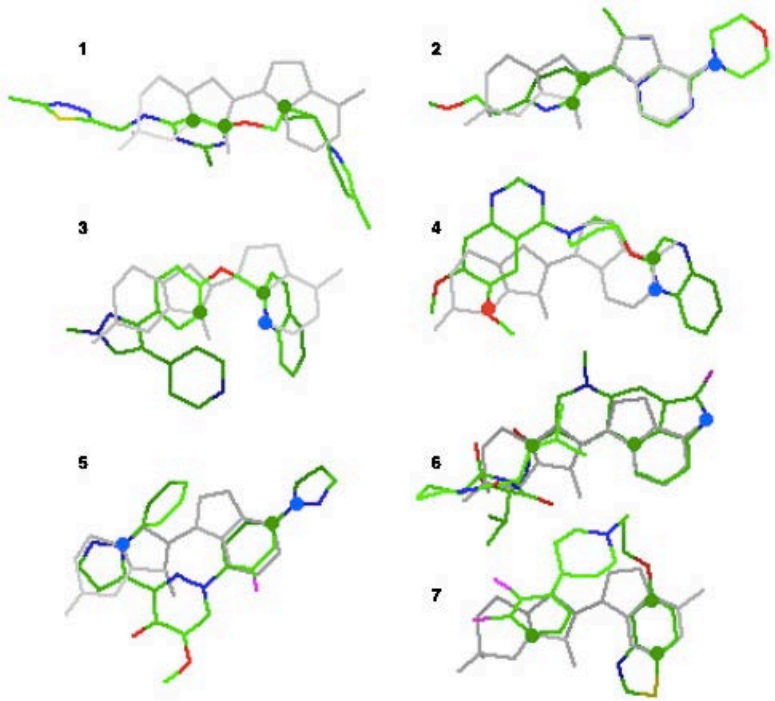

Figure 4. Fits of phosphodiesterase 10 A inhibitors (1 - 5) and β-arrestin2 selective agonist (6) structures to cAMP template (grey). MK-8189, 2 JNJ-42314415, 3 MP-10, 4 PQ-10, 5 TAK-063, 6 bromocriptine, 7 UNC9994.

The template fitting-points and pharmacologic properties of the third generation drugs differ markedly. This is not surprising, as they have affinities for several classes of receptors (pubchem.ncbi.nim.nih.gov.) [27]. Cariprazine is the first available APD with preferential partial agonist binding at D3R and also has 5-HTR antagonist activity. Iloperidone antagonises dopamine and 5-HT receptors, whereas amisulpride antagonises D2R and D3R. Xanomeline targets muscarinic and 5-HT receptors as a receptor agonist. Aripiprazole binds to several receptor types, partially activates the D2R G_{α} protein and antagonises $G_{\beta/\gamma}$ subunit signalling [3]. UNC9994, a derivative of aripiprazole, is a D2R-β-arrestin2 agonist in mouse prefrontal cortex and an antagonist of D2R on striatal medium spiny neurons (MSN); properties that may counteract cortical hypodopaminergia and striatal hyperdopaminergia-induced symptoms of schizophrenia [27]. In combination, low dose haloperidol and UNC9994 ameliorate behavioural symptoms in a rodent model of schizophrenia [28]. Haloperidol, flupentixol, iloperidone, xanomeline and aripiprazole are regarded as inverse or partial agonists. In regard to the current ATP template fits, the partial agonism of APDs may relate to partial interaction with the nucleotide structure and receptor (see **Figure 3**).

The potential benefit of multi-target drugs has been a discussion point for some

time and is a strategy currently applied to the treatment of schizophrenia [1]. Whereas multi-target receptor pharmacology appears to make our understanding of the physiological basis of treatment more complex, this may not be so if the focus is on nucleotide status and the aim of achieving a better striatal nucleotide balance. Most drug receptor classes initiate changes in the cAMP/protein kinase A pathway, as drug structures appear to be based on nucleotide structure [29]. The relative molecular similarity shared by APDs, PDE inhibitors and nucleotide structures, as demonstrated in this study, reveals why these compounds interact mechanistically. Experimental evidence for this interaction is supported by work on rodents, in that the combined treatment of TAK-063 with suboptimal doses of haloperidol or olanzapine enhances antipsychotic effects [30]. Of the PDE types, PDE1, PDE2, PDE3, PDE4 and PDE10 inhibitors are of most interest as potential therapeutic choices for schizophrenia patients [31]. PDE10A inhibitors hydrolyse cAMP in both direct and indirect pathways, whereas blockade of D2R up-regulates cAMP levels. PDE10A inhibition has the potential to affect a balance between striatal D1 and D2 pathways, mimicking the action of D1 agonists and D2 antagonists [32]. The β-arrestin protein recruits PDEs to activated GPCRs. In regard to the β-adrenergic receptor, translocation of PDEs is recognised as a mechanism regulating the cAMP signal in sub-cellular locations, including the nucleus [10].

The binding of TAK-063 and MP-10 to the substrate site of PDE10A reflects the potential for competition with cyclic nucleotides in this domain [2]. In brain sections TAK-063 is more sensitive than MP-10 to binding inhibition by cyclic nucleotides [2]. The slower off-rate binding property of MP-10 inhibits PDE10A more potently than TAK-063 in the presence of high cyclic nucleotide levels, whereas TAK-063 binding to PDE10A is more readily inhibited by lower concentrations of cAMP. The off-rate binding properties of PDE10A inhibitors and balanced activation of the direct and indirect pathways characterise pharmacological profiles in the regulation of MSN pathways [2]. MP-10 is not found to be superior to placebo in patients with an acute exacerbation of schizophrenia. However, schizophrenia patients appear to have normal brain regional values of PDE10A [33].

The link between schizophrenia and gastrointestinal symptoms is worth noting in regard to pathogenesis [34] [35]. The same brain tissues and D2 receptors are implicated. Anti-emetic drugs such as haloperidol and trifluoperazine are prescribed for both conditions and PDEs have an important role with type specific inhibitors available for treatment [36]. Experimental studies on gastroparesis have reported PDE4 inhibitor-induced competition with drug antagonists and cAMP, synergy between receptor agonists and PDE4 antagonists in facilitating acetylcholine release, and PDE4 regulation of receptor agonists [36].

In conclusion, the interaction of neurotransmitters, β-arrestins and PDEs within neural circuits maintains a natural flux in nucleotide levels, disrupted in schizophrenia. Recently developed APDs with multi-receptor targets may regulate dopamine pathways in a more natural way. This investigation by identifying rela-

tive molecular similarity within the above structures supports the need for a research focus on the regulation of neural cAMP pathways. The limitations of the study lie in the simplicity of the methodology that provides no measure of equivalence between structural similarity and physiological effect. More generally, relative nucleotide molecular similarity provides an explanation for the pleiotropic nature and repurposing potential of drugs, and the difficulty of creating drugs without side effects.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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