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Nucleotide Relative Molecular Similarity within Anti-Emetic/Pro-Kinetic Drug Structures

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Abstract

The physiology of the central and enteric nervous systems and gastric muscle contributes to the complexities encountered in the research and clinical management of gastroparesis. A wide range of prescription drugs target the underlying neurotransmitter imbalances and adjust nucleotide levels in appropriate tissues, but treatment is unsatisfactory, as our understanding of the condition is far from complete. In this study, computational software is used to focus on the adenine nucleotide, ATP, as a comparative template for the structures of drugs used in gastroparesis treatment. The results demonstrate that muscarinic, dopamine, serotonin (5-HT) and histamine receptor ligand classes relate structurally and differentially to the molecular structure of ATP. In these neurotransmitter classes, compounds do not target cell membrane receptor G-protein signal transduction in a manner that provides a single mechanism for improving gastroparesis symptoms. The exploration of alternative nucleotide-based deficiencies of KATP channels, Na+/K+ATPases and guanine nucleotide directed nitrergic mechanisms should enhance our experimental approach to understanding this condition.

Keywords

Gastroparesis, Adenine Nucleotides, Neurotransmitter Agents, Molecular Structure

1. Introduction

Symptoms of gastroparesis, namely loss of appetite, nausea and vomiting, are associated with diabetes, surgery, medicines and viruses, although the major grouping (around 36%) is idiopathic [1] [2]. Gastroparesis has a multifactorial

relationship with gastroesophageal reflux disease (GERD) and functional dyspepsia. Under Rome IV criteria, the condition is considered a disorder of gut-brain interaction [3] [4]. A significant proportion of idiopathic gastroparesis cases may arise from olfactory stimulation, modulating metabolic processes and visceral function through the supraciasmatic nucleus [5]. Sinusitis, allergic rhinitis and asthma are significantly associated with GERD [6]. Reported prevalences of nasal symptoms with gastritis and GERD in patients with no nasal disturbance, allergic rhinitis, non allergic rhinitis or sinusitis range from 23% - 40%. [7]. Cyclical patterns of gastroparesis and anti-emetic use [8] [9] may be influenced by the periodicity of seasonal allergy and pre-menstrual syndrome.

Drug therapy for gastroparesis is well established but poorly effective. Patient satisfaction scores for treatment of vomiting and stimulation of gastric function range from 23% - 67% [10]. Drugs with the property of improving gastric motility are based mainly on the modulation of neurotransmitter action. Dopamine slows the fractional emptying of gastric contents in healthy volunteers, a process countered by cisapride [11]. Anti-emetic/prokinetic medicines, such as metoclopramide and domperidone, enhance the contractility of gut muscle and movement of gut contents by targeting a range of receptors. Changes in gastric motor function reach the brainstem via abdominal vagal afferents with receptors for 5-HT_3 and neurokinin (NK) antagonists [10]. The drug brainstem receptors blocking nausea/vomiting are those for acetylcholine, dopamine, serotonin (5-HT), NK1 and histamine, whereas peripheral anti-emetic receptors are evident for 5-HT_4, acetylcholine and motilin [10]. Acetylcholine and dopamine activity within the striatum is crucial to basal ganglia function, involving opposition and cooperation [12]. The therapeutic mechanisms of the drugs prescribed for gastroparesis are ambiguous, due in part to lack of receptor specificity and indirect actions on gastric muscle [13]. Metoclopramide has a complex pharmacological profile, including 5-HT_3/D_2 receptor antagonism and 5-HT_4 agonism [14]. Domperidone has similar affinities for D_2 and D_3 receptors and at higher concentrations, is an α_1-adrenoceptor antagonist [14]. One outpatient survey (n = 150, 40% with gastroparesis as a primary cause of nausea) identifies significantly higher efficacy scores for the use of marijuana, ondansetron and promethazine [15]. A meta-analysis of 25 trials rates only clebopride and domperidone as superior to placebo, with metoclopramide ranking first in one small trial for reduced nausea and bloating; dopamine and tachykinin-21 antagonist classes are considered to be efficacious [16]. A recent literature review points to the poor rationale supporting receptor antagonist use in the control of vomiting and the variable efficacies of metoclopramide, clebopride and 5-HT_4 agonists for improving gastric emptying [10].

Studies with a focus on the structure-activity characteristics of compounds currently used in gastroparesis treatment should generate comparative data enabling the design of better drugs. The computational modeling of drugs and endogenous molecular structures provides a resourceful approach to this endeavour. Dopamine, muscarinic, histamine and 5-HT cell membrane receptors modulate second

messenger cAMP levels via G-protein regulation of adenyl cyclase [17]. The contribution of cAMP metabolism to the initiation of gastric symptoms is made evident by the nauseous side-effects of dopamine (D_2/D_3) agonists, and selective phosphodiesterase inhibitors (PDE4) which find clinical use in COPD, psoriasis and atopic dermatitis [18]. In general, PDE4 inhibitors impair gastric emptying and induce vomiting, as is the case for α_2-adrenoceptor agonists [19]. This study examines the premise that anti-emetic/pro-kinetic effects of compounds currently used in the treatment of gastroparesis may reside in their modulation of adenine nucleotides. The computational data compare the chemical structures of anti-emetic compounds and adenine nucleotides for relative molecular similarity and similar template-fitting patterns.

2. Materials and Methods

2.1. Compound Structures

Representative compound structures are taken from the major classes of drugs prescribed for the treatment of gastroparesis over recent decades, and those drugs showing benefits in experimental studies: primarily small molecular weight ligands of 5-HT, dopamine, histamine and muscarinic receptors [3] [10] [14]. Compounds in use as PDE inhibitors and KATP channel modulators are also investigated. A comprehensive list of investigated compounds is given in **Table 1**, along with specific references to these compounds within the discussion section. The compound structures are taken from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and IUPHAR/BPS [17] websites.

Table 1. Values for fitting compound structures to ATP and cAMP* nucleotide templates.

compound	primary receptor	fitting points	interatomic distances (Å)	RMS (Å)
α-bisabolol	-	C2N1C5	0.06, 0.08, 0.14	0.0031
BIMU8	5-HT4	C1'C8C2	0.03, 0.05, 0.07	0.0039
NMPB	M2	O9C1'C8	0.13, 0.08, 0.09	0.0051
allantoin	-	N7C8C4	0.03, 0.04, 0.01	0.0080
blonanserin	D2, 5-HT2A	C2C4N6	0.06, 0.06, 0.01	0.0017
carbamazepine	-	C1'N9C8	0.03, 0.06, 0.04	0.0010
clebopride	D2, 5-HT4	N6C4C2	0.03, 0.06, 0.08	0.0154
cisapride	5-HT4, 5-HT7	C1'N9N1	0.03, 0.08, 0.08	0.0015
clobenpropit	H3, H4	N7C8O3	0.02, 0.03, 0.00	0.0021
domperidone	D2, D3	N6C6O3	0.03, 0.12, 0.12	0.0042
domperidone		N7N9C2	0.01, 0.05, 0.05	0.0103

Continued

felcisetrag	5HT4	O9C1'C4	0.05, 0.07, 0.04	0.0123
fexofenidine	H1	C2'C1'N9	0.06, 0.11, 0.09	0.0174
glibenclamide	KATP	N9N7C8	0.09, 0.08, 0.07	0.0085
haloperidol	D, 5-HT	C5C2C6	0.03, 0.02, 0.05	0.0010
hexbutinol	M4, M1	O9C1'N9	0.02, 0.06, 0.04	0.0159
meclizine	H1	N9C1'C2'	0.02, 0.02, 0.01	0.0008
mitiglinide	KATP	N7N9C8	0.06, 0.04, 0.09	0.0183
metoclopramide	D2, 5-HT4	N6C2C2'	0.03, 0.05, 0.03	0.0002
metoclopramide	D2, 5-HT4	C5N6C2	0.04, 0.04, 0.07	0.0013
metoclopramide	D2, 5-HT4	O9C1'N9	0.05, 0.07, 0.05	0.0202
promethazine	H1	C2'C1'N9	0.06, 0.09, 0.04	0.0172
prucalopride	5-HT4	C4'N9C1'	0.03, 0.07, 0.05	0.0020
ondansetron	5-HT3	N6C6C2	0.04, 0.09, 0.06	0.0171
resveratrol	-	C6C2C4	0.02, 0.07, 0.07	0.0152
rolipram*	PDE4	C3'N3C1'	0.05, 0.06, 0.12	0.0138
rolipram**	PDE4	O4O5C1'	0.02, 0.01, 0.05	0.0038
romflumilast	PDE4	C1'N9C4	0.01, 0.04, 0.02	0.0102
romflumilast*	PDE4	O3C3'C2	0.05, 0.07, 0.11	0.0032
rosiglitazone	KATP	09C1'C6	0.07, 0.07, 0.02	0.0098
sumatriptan	5-HT1, 5-HT7	C8N7C2	0.06, 0.02, 0.06	0.0028
tegaserod	5-HT4, 5-HT2	O9C8C5	0.01, 0.01, 0.01	0.0017
trazpiroben	D2, D3	N6C6C2'	0.12, 0.10, 0.12	0.0090
trifluoperazine	D2, 5-HT2A	C2'C1'N6	0.08, 0.09, 0.01	0.0070

**Fit of rolipram to romflumilast; NMPB: N-methyl-4piperidyl benzylate.

2.2. Molecular Modeling

Use of the Nemesis computational tool confers advantages of simplicity and consistency, in that the results generated may be compared with data from previous studies by the author. Compound structures are built from contents of the Nemesis software program fragment file (Oxford Molecular version 2.1) and minimised by conformational analysis to provide a minimum energy conformer of each compound, in an uncharged form, suitable for fitting. The conformation of the ATP structure is described by the torsion angle (bond angle described by 4 adjacent atoms) C8N9C1'O9-38˚ (see Figure 1). The second stage of the process involves repeated manipulation and superimposition of the compound structure

on the nucleotide template, to obtain a best fit and determine if a specific fitting pattern is identifiable for each drug receptor class. The Nemesis program fits the 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. 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.

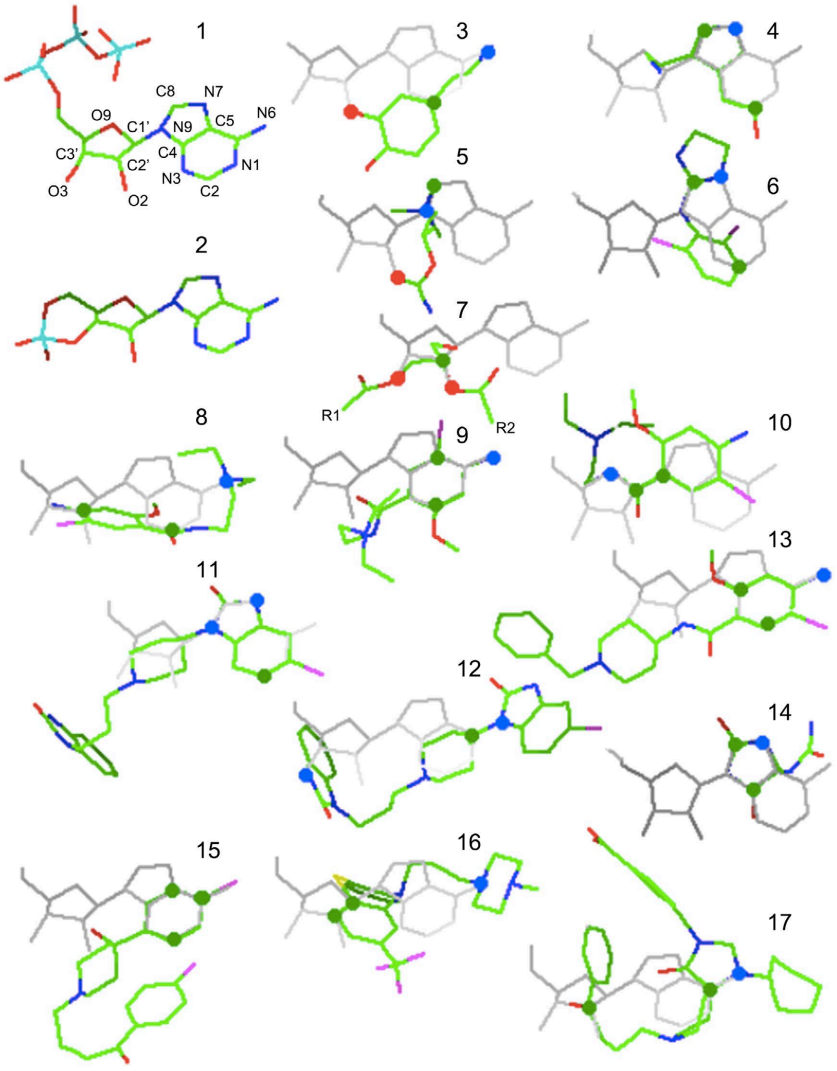

Figure 1. Fits of neurotransmitter and dopamine antagonist structures to 1 ATP template (grey), 2 cAMP, 3 dopamine, 4 serotonin, 5 bethanechol, 6 clonidine, 7 DAG, 8 metoclopramide, 9 metoclopramide, 10 metoclopramide, 11 domperidone, 12 domperidone, 13 clebopride, 14 allantoin, 15 haloperidol, 16 trifluorperazine, 17 trazpiroben.

3. Results

Figure 1 gives the fitting-template of ATP nucleotide (1), molecular structures of cAMP nucleotide (2) and modulators of adenyl cyclase (3 - 7). The adenyl cyclase modulators include neurotransmitters (3, 4) and synthetic agonists (5, 6). Diacylglycerol (DAG, 7) is a second messenger product of phospholipase C. The remaining fitted structures, apart from allantoin, represent dopamine antagonists. The pharmacological specificity of these antagonists for dopamine receptors is variable, in binding to more than one type of dopamine receptor or to different classes of receptor (Table 1). Metoclopramide (8-10) and clebopride (13) are substituted benzamide structures. The clebopride structure does not provide a good fit to the ATP template unless this is made with the substituted benzene ring. Similarity is evident in the fits of serotonin (4) and domperidone (11) structures. Metoclopramide (9), clebopride (13) and haloperidol (15) provide similar fits on the adenine ring and share fitting-points with dopamine (3). Allantoin (14), an inhibitor of clonidine binding at the α_2-adrenoceptor, has fitting-points in common with clonidine. The fits of trifluoperazine (16) and trazpiroben (17) are more similar to the metoclopramide fit of template 8.

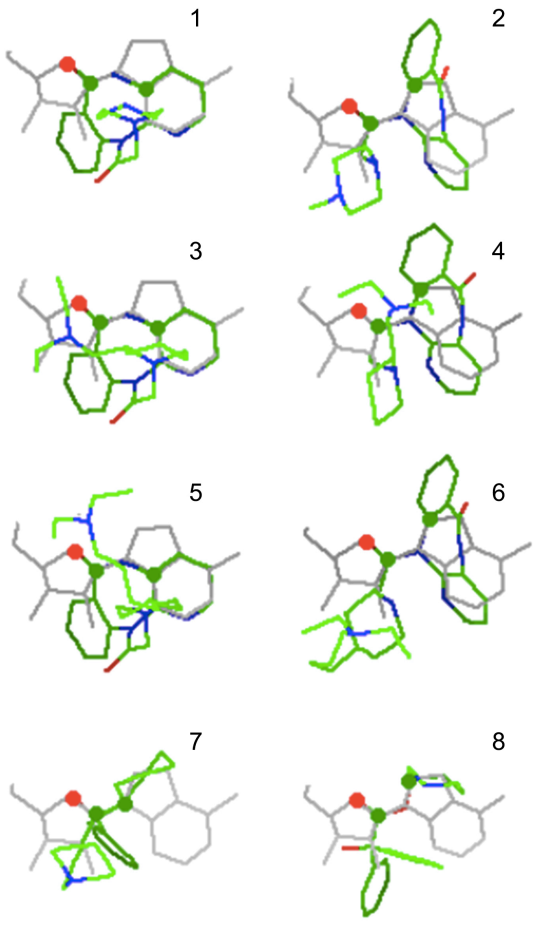

Figure 2. Fits of anticholinergic structures to ATP template (grey). 1 and 2 pirenzepine, 3 and 4 AF-DX-[116], 5 and 6 AQ-RA-741, 7 hexbutinol, 8 NMPB.

The template fits of tricyclic anticholinergic and muscarinic antagonist structures, in Figure 2, focus on the linkage between the adenine and ribose rings of ATP. Compounds with a tricyclic ring (AF-DX116, AQ-RA-741 and pirenzepine) demonstrate two types of fit involving O9C1'C4 (0.12, 0.06, 0.06Å) or O9C1'C8 (0.11, 0.08, 0.07Å) fitting-points (RMS values 0.0008 - 0.0026Å). Fitting values of these three antagonist structures are not given in Table 1 because they are identical. Each fit places a cyclic ring in the vicinity of the ribose O2 hydroxyl group, which could interfere with agonist modulation of ATP (see Figure 1, templates 3 and 5). The fit of hexbutinol differs slightly from the tricyclic compounds. NMPB is a compound used to quantify muscarinic receptors.

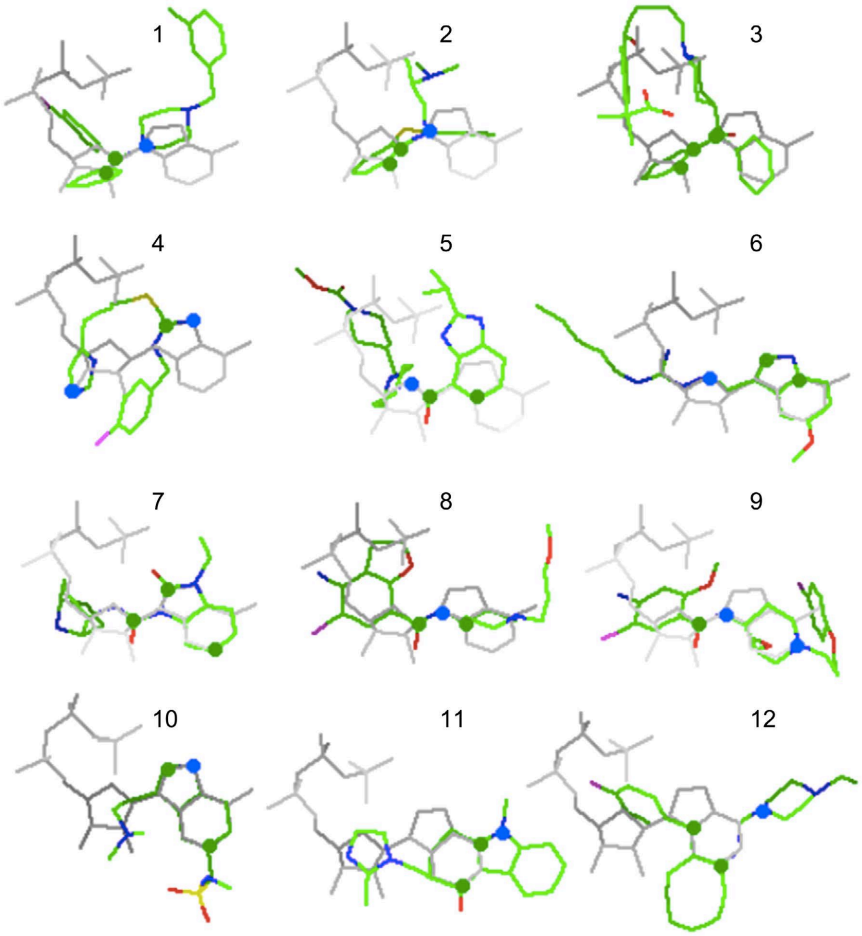

Figure 3. Fits of histamine and serotonin ligand structures to ATP template (grey). 1 meclizine, 2 promethazine, 3 fexofenidine, 4 clobenpropit, 5 felcisetrag, 6 tegaserod, 7 BIMU8, 8 prucalopride, 9 cisapride, 10 sumatriptan, 11 ondansetron, 12 blonanserin.

Histamine and 5-HT compound structures (Figure 3) again relate to different sub-types within a receptor class, or possess dual receptor specificity (Table 1). H_1 antagonists (1 - 3) use the same template fitting-points (N9C1'C2') which differ from the fit of clobenpropit (H_3/H_4). Fitting of the serotonin indole moiety to the adenine ring of ATP is evident for 5-HT_4 agonist structures (5 - 9). Fitted 5-HT_4

structures have a cyclic ring or alkyl chain substituent in proximity to the triphosphate chain of ATP, whereas metoclopramide (Figure 1, 10) has a tertiary amine group in this position. The fitting-points of 5-HT_1 and 5-HT_3 antagonists (10, 11) are confined to the adenine ring. The fit of the blonanserin structure is similar to that of metoclopramide (Figure 1, 9); the N6 fitting-point of the former structure forms part of a piperazine ring.

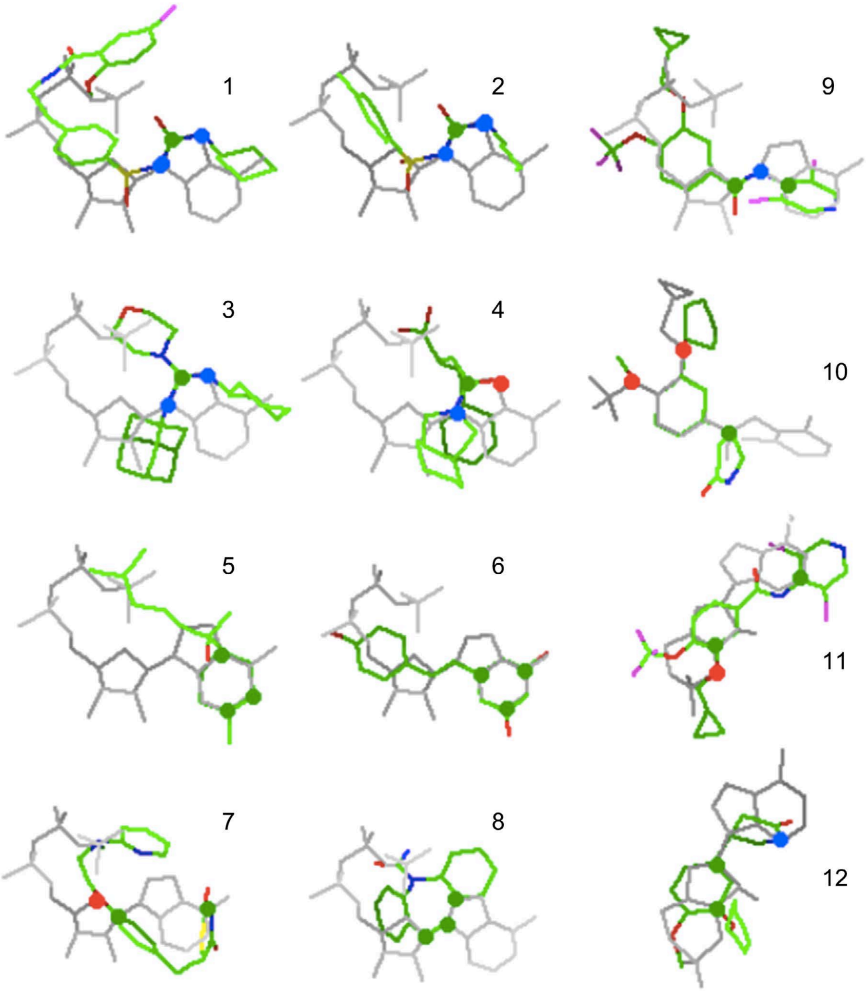

Figure 4. Fits of compound structures with KATP inhibitory properties to ATP template (grey). 1 glibenclamide, 2 tolbutamide, 3 PNU 37833A, 4 mitiglinide, 5 *α*-bisabolol, 6 resveratrol, 7 rosiglitazone, 8 carbamazepine, 9 roflumilast. Fit to roflumilast template (grey) 10 rolipram. Template fits of phosphodiesterase inhibitors to cAMP (grey), 11 roflumilast, 12 rolipram.

Inhibitors of the KATP channel (Figure 4) demonstrate different template fits, with the focus of sulphonylurea and meglitinide class diabetic drugs (1 - 4) on the imidazole moiety of the adenine ring. In contrast, the structures of *α*-bisabolol and resveratrol (5, 6), compounds with several non clinical uses, fit to the 6-aminopyrimidine moiety. The fits of rosiglitazine (7) and carbamazepine (8) also differ substantially from the conventional KATP channel inhibitors. The common

feature uniting the fits of these different structures is the interaction of side-chain or cyclic ring substituents with the triphosphate chain of ATP. Two PDE4 specific inhibitor structures, roflumilast and rolipram, are given in this figure (9-12). Roflumilast (9) provides a good fit to ATP with fitting-points that link the adenine and ribose rings. The smaller rolipram structure (template 10) fits well to romflumilast via two shared methoxy groups (O4, O5). Templates 11 and 12 provide fits of rolipram and romflumilast to a cAMP template. Fitting values for compound structures in **Table 1** range from 0.01 - 0.14Å and RMS values are less than 0.0210Å.

4. Discussion

The nucleotide template-fitting data generated in this study demonstrate that the investigated anti-emetic drugs relate to the structure of ATP; an observation relevant to modulation of nucleotide function. The major receptor targets of anti-emetic/pro-kinetic drugs, dopamine (D_2/D_4), muscarinic (M_2/M_4), serotonin (5-HT_4) and histamine (H_1), promote cell signal transduction processes via different Gα-proteins with specific intracellular pathways [17]. In contrast to the agonist properties of 5-HT_4 compounds, anti-emetic drugs are generally receptor antagonists. 5-HT_4 agonists transduce adenyl cyclase promoting effects via $G_s\alpha$; M_2/M_4 and D_2/D_4 compounds antagonise the effects of adenyl cyclase inhibition via Gi/Go; H_1 receptor antihistamines inhibit phospholipase C production of second messengers, inositol triphosphate and DAG, via G_q/G_{11}. A treatment rationale for gastroparesis based solely on G-protein modulation of cAMP is unlikely, as 5-HT agonists increase cAMP levels whereas dopamine and muscarinic antagonists block the effects of agonists inhibiting cAMP. **Figure 1** demonstrates that relative molecular similarity is evident between cAMP and the G_q/G_{11} promoted structure of DAG, supporting their mutual inhibitory effects and the reciprocal changes in levels observed in several different cell types [20]. In airway smooth muscle, G_s protein activation counterbalances G_q/G_{11} signalling through prostaglandin secretion, and DAG kinase functions as a switch in terminating DAG signalling [21]. The nucleotide template-fitting patterns of molecular structures within a receptor class are quite similar. Dopamine and muscarinic antagonists provide evidence of potential antagonistic action in regard to the cyclisation of ATP and differ from those of serotonin agonists.

The experimental and clinical effects of the investigated receptor ligand structures are reasonably well documented. Clebopride antagonises the effects of dopamine and clonidine on the contraction of guinea-pig stomach, acting on D_2 receptors and α_2-adrenoceptors of post-ganglionic cholinergic neurons to release acetylcholine [22]. Inhibition of clonidine binding to the α_2-adrenoceptor by allantoin stimulates acetylcholine release and improves gastric emptying [23]. Haloperidol and domperidone antagonise the dopamine D_2 receptor, which inhibits a post-ganglionic pathway controlling gastric tone and motility in several animal species [24] [25], although Nagahata *et al.* [26] maintain that this dopamine effect is

independent of extrinsic innervation. Ondansetron, a 5-HT_3 ion channel antagonist, is in use clinically to counter nausea from chemotherapy and IBS symptoms. The 5-HT_1 agonist sumatriptan relaxes the stomach and delays gastric emptying in healthy human subjects [27]. A nitrergic pathway, in cats, contributing to 5-HT_1 gastric relaxation [28] is relevant to the human gastric fundus muscle [29] [30]. Research evidence implicating NO in gastric dysmotility has not yet led to efficacious treatment of the human condition. In regard to antihistamines, promethazine is an antagonist at mesolimbic dopamine and α-adrenergic receptors [31]. Clobenpropit, a potent antagonist/inverse agonist of the H_3 receptor, inhibits dopamine uptake by rat striatal and cerebrospinal-cortical synaptosomes [32].

Gershon [33] identifies different roles for 5-HT receptor (R) in improving gastrointestinal motility: 5-HT_4R enhances neurotransmitter release, 5-HT_3R activates extrinsic sensory nerves, and 5-HT_{1p}(R) contributes to prolonged depolarisations within the enteric nervous system. The existence of 5-HT_{1p}(R) is recently confirmed following the synthesis of a specific ligand [34]. Enhancement of neurotransmitter release by 5-HT_4 pharmaceuticals, tegaserod and felcisetrag, significantly improves gut transit in patients [35]. In contrast to the verified release of acetylcholine from stomach neurons by 5-HT_4 agonists, such as cisapride, metoclopramide and tegaserod, Sanger and Andrews [10] consider that scientific rationales supporting use of D_2, H_1, 5-HT_3 and α_2-adrenoceptor antagonists are weak, Even so, trazpiroben, a D_2/D_3 receptor antagonist with low brain penetration, has achieved a good pre-clinical evaluation in the management of gastroparesis [36].

The impairment of gastric emptying and onset of gastroparesis in mice by PDE4, a cAMP specific phosphodiesterase, is relieved by metoclopramide [19]. Gastric contractions are considered to be enhanced by 5-HT_4 agonists, because endogenous phosphodiesterases limit the effects of 5-HT_4 receptor agonism by degrading cAMP [37]. PDE4 inhibitors and α_2-adrenoceptor antagonists both elevate cAMP with the potential for synergy between their receptors. A reduction in cAMP levels through α_2-adrenoceptor activation may reduce the release of synapse neurotransmitters involved in initiating emesis [38]. McDonough *et al.* [19] have demonstrated, however, that α_2-agonism, not antagonism, induces gastroparesis in mice. In mouse airway, PDE4 has an essential role in cAMP homeostasis; airways made deficient in PDE4D are no longer responsive to cholinergic stimulation [39]. In mouse brain, decreased binding of dopamine and muscarinic antagonists in the presence of the specific PDE4 inhibitor rolipram is attributed to increased cAMP levels in the receptor microenvironment [40]. Pauwelyn *et al.* [37] have reported on the synergy between 5-HT_4 receptor stimulation and PDE4 inhibition in facilitating acetylcholine release in the muscle of human large intestine. Rolipram and roflumilast enhance release of acetylcholine by prucalopride; each drug has the property of increasing cAMP. Interestingly, the template fits of roflumilast (**Figure 4**, 9) and prucalopride (**Figure 3**, 8) use the same fitting-points and both structures impact the same regions of the ATP template. As one would

expect, molecular similarity is evident within the smaller rolipram structure and romflumilast (**Figure 4**, 10). It seems likely that molecular similarity shared within PDE4 inhibitor and prucalopride structures enables nucleotide modulation in the same way. The cAMP molecule exerts a control on neurotransmitter release and the insertion of neurotransmitter receptors into the neural membrane [41]. PDE5, a specific cGMP phosphodiesterase, also has an impact on gastric function. The PDE5 inhibitor sildenafil increases cGMP and NO release from inhibitory NANC neurones of the myenteric plexus, inhibiting gastric accommodation and gastric emptying in healthy subjects [42] [43]. Structural similarity within the purine nucleotide structures permits fits of some of the investigated drug structures to a GTP template (not shown), in particular those given in **Figure 3** and **Figure 4**.

The association of diabetes with gastric and KATP channel dysfunction is relevant to the wider investigation of gastroparesis [44]. Cellular ATP:ADP ratios regulate membrane excitability via nucleotide-binding domains on sulphonylurea receptors (SUR) of KATP channels [44]. Glibenclamide and meglitinide also stimulate Na+/K+ATPase which participates in the generation of resting membrane potential, reducing ATP levels in mouse pancreatic islets [45]. KATP channels of human stomach muscle are relaxed by the channel opener pinacidil and antagonised by glibenclamide [46]. Pinacidil also inhibits acetylcholine contractions in a glibenclamide sensitive manner [44]. ATP, co-released from synapses with acetylcholine, may modulate subsequent acetylcholine release after hydrolysis via postsynaptic acetylcholine receptors [46]. The effects of resveratrol on binding to SUR, and of α-bisabolol on rat gastric lesions, are modulated by glibenclamide [47] [48]. Carbamazepine and mitiglinide although not SUR antagonists share the same inhibitor pocket, disrupting the stimulatory effect of SUR ATPase [49]. The fitting-data of the above compounds (**Figure 4**) demonstrates their potential to modulate ATP metabolism and the function of KATP channels.

Several study limitations are apparent. There is no relationship between molecular similarity and drug-nucleotide affinity at receptor sites, although the template fits of agonist and antagonist structures with their established properties infer modulation of cAMP levels. The investigated drugs are primarily confined to small molecular weight ligands of neurotransmitter receptors and adenine nucleotides. With reference to the above discussion, other drug and nucleotide types are also relevant to gastroparesis. Although experimental studies demonstrate the potential benefits of nucleotide modulation as a component of gastroparesis treatment, this is an area that requires considerably more investigation.

In conclusion, this study identifies molecular similarity within the ATP nucleotide and anti-emetic/pro-kinetic structures of cholinergic, dopamine, histamine, serotonin and phosphodiesterase drug classes. Molecular similarity is indicative of the potential for nucleotide interaction with neurotransmitter function, and its modulation by anti-emetic/pro-kinetic drugs. At the cellular level, normal gastric motility and function appear dependent on maintaining adequate concentrations and ratios of adenine nucleotides in optimum phosphorylation and conformation

states. Treatment of the condition is facilitated by neuron enhancement of acetylcholine release. Further investigation of potential deficiencies in gastric KATP channels and nitrergic status should improve our understanding of the physiological deficiencies contributing to gastroparesis.

Conflicts of Interest

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

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