

Purine Quadruplexes Stabilised by a Modified Porphyrin Analogue have Implications for mRNA Viral Replication

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Abstract

Recent research has clearly demonstrated that suppression of replication in mRNA viruses may be possible by stabilising viral guanine quadruplexes (G4s). Whilst it has been previously only proposed that G4s could fold in the SARS-CoV 2 genome, research confirming their definitive presence has since been published. A suggestion was made that polyadenylation of SARS-CoV 2 might allow adenine quadruplexes (A4s) to fold as the necessary sequence was available. The quadruplex topology appeared relatively stable. This further implies that there is potential for purine quadruplexes to compromise the viral replication mechanism by improved stability. A4s in this scenario could compromise effective functions in the poly(A) tail. However, whilst telomestatin and pyridostatin stabilise G4s, both are large molecules and are not approved in general use. Furthermore, both have poor solubility and bioavailability. Moreover, both have been trialled in G4 research with inconclusive outcomes. This current project designed and assessed a smaller, porphyrinoid tetra-thionated analogue, PTTA, derived from an oxidised norcorrole as a possible acceptable alternative. Molecular dynamics, ADMET and pharmacokinetic data were compared with results for telomestatin, pyridostatin and porphyrin. By these metrics and comparators, PTTA is characterised by enhanced stabilisation of purine quadruplexes and with a pharmacokinetic potential to reduce cytotoxicity.

Keywords: SARS-CoV 2, Oncogenesis, Purine Quadruplex, Telomerase Suppression, Porphyrin Scaffold

1. Introduction

Interest in guanine quadruplexes has been greatly amplified by macro-scale analysis of vertebrate genomes [1]. Numerous sequences capable of folding into G4s were found to be prevalent [2]. Subsequently, bacterial and mitochondrial genomes were also found to contain similar sequences [3]. Therefore, in vivo G4s have an implicit biological role.

If unregulated, terminal regions of chromosomes would undergo adverse reiterative extension. Such a runaway process could be interpreted by cellular oversight mechanisms simply as damaged DNA and flagged accordingly as deleterious. Enzymatic repair in this circumstance would be inappropriate. In effect, G4s as telomeric structures, signal an alternative to repair. Where possible therefore, a d(TTAGGG)_n sequence folding into G4s disallows telomerase from inconsonant extension of the chromosome.

Although telomeric G4s are closely associated with telomerase inhibition, and since telomerase affinity is preferential to linear DNA, the enzyme may also have the capacity to dismantle G4s [4,5].

The original proposal of the d(TTAGGG)_n sequence as crucial to G4 folding was displaced as the possibility of non-telomeric G4s also became apparent [6]. Some 350 000 genomic sites capable of supporting G4 folding were predicted with numerous other guanine-rich sequences [7]. However, understanding of G4 function is confounded by observations suggesting both adverse and beneficial roles for the structures [8]. This paradox is exemplified by telomeric extension remaining unchecked and subsequent oncogenesis despite the presence of G4s. The issue is currently unresolved with the implicit positive and negative roles of G4s as persistently controversial [9].

Despite noted adverse aspects, G4s are strongly associated with suppression of telomerase [10]. Accordingly, drug design has often focussed on stabilising ligands. Porphyrin ring structures resemble guanine quartets and some analogues are characterised by substantial binding affinity [11]. Both characteristics suggest an encouraging anti-cancer propensity. Poor selectivity remains a challenge however, as ligands do not discriminate between duplex DNA and neoplastic telomeres. Specificity is therefore a major concern of drug design.

Whilst G4s folding in DNA have received widespread attention, research surrounding RNA quadruplexes is still undeveloped. Compromising replication in these species may be possible by stabilising viral G4s [12]. Guanine quadruplexes are known to arise with a maximum abundance during viral replication within the host nucleus [13].

Given the proportion of viral to host G4 population may be several orders of magnitude, this suggests promising selectivity as only infected cells will have greatly increased numbers of G4s [14]. Furthermore, viral G4s are known to regulate regulation for some viruses during lytic and latent conditions [14]. This hints at the intriguing possibility of intervention at all stages of the viral life cycle and a dividend for rational design of small neoteric ligands targeting supramolecular complexes. For example, carboxy pyridostatin has high affinity for guanine quadruplexes; earlier work established adenine quadruplexes also have this property [15]. Whilst it had been tentatively proposed that G4s could fold in SARS-CoV 2, research confirming their presence has since been published [16].

Although direct evidence for RNA G4s in viruses is currently still putative, there is a strong consensus for the likelihood of their presence [17]. There is a broad agreement of RNA G4 potential contribution to viral pathogenesis, but opinions of specifics differ [18,19]. A pyridyl porphine is known to be an efficient stabiliser of G4s in Zika virus [12].

Viral persistence in host cells and avoidance of detection may depend on G4s inhibiting viral proteins, repression of transcription and influence viral replication [20-22]. In SARS-CoV-2, potential

G4-folding sequences interact with nsp13, a helicase responsible inter alia for catalysis of G4 unfolding. The complex appears to act as a brake on self-destruction [23]. Quadruplex topology and variation in quartet bases may also underpin G4 unfolding [17].

A concurrent view of G4s as adverse in the viral replication cycle, points to natural selection. A depletion of G4s from the viral genome might be advantageous [24]. Non-transient G4s compromise of replication or transcription would be obviated and viral G4s may avoid a host recognition cascade by cellular binding proteins. Two consequences may follow the prevalence of G4s and their corresponding folding sequences. A low (or zero) population would facilitate rapid infectivity, but greater ubiquity would require a more covert strategy of invasion. Such a tactic could resolve persistence of infection and favours a hypothesis of SARS-CoV-2 behaviour [17]. The genomic impact of viral G4s extending to adenine quadruplexes seems plausible. All the observations referenced here suggest allocating an adverse impact for indigenous supramolecular structures to RNA viruses. A feasible corollary would be further investigation as suitable targets for chemotherapy. Given that a porphyrin molecule is smaller than other porphyrin species, it may better resemble G4 or A4 geometry.

In addition, some consideration was given to exploring the potential for stabilised adenine quadruplexes to compromise the replication mechanism within polyadenylated SARS-CoV 2. Genomic sequences in the virus that could fold into G4s have been noted; some latitude in the current study was given to the possibility of adenine structures that could also fold. This latter concept has implications for viral replication.

1.1. Polyadenylation in Viral Replication

Genomic polyadenylation in eukaryota and prokaryota is a stabilising mechanism that sustains the export of mRNA from nucleus to cytoplasm and allows protection from enzymatic disposal [25]. The role of this feature, a poly(A) tail, differs distinctly in viruses as evidenced by the expropriation of host biology for solipsistic viral replication [26]. The poly(A) tail of SARS-CoV-2 is located downstream of the 3' untranslated region (3'-UTR) in figure 1.

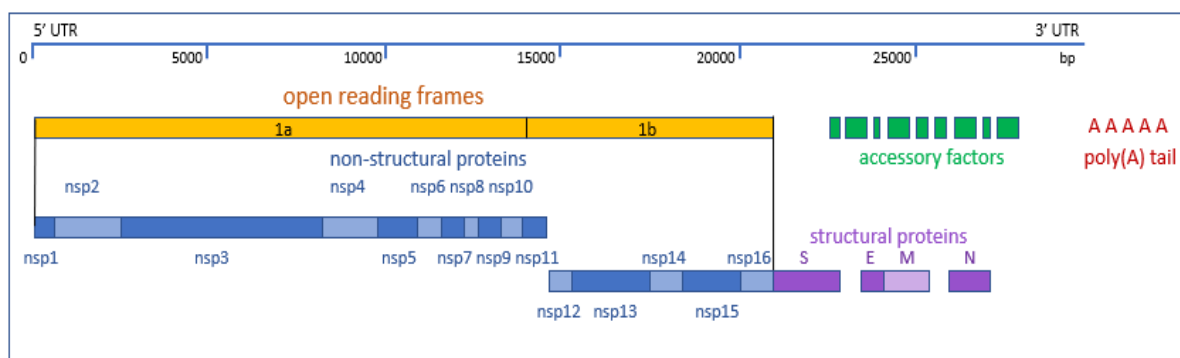


Figure 1: Positive Sense Single-Stranded RNA Viruses are capped at the 5' terminus and further stabilised by the addition of a series of adenines at the 3' terminus. Unlike open reading frames (ORF), regions coding for the spike protein and non-specific proteins, the poly(A) tail appears not to have a direct coding function. S (structural protein), E (envelop protein), M (membrane protein), N (nucleocapsid protein). Accessory factors are proteins with poorly understood functions but have an overall impact on pathogenesis. Their locations are interspersed amongst the structural proteins. Non-specific proteins have a range of enzymatic activity.

The inherent sequence of adenines in the poly(A) tail could allow quadruplexes to fold. If such events were to occur, their impact on viral architecture may be significant. Furthermore, other RNA viruses are typified by polyadenylation and include Polio, Hepatitis C and HIV. Perusal of theoretical interactions between this genomic element and supramolecular purine structures may

elicit prospects of chemotherapy. Accordingly, an investigation should start with a survey of the polyadenylation process in RNA viruses and its purpose in their replication. Sites identified in this survey for A4s to fold in the SARS-CoV2 genome are shown in figure 2.

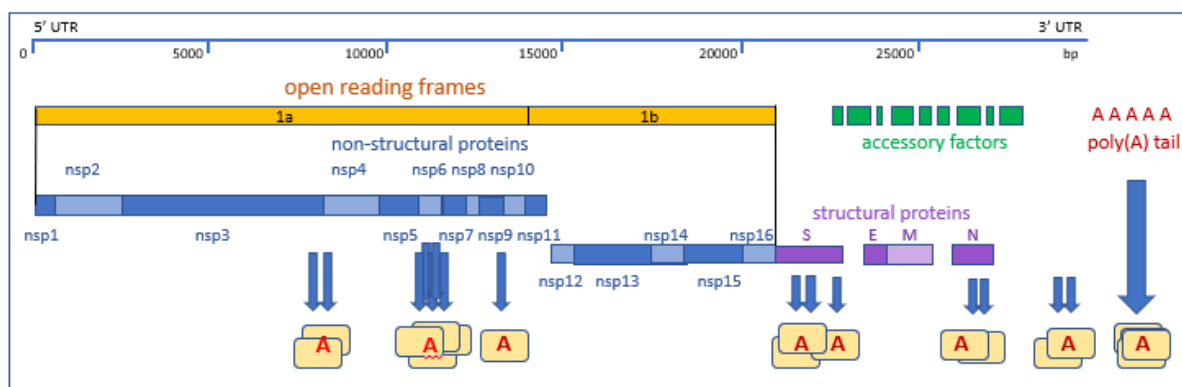


Figure 2: Potential A4s for Biplanar RNA Adenine Quadruplexes Folding Show some Traits of Grouping. Two Sequences are Located Immediately Prior to the Poly(A) Region

1.2. Modified Porphyrins

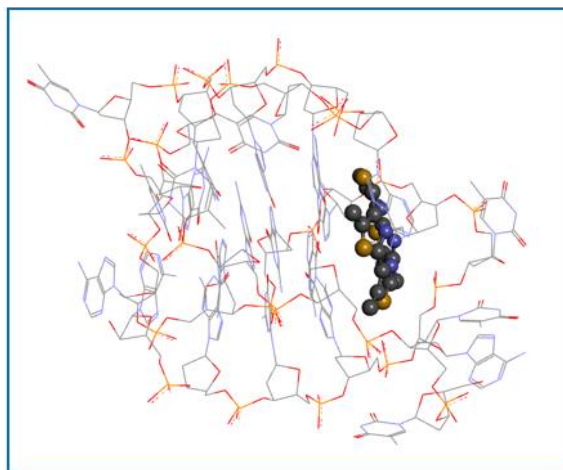
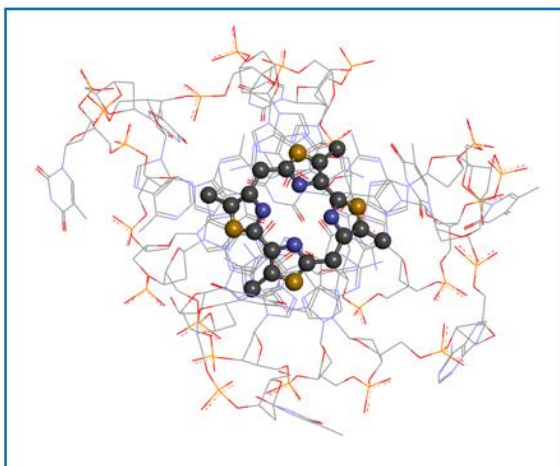
There have been some biomedical issues regarding formulation of metallo-porphyrins generating cytotoxic reactive oxygen species and accurate targeting. Recent nanotechnology appears to be addressing these challenges [27]. Based on its specificity for G4s over duplex DNA, telomestatin should be a suitable scaffold. Modifications should encompass the Lipinski guidelines: a molecular weight <500, low lipophilicity (logPo/w typically between 2 and 5), good solubility and oral bioavailability. Blood Brain Barrier (BBB) permeance would be advantageous and also resistance to effluence by the phospho-glycoprotein (P-gp) mechanism. G4 inhibition of telomerase in cortical cells could reduce neural neoplasms. However, designing drugs capable of

crossing the BBB has proven very challenging, and many are rendered less effective by the cellular efflux action of P-gp [28]. Although telomestatin has a high affinity for telomeric G4s, and may enhance quadruplex stability, it has characteristics that contravene three Lipinski requirements. It has very poor solubility and gastrointestinal absorption. Moreover, it is a substrate for P-gp and not BBB permeant. Nevertheless, telomestatin was selected as a scaffold despite the higher affinity of pyridostatin for G4s and carboxy-pyridostatin characterised by selectivity of RNA models over DNA equivalents [29]. A smaller telomestatin analogue should facilitate docking protocols and monitoring.

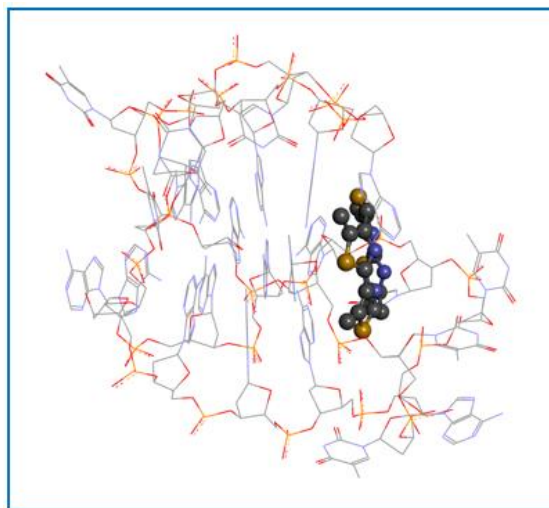
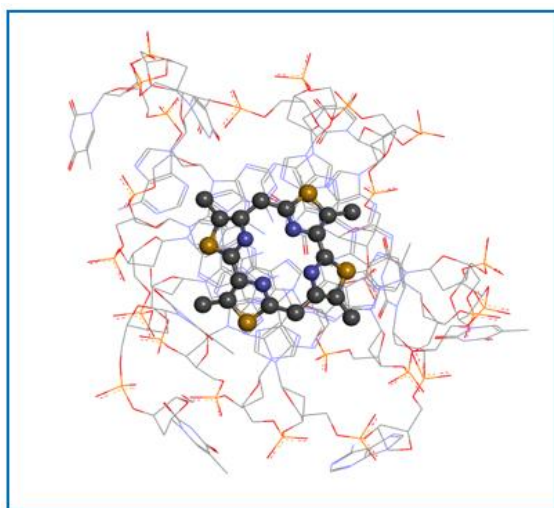
1.3. Binding with Guanine and Adenine Quadruplexes

Configurations are very similar for both models (figures 3a,3b, 4a and 4b). Docking software, (AutoDock Vina), ligand

parametrisation (CHARMM-GUI) and molecular dynamics analysis (NAMD) agree closely that the planar PTTA structure realigns marginally to a semi-lenticular topology.



Figures 3a and 3b: PT TA Bound with Guanine Quadruplex 2MB3



Figures 4a and 4b: PT TA Bound with Adenine Quadruplex (Modified 2MB3)

2. Methods

A pharmacophore within telomestatin was tentatively identified as the planar nature of a nitrogen octet. This structure has a very electronegative exterior and associated lipophobic character which may underpin its non-BBB permeance. The relatively low lipophilicity and co-ordination with Fe^{2+} supports this notion. A

preliminary design removed the cation and reduced the structure to a planar cyclic pyrrole quartet with no overall charge as an initial reference model. Molecular designs for this study retained the planar porphyrin structure and the model was thionated at C2,C10,C11,C16. The design was named PT TA (A, Figure 5).

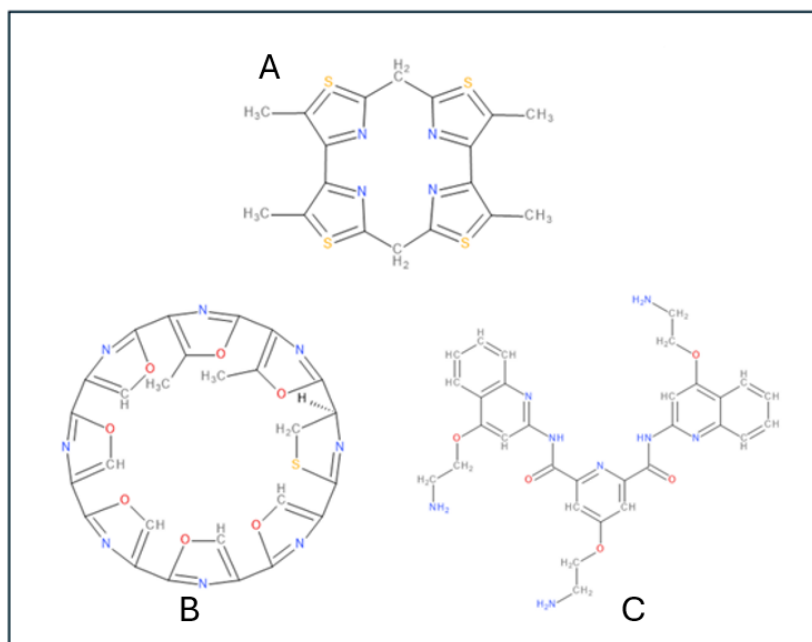


Figure 5: A: PTTA, B: Telomestatin, C: Pyridostatin

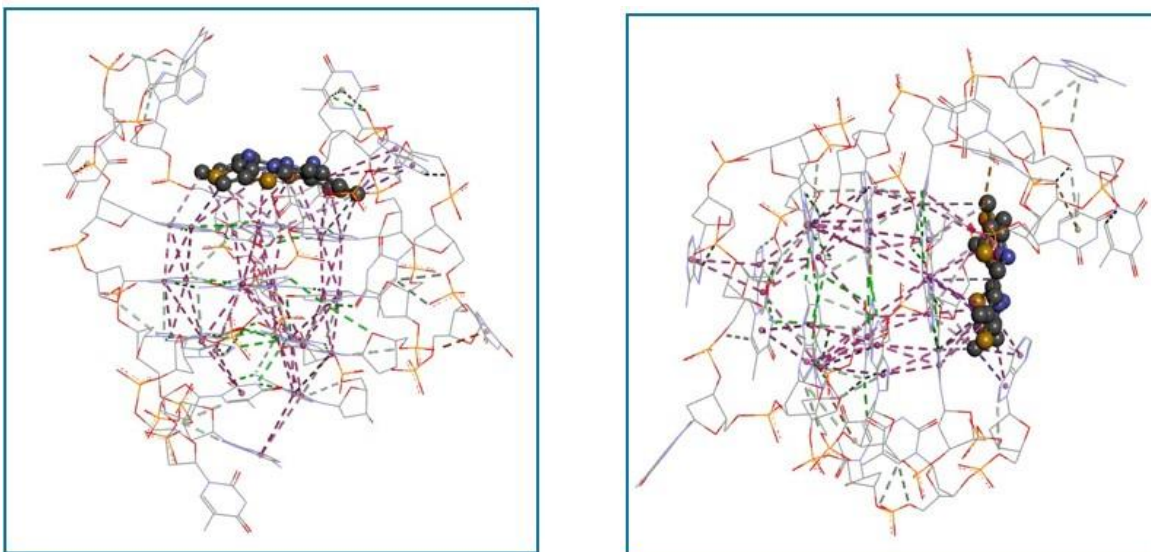
Scripts were drafted for Molecular Dynamics analyses of supramolecular models for simulation times of 500ns. Three Linux servers were accessed for molecular dynamics and molecular work: on-campus PowerEdge T640 96-core, 16-core and 8-core personal Desktops. All servers were supported by Linux OS. Data were collated with a Microsoft OS 8-core personal Desktop. NanoMolecular Dynamics and Visual Molecular Dynamics were the primary research tools, supported by Discovery Studio (accessibility configured for Microsoft), and Chimera modelling software. Docking protocols were submitted to AutoDock and AutoDock Vina accessed in both Linux and Microsoft. Metrics used to evaluate trajectories were Root Mean Square Deviation (RMSD), ellipsoidal RMSD, Radius of Gyration (RoG), estimation of the glycosidic angle and frequency of hydrogen bond formation. For the latter, a donor- acceptor distance was set to the defaults of a maximum 3 Å and an angle cut-off at 100° either way from a

notional perpendicular bond.

Ellipsoidal RMSD is more specific to nucleic acid structures and was evaluated with Anaconda3 and Barnaba software. Plotting programmes were XmGrace, Multiplot, OriginLab and GraphPad Prism.

3. Results

The four pyrrole rings of PTTA promote π -stacking with the four guanines or adenines of an outer quartet. Figures 6a and 6b show H-bonds and π -bonding between each pyrrole and both rings of each heterocyclic, hence eight bonds in total. The binding configuration suggests ligand / purine quadruplex interaction is a continuation of the internal π -stacking within the quadruplex. The distance between ligand and outer quartet was found to be $2.7\text{Å} \pm 0.5\text{Å}$ in both models.



Figures 6a and 6b: Predicted Bonding Characteristics of PTTA with G4 (left) and A4 (right). H-Bonding in Green and π -Bonding in Mauve.

Semi-lenticular convex conformation was noted for both A4 and G4 ligations. In addition, a localised shell of waters was predicted adjacent to the bound molecule (figure 7).

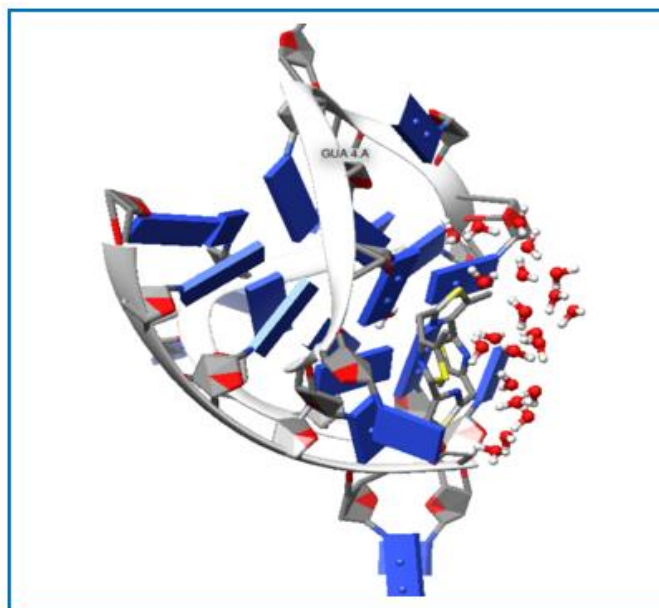


Figure 7: PTTA Bound to G4 After 500ns Molecular Dynamics Simulation. A Small Hemispheric Shell of Waters is Predicted by NAMD and Localised to the Planar Molecule

Molecular dynamics data are similar for binding to either purine stable configuration of binding and correlates well with the lower eRMSD values. A reasonable population of H-bonds is also noted.

	PTTA_G4	PTTA_A4	porphyrin	telomestatin	pyridostatin
RMSD	3.58 0.33-6.83	3.53 0.30-6.77	4.54 3.21-7.28	5.18 3.36-7.41	5.64 3.25-8.64
eRMSD	1.11 0.82-1.33	1.05 0.6-1.51	1.31 0.8-1.63	1.49 0.82-1.71	1.52 0.92-1.54
RoG	11.4 8.1-13.2	11.01 6.7-13.4	11.8 8.8-12.79	12.1 8.9-13.77	12.7 10.5-14.3
H-bond	8 0-14	9 0-16	6 0-14	7 0-15	6 0-14
Chi	110 100-120	110 100-120	100 80-120	25 19-31	85 80-90

Table 1: Molecular Dynamics Data Value Ranges Shown in Smaller Font

ADMET values for PTTA were: bioavailability 0.74, synthetic accessibility 8.1. Further ADMET data are shown in Table 2.

model	MW	log P _{o/w}	solubility	G-I	BBB	P-gp	Lipinski
telomestatin	582.5	2.2	very poor	low	no	yes	no
pyridostatin	596.6	1.5	moderate	low	partial?	no	no
porphyrin	308.3	2.3	soluble	high	yes	no	yes
PTTA	401.1	3.3	poor	high	yes	no	yes

Table 2: ADMET Data for Telomestatin, Porphyrin and PTTA. Properties regarded as favourable are: moderate or good solubility, high gastro-intestinal availability, no substrate interaction with P-gp and compliance with Lipinski Rule of Five. Porphyrin and PTTA satisfy all metrics

ADT (AutoDock Tools) calculated three binding interactions for each of the ligands when docked with 2MB3. All were exothermic. The optimum values are listed in Table 3 together with pharmacokinetic data predicted by MDS (molecular docking server).

model	affinity kcal/mol	K _i	VDW+H-bond+solvation energy kcal/mol	electrostatic energy kcal/mol
telomestatin	-5.04	203.13	-7.15	-0.10
porphyrin	-6.35	22.18	-6.28	-0.07
pyridostatin	-3.98	255.1	-7.93	-0.14
PTTA	-6.08	34.83	-7.15	-0.10

Table 3: Binding Data Predicted by ADT And MDS for Telomestatin, Porphyrin, Pyridostatin and PTTA Docked to 2MB3. The Values are Optimum Predictions

Both methodologies find PTTA is exactly parallel with the three tetrads and located directly on a line perpendicular with the central core of either purine quadruplex. Transferring the docking data to Chimera, Figure 8 shows the predicted alignment in MDS with a VDW surface imposed on the quadruplex. The distance

between the planar centre of PTTA to the planar centre of the outer guanine quartet (3.0 Å) is significantly less than that calculated for telomestatin (~9Å). The complex binds at the same site for the adenine quadruplex, in the same orientation as the guanine homologue and at a very similar distance.

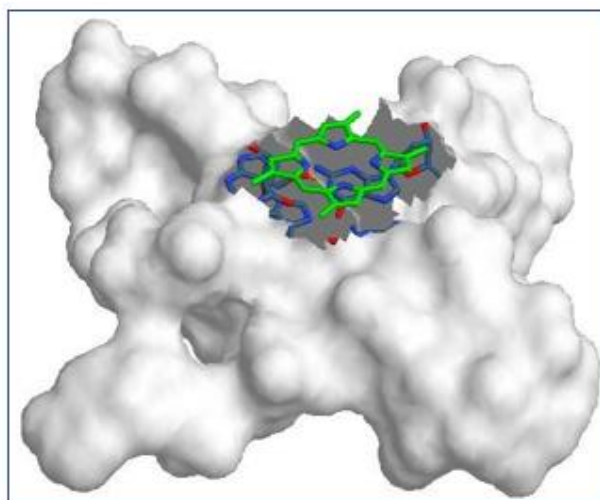


Figure 8: Chimera Interpretation of PTTA Docked to 2MB3 with a VDW Surface Imposed on the Quadruplex

Dynamic activity early in the RMSD data resonates to some extent with NAMD calculations for radius of gyration. The trajectory shows a brief near-symmetrical cycle of relaxation and expansion prior to maintaining steady values centred on $\sim 13\text{\AA}$.

Taken together, an overview of the molecular dynamics results indicates a stable interaction between PTTA and a triplanar guanine or adenine quadruplex. ADT predicted three exothermic conformations for binding with 2MB3, two of which align parallel to one particular outer quartet of the quadruplex. But a third docking conformation locates PTTA to the other outer quartet. Since the ligand cannot physically travel through the G4, the software implicitly finds that site is also favourable for docking the planar molecule.

4. Conclusion

Specific adenine-rich sequences in DNA and RNA have the ability to fold into simple triplanar quadruplexes constructed from experimentally validated adenine quartets (A4s). These systems are analogous to guanine supramolecular structures (G4s). A porphyrinoid tetra-thionated analogue (PTTA), ligated with either purine system, suggested an enhanced stability comparison with current drugs. Pharmacokinetic data predicted marginal improvements for PTTA. Both species were characterised in molecular dynamics simulations by stable configurations to 500ns.

The possibility arises that non-transient A4s could fold in the poly(A) tail of RNA viruses. These structures appear to be dismantled during viral replication or prior to it. The inference made here is that if the process were compromised, any promotion of stability would be beneficial. Hence, potential subsequent impact on viral replication could be a promising route for chemotherapy.

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