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Synthesis and anti-HSV activity of tricyclic penciclovir and hydroxybutylguanine derivatives

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ABSTRACT

A series of tricyclic penciclovir (PCV) and hydroxybutylguanine (HBG) derivatives have been prepared with enhanced lipophilicity following an efficient synthetic route. All the novel tricyclic derivatives were evaluated for inhibitory activity against herpes simplex virus 1 and 2 (HSV-1, HSV-2) and thymidine kinase deficient (ACV resistant) HSV-1. The tricyclic HBG derivatives were devoid of inhibitory activity however several of the tricyclic PCV derivatives showed promising antiviral activity, in particular **9g** (R = 4-MeO-C_6H_4) displayed good inhibitory activity (HSV-1 EC_{50} 1.5 μM, HSV-2 EC_{50} 0.8 μM) and retained inhibitory activity in HSV-1 TK^- cells (EC_{50} 0.8 μM). Computational docking experiments supported the biological data observed and this preliminary study provides useful data for further development of tricyclic acyclic nucleoside derivatives with improved lipophilicity and retention of activity in HSV-1 TK deficient strains. Also, the new tricyclic derivatives were evaluated against a broad range of other DNA and RNA viruses, but were found to be inactive at subtoxic concentrations. In addition, weak to moderate cytostatic effect was observed for the new compounds.

1. Introduction

The herpes simplex virus (HSV), like all herpes viruses, establishes lifelong latency following a primary infection. HSV-associated diseases can range from mild orolabial ulcers (cold sores) to severe encephalitis.[1] Herpes simplex viruses are categorised into two types: HSV-1, which is mainly transmitted through oral-oral contact resulting mainly in cold sores;[1] and HSV-2, which is mainly sexually transmitted resulting in the most common infection of genital herpes.[2] Globally two thirds of the population under the age of 50 are estimated to be infected with HSV-1.[3]

Herpes simplex encephalitis (HSE) is the most common cause of sporadic fatal viral encephalitis, accounting for almost 20% of all cases of encephalitis.[4] HSE presents as an acute focal necrotising infection of the brain, which, if untreated, has a 70% mortality rate.[5] The first line treatment of HSE is aciclovir (ACV), administered intravenously for 14–21 days, however even when treated, HSE is associated with a 30% mortality rate and permanent neurological damage.[6–8] Limitations of ACV therapy for HSE are the development of viral resistance[9] and low CNS uptake.[10]

Tricyclic ACV and ganciclovir (GCV) derivatives (Fig. 1) were shown to be effective inhibitors of HSV-1 thymidine kinase (TK) and are of interest as they maintain the inhibitory activity against the enzyme and, as they are more lipophilic than the current medications, may be valuable agents for the treatment of CNS infections.[11–13] Moreover, these tricyclic compounds were found to exhibit strong intrinsic fluorescent properties, which allows for sensitive concentration monitoring and optimal therapeutic dosing.[11–13] Penciclovir (PCV) and hydroxybutylguanine (HBG) (Fig. 1) are the carbocyclic analogues of GCV and ACV, respectively. The spectrum of activity of PCV against human herpesviruses was found to be similar to that of ACV, however in certain circumstances PCV was more active than ACV owing to the higher stability of PCV-TP in infected cells relative to ACV-TP.[14] Also, at concentrations up to 100 μg/mL, it was confirmed that PCV, like ACV, was highly selective and subsequently did not exhibit any toxicity in cell culture.[14] Similarly, HBG is reported to have higher affinity for HSV-1 TK than ACV in addition to relatively comparable selectivity for inhibition of viral DNA synthesis and good safety profile in cell

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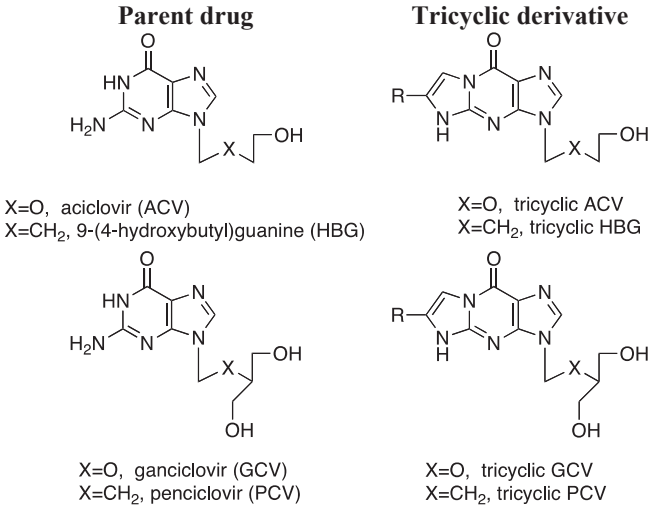


Fig. 1. Parent acyclic nucleosides and tricyclic derivatives.

culture.[15]

Application of the tricyclic scaffold modification to PCV and HBG was of interest to determine whether antiviral activity was maintained and, importantly, modification of the nucleobase moiety with an additional ring may result in beneficial physicochemical properties (enhanced lipophilicity, fluorescence) and/or enhanced enzyme binding interaction. A library of tricyclic PCV and HBG derivatives (Fig. 2) was designed and synthesised to evaluate antiviral activity and study structure–activity relationships, supported by computational docking analysis.

2. Results and discussion

2.1. Chemistry

PCV (**6**) and HBG (**7**) were prepared as previously described by reaction of 2-amino-6-chloropurine (**1**) with 5-(2-bromoethyl)-2-phenyl-1,3-dioxane (**2**)[16] or 4-bromobutylacetate (**3**)[17] with subsequent acid hydrolysis of the protected derivatives (**4**) and (**5**) (Scheme 1).

The new tricyclic analogues of PCV and HBG, 3-[4-hydroxy-3-(hydroxymethyl)butyl]-6-(aryl)-3,5 dihydro-9*H*-imidazo[1,2-*a*]purin-9-one (**9**) and 3-(4-hydroxybutyl)-6-(aryl)-3,5-dihydro-9*H*-imidazo[1,2-*a*]purin-9-one (**10**) were obtained upon reaction of the sodium salt of PCV (**6**) and HBG (**7**), generated *in situ* on treatment with NaH, and the appropriate bromoketone (**8**) in 38–79% yield (Table 1). The new compounds were purified by flash column chromatography using a gradient eluting mixture of CH_2Cl_2-MeOH followed by recrystallisation (Scheme 1). The procedure used for the preparation of the new derivatives mostly followed a previously reported method for the preparation of analogously modified guanosine and other tricyclic derivatives.[12]

The tricyclic derivatives showed some sensitivity towards light and air, so were protected by wrapping with foil and rapid storage in amber coloured vials. The 6-thien-2-yl group was highly unstable to light and air and in the case of the PCV derivative decomposed rapidly during collection. Conversely, its HBG congener (**10h**) was stable enough to be collected safely.

2.2. Biological evaluation

2.2.1. Antiviral activity

The tricyclic compounds (**9** and **10**) were screened as inhibitors of HSV using herpes simplex virus-1 (KOS strain), herpes simplex virus-2 (G strain), thymidine kinase deficient (aciclovir resistant) herpes simplex virus-1 (HSV-1 TK–KOS ACV^r strain) in human embryonic lung (HEL) cells. None of the tricyclic HBG derivatives (**10**) showed any inhibitory activity (EC_{50} > 100 μM) or cytotoxicity (> 100 μM) against HSV-1 or HSV-2. However, some of the tricyclic PCV derivatives (**9**) exhibited anti-herpetic activity (Table 2).

Of the newly synthesised tricyclic PCV derivatives, compounds **9a**, **9c**, **9d** and **9j** were inactive as antiviral agents. Compounds **9h** and **9i** showed anti-HSV-1 activity only at a relatively high concentration (EC_{50} = 76.5 and 44.7 μM, respectively), compounds **9b** and **9e** showed moderate anti-HSV-1 activity (EC_{50} = 8.9 and 20.00 μM/mL, respectively), whereas **9g** and **9f** were the most active and were inhibitory to HSV-1 replication with EC_{50} = 1.5 and 7.6 μM, respectively. Similar to anti-HSV-1 results, among the synthesised tricyclic PCV compounds, compounds **9g** and **9f** were the most active against the HSV-2 strain and showed marked inhibition (EC_{50} = 0.8 and 2.3 μM, respectively). Also, compounds **9b**, **9e** and **9i** showed moderate activity against HSV-2 strain (EC_{50} = 28–40.9 μM), whereas the remaining compounds did not show any activity against the HSV-2 strain. Two compounds, **9b** and **9g**, retained activity against the TK^- ACV resistant strain of HSV-1.

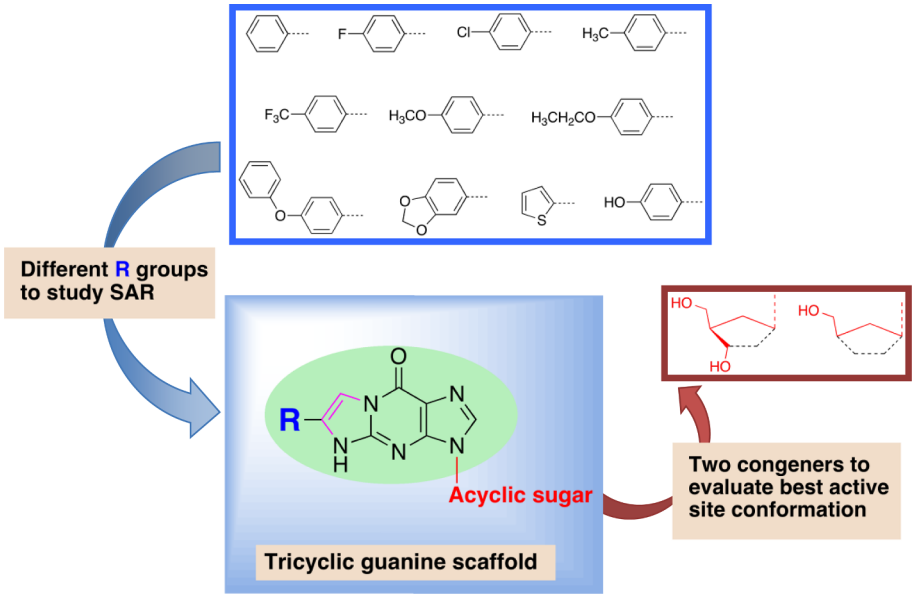
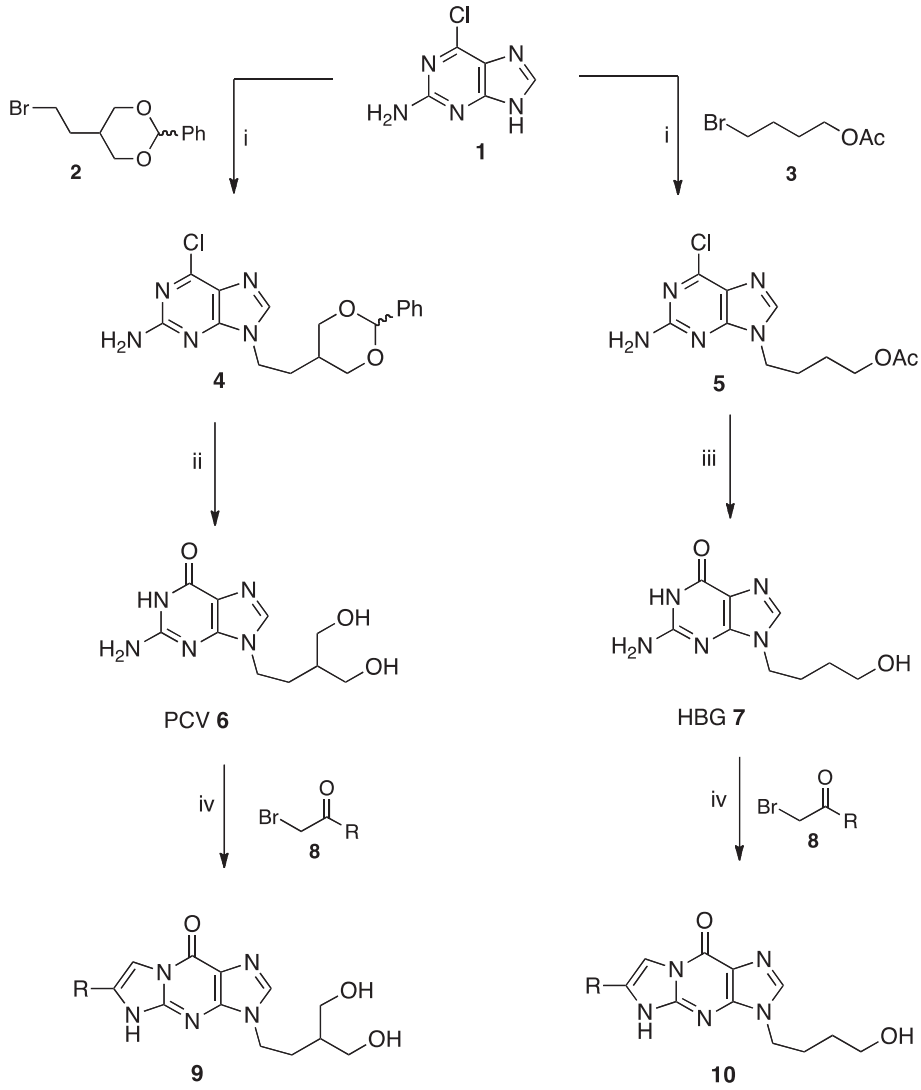


Fig. 2. Library for the designed tricyclic PCV and HBG nucleosides.



Scheme 1. *Reagents and conditions*: (i) K_2CO_3, 18-crown-6, DMF, r.t. 72 h for synthesis of **4**, 94%, 16 h for synthesis of **5**, 81% (ii) (a) 2 M aqueous HCl, 90 °C, 3 h (b) 10% aqueous NaOH, 4 °C 24 h, 77% (iii) (a) 2 M aqueous HCl, THF, 75 °C overnight (b) 10% aqueous NaOH, 4 °C 24 h, 81% (iv) NaH, DMF, r.t. 6 h, 38–79%.

Compound **9g** showed potent inhibitory activity against HSV-1 TK^- (EC_{50} = 0.8 μM), whereas compound **9b** was moderately active against HSV-1 TK^- (EC_{50} = 12 μM). The data suggest that in the case of the resistant strain TK^-, compounds **9f** and **9g** are independent of viral TK catalysed phosphorylation for antiviral activity and/or may use a different metabolic activation pathway and/or display a unique mechanism of antiviral action by the un-metabolised nucleoside analogue.

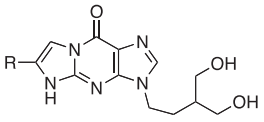
In addition to HSV all the tricyclic derivatives (**9** and **10**) were screening against a broad range of DNA and RNA viruses including vaccinia virus, adenovirus-2, human coronavirus (229E), human cytomegalovirus (HCMV) (AD-169 strain and Davis strain), varicella-zoster virus (TK^+VZV OKA strain and TK^- VZV 07–1 strain), vesicular stomatitis virus, Coxsackie virus B4, respiratory syncytial virus, parainfluenza-3 virus, reovirus-1, Sindbis virus, Punta Toro virus, yellow fever virus, influenza A virus (H_1N_1 and H_3N_2 subtypes) and influenza B virus. Of all the compounds, only a few displayed any inhibitory activity < 100 μM against VZV and HCMV (Table 3): **9e** (R = CF_3-C_6H_4-) showed weak inhibitory activity against cytomegalovirus AD-169 strain and Davis strain (EC_{50} = 63.1 μM and 76.5 μM respectively) compared with GCV as the reference compound (EC_{50} = 6.5 μM and 4.6 μM respectively) and the TK + VZV Oka strain (EC_{50} = 49.5 μM); **9f** (R = HO-C_6H_4-) showed inhibitory activity against varicella-zoster virus TK^+VZV OKA strain and TK^- VZV 07–1 strain (EC_{50} = 9.6 μM and ≥ 74.5 μM respectively) compared with ACV as the reference compound (EC_{50} = 5.0 μM and 59.2 μM respectively); **9d** and **9j** only displayed minimal activity against the VZV TK + strain Oka (EC_{50} = 63 μM). It should be noted that in contrast to HSV, HBG (**7**) proved inactive against HCMV and poorly inhibited the VZV TK + strain (EC_{50} = 76.5 μM). PCV was not inhibitory to HCMV but inhibited VZV with EC_{50} values comparable with those of ACV, i.e. 3.5 and 33.4 μM, respectively for TK + and TK- VZV strains (Table 3).

2.2.2. Cytostatic activity

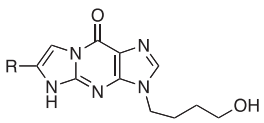
The new compounds were screened for their potential cytostatic activity against eight human cancer cell lines. The 50% cytostatic inhibitory concentration (IC_{50}) causing a 50% decrease in cell proliferation was determined against retina (non-cancerous) hTERT RPE-1, pancreatic adenocarcinoma Capan-1, chronic myeloid leukaemia Hap1, lung carcinoma NCI-H460, acute lymphoblastic leukaemia DND-41, acute myeloid leukaemia HL-60, chronic myeloid leukaemia K-562 and non-Hodgkin lymphoma Z-138 (Table 4).

Among the tricyclic PCV derivatives compounds **9e** (R = CF_3-C_6H_4-) and **9j** (R = C_6H_5-O-C_6H_4-) showed moderate cytostatic activity against at least six cell lines in the range of 12.5–76.1 μM and 16.9–90.4 μM respectively. The tricyclic HBG derivatives (**10**) were generally inactive or displayed very weak cytostatic activity. Of the tricyclic HBG

Table 1
Yields and mp data for final tricyclic PCV and HBG derivatives **9** and **10**.



9



10

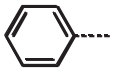
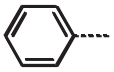
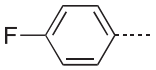
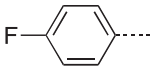
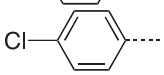
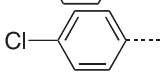
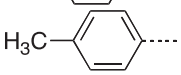
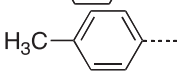
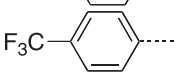
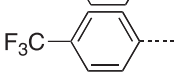
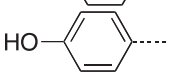
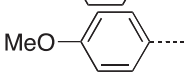
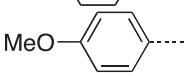
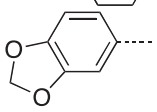
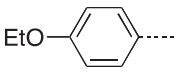
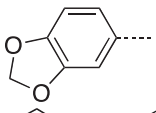
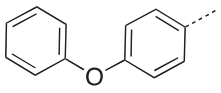
No.	R	Yield (%)	m.p. (°C)	No.	R	Yield (%)	m.p. (°C)
9a		68	212–214	**10a**		61	248–250
9b		65	> 300	**10b**		62	288–290
9c		62	258–260	**10c**		62	280–282
9d		61	112–114	**10d**		67	260–261
9e		55	> 300	**10e**		71	292–293
9f		38	> 300	**10f**		61	252–254
9g		79	202–203	**10g**		69	272–274
9h		77	276–278	**10h**		64	246–247
9i		68	259–260				
9j		75	276–278				

Table 2
Inhibitory activity of tricyclic PCV derivatives (**9**) against HSV and cytotoxicity data. The grey shades highlight the most interesting data.

Compound	Antiviral activity EC_{50} (μM)[a]			Cytotoxicity (μM)
	HSV-1 (KOS)	HSV-2 (G)	HSV-1 TK^- KOS ACV^r	Cell Morphology (MCC)[b]
PCV (**6**)	0.8	0.2	0.2	>100
9a	>100	>100	>100	>100
9b	8.9	28	12	>100
9c	>100	>100	>100	>100
9d	>100	>100	>100	>100
9e	20	31.7	>100	>100
9f	7.6	2.3	>100	>100
9g	1.5	0.8	0.8	>100
9h	76.5	>20	>100	>100
9i	44.7	40.9	>100	>100
9j	>100	>100	>100	>100
HBG (**7**)	1.5	2.1	10	>100
GCV	0.07	0.4	0.8	>250
CDV	2.0	2	5	>250
ACV	0.9	0.9	100	>250
BVDU	0.04	>250	14	>250

[a]Required to reduce virus-induced cytopathogenicity by 50%.
[b]Required to cause a microscopically detectable alteration of normal cell morphology.
Aciclovir (ACV), Brivudin (BVDU), Cidofovir (CDV), Ganciclovir (GCV).

Table 3
Inhibitory activity of tricyclic PCV derivatives (**9**) against VZV and HCMV and cytotoxicity data. The grey shades highlight the most interesting data.

Compound	Antiviral activity EC_{50} (μM)[a]				Cytotoxicity (μM)
	VZV TK+ Oka strain	VZV TK- 07-1 strain	HCMV AD-169 strain	HCMV Davis strain	Cell Morphology (MCC)[b]
PCV (**6**)	3.5	33.4	>100	>100	>100
9a	>100	>100	>100	>100	>100
9b	>100	>100	>100	>100	>100
9c	>100	>100	>100	>100	>100
9d	63.14	>100	>100	>100	>100
9e	49.5	100	63.1	76.5	100
9f	9.6	≥74.5	>100	>100	>100
9g	66.87	100	>100	>100	>100
9h	>100	>100	>100	>100	>100
9i	>20	>100	>100	>100	100
9j	62.8	>100	>100	>100	>100
HBG (**7**)	76.5	>100	>100	>100	>100
GCV	ND	ND	6.5	4.6	>250
CDV	ND	ND	0.72	0.87	>250
ACV	5.0	59.2	ND	ND	>250
BVDU	0.037	7.9	ND	ND	>250

[a]Required to reduce virus-induced cytopathogenicity (HCMV) or plaque formation (VZV) by 50%.
[b]Required to cause a microscopically detectable alteration of normal cell morphology.
Aciclovir (ACV), Brivudin (BVDU), Cidofovir (CDV), Ganciclovir (GCV).
ND: not determined.

Table 4
Cytostatic activity results of compounds **9** and **10**. The grey shades highlight the most interesting data.

No.	IC_{50} (μM)[a]							
	hTERT RPE-1	Capan-1	Hap1	NCI-H460	DND-41	HL-60	K-562	Z-138
PCV	>100	93.0	>100	>100	>100	>100	>100	>100
9a	78.6	58.3	>100	>100	>100	>100	>100	>100
9b	>100	82.8	>100	>100	>100	>100	>100	>100
9c	>100	84.8	>100	>100	>100	>100	>100	>100
9d	>100	>100	>100	>100	>100	>100	>100	>100
9e	51.5	17.2	37.8	12.5	56.5	55.3	>100	76.1
9f	>100	>100	>100	>100	>100	>100	>100	>100
9g	>100	>100	>100	>100	>100	>100	>100	>100
9h	>100	>100	>100	95.4	>100	>100	>100	>100
9i	>100	78.8	>100	>100	>100	>100	>100	>100
9j	16.9	46.4	44.0	47.2	90.4	63.3	>100	>100
HBG	>100	72.7	>100	>100	>100	>100	>100	>100
10a	>100	69.1	>100	>100	>100	>100	>100	>100
10b	>100	56.1	>100	55.5	>100	>100	>100	>100
10c	>100	64.4	>100	>100	>100	>100	>100	>100
10d	>100	78.9	>100	>100	>100	>100	>100	>100
10e	>100	36.1	63.8	52.5	>100	>100	>100	>100
10f	>100	98.9	>100	>100	>100	>100	>100	>100
10g	>100	92.8	>100	>100	>100	>100	>100	>100
10h	>100	>100	>100	>100	>100	>100	>100	>100
Docetaxel	25.0	0.95	1.19	0.89	1.63	1.94	3.00	3.00
Etoposide	0.23	0.15	0.04	1.35	0.06	0.03	0.54	1.06
Stauroporine	0.25	0.66	3.55	11.50	21.5	9.24	23.10	21.50

[a]50% Inhibitory concentration or compound concentration required to inhibit cell proliferation by 50%.
hTERT RPE-1 *retina (non cancerous)*; Capan-1 *pancreatic adenocarcinoma*; Hap1 *chronic myeloid leukemia*; NCI-H460 *lung carcinoma*; DND-41 *acute lymphoblastic leukemia*; HL-60 *acute myeloid leukemia*; K-562 *chronic myeloid leukemia*; Z-138 *non-Hodgkin lymphoma*.

derivatives the trifluoromethyl aryl derivative of HBG **10e** (R = CF_3-C_6H_4-) was the most effective against the range of cancer cell lines. Proliferation of the pancreatic adenocarcinoma Capan-1 cell line was slightly inhibited by most of the new tricyclic compounds as well as the parent compounds PCV and HBG (Table 4).

2.3. Molecular modelling

Molecular modelling of the compounds was performed using Molecular Operating Environment (MOE) software[18] and the crystal structure of HSV-1 thymidine kinase co-crystallised with PCV (PDB 1KI3)[19] and 9-(4-hydroxybutyl)-N2-phenylguanine (HBPG) (PDB 1QHI).[20]

The crystal structures of HSV-1 TK do not include an ATP molecule and a sulphate ion is observed at the supposed position of the *β*-phosphate of ATP.[19,20] Therefore, the distance between OH of the acyclic chain and SO_4 was measured to give an idea about the proper orientation of the ligand within the active site and the possibility for the compound acyclic OH to be phosphorylated by the enzyme. Results indicated that PCV analogues **9a-j** display distances in the range of 2.73–6.82 Å compared with PCV (4.61 Å). The HSV-1 TK pocket is predominately lipophilic with several regions of hydrophilicity. PCV and HBPG probe the space of the enzyme active site in a manner that maintains both the base moiety (guanine) and the acyclic sugar hydroxyl groups in a good geometry.

Overall docking results revealed some important interactions for the binding of the reference ligands PCV and HBPG within the active site (Fig. 3). The base moiety is lying in a location that stacks with Tyr172 and makes hydrophobic interactions with the amino acid residues; Tyr172, Met128, His58. Also, H-bond interactions are observed between the carbonyl group as well as the top ring nitrogens with Arg176 and Gln125. The acyclic sugar moiety forms two important H-bond interactions with amino acid residues Arg163 and Glu83 (Fig. 3).

The tricyclic PCV compounds lead to interactions with additional

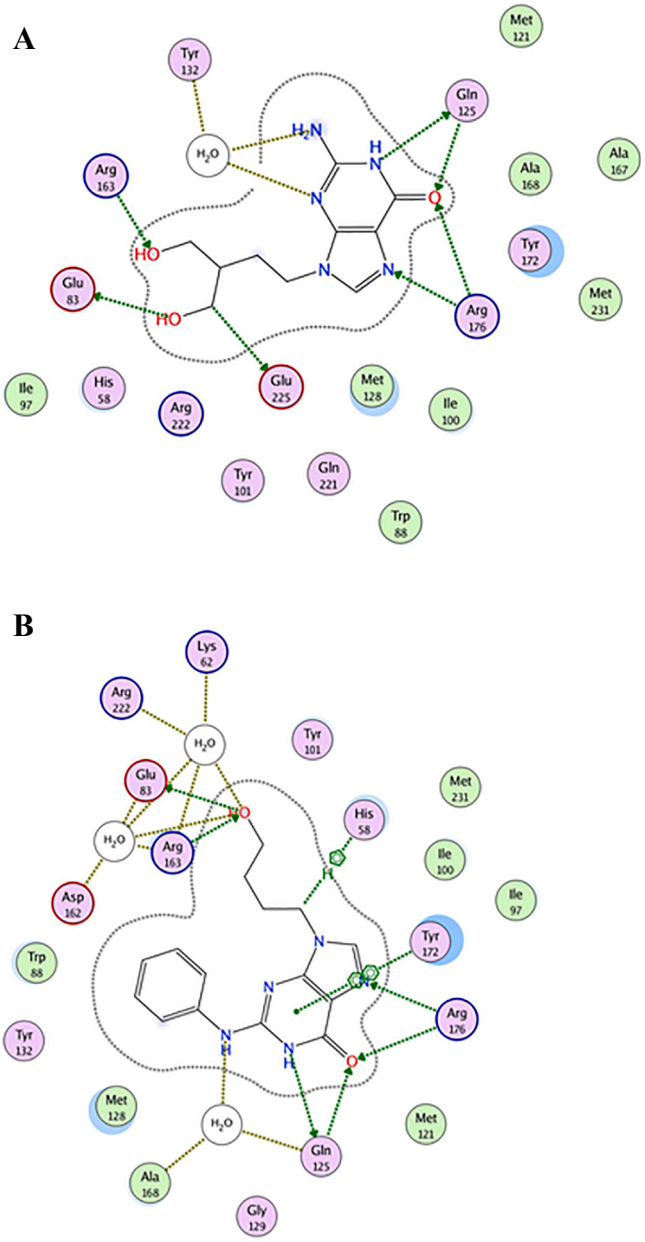


Fig. 3. 2D Ligplots illustrating the amino acids in HSV-1 TK active site involved in binding interactions with (A) PCV and (B) HBPG.

amino acids and, amongst the new compounds, the observed interactions of the most active compounds **9f** and **9g** (R = 4-HO-C_6H_4, and 4-MeO-C_6H_4) closely mimic the interactions observed with PCV binding. However, rather than Gln125, the 4-*HO*-C_6H_4 and 4-*MeO*-C_6H_4 form a H-bond interaction with Ala168 or water-bridged H-bonds with Ala168 and Gln125 (Fig. 4). The moderately active fluoro substituted analogues, **9b** and **9e**, showed almost similar binding modes, although the small fluoro substituent was better docked within the base pocket with the tricyclic moiety forming π–π interaction with Tyr172.

As the tricyclic purine moiety is longer than the guanine base of PCV, the orientation of the 6-arylgroup has an impact on the geometry of the acyclic hydroxyl groups and hence the stability of the formed complex for further phosphorylation. PCV analogues **9h**, **9i** and **9j** with relatively more bulky ether moieties (4-EtO-C_6H_4, 3-OCH_2O-4-$C_6H_3$and 4-C_6H_5O-C_6H_4) formed weak interactions within the acyclic sugar binding pocket. In addition a steric clash was observed in the case of compound **9j**. The steric effect might consequently diminish or abolish their complex stability.

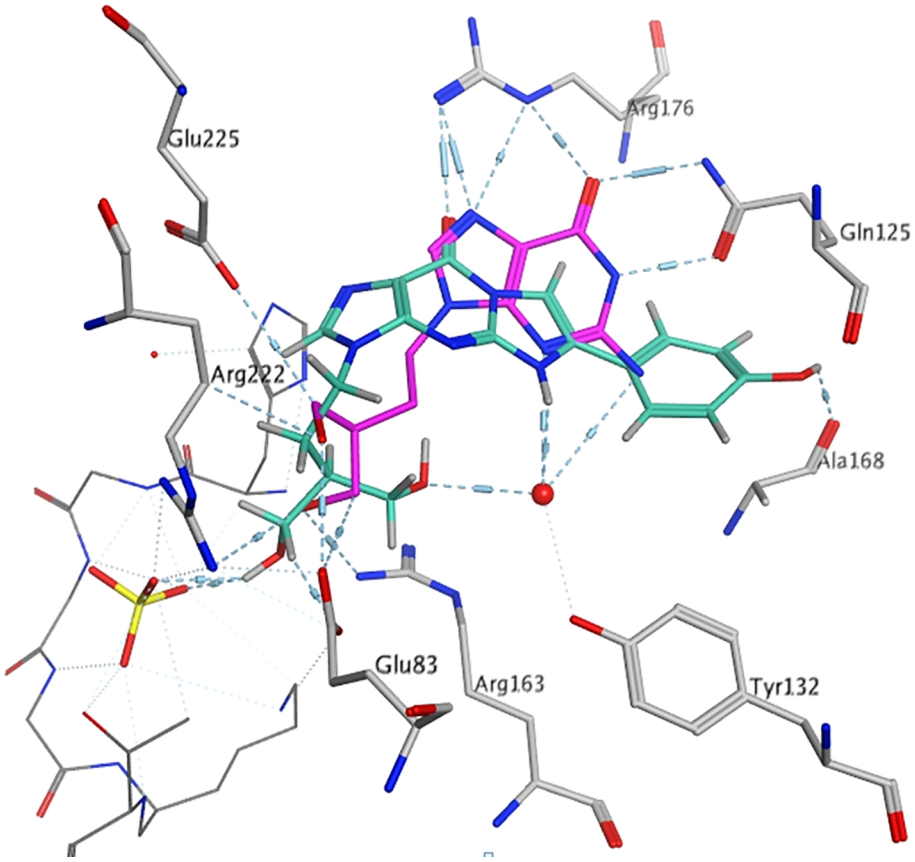


Fig. 4. Docking of representative tricyclic PCV derivative **9f** (cyan) in the HSV-1 TK active site compared with PCV (magenta).

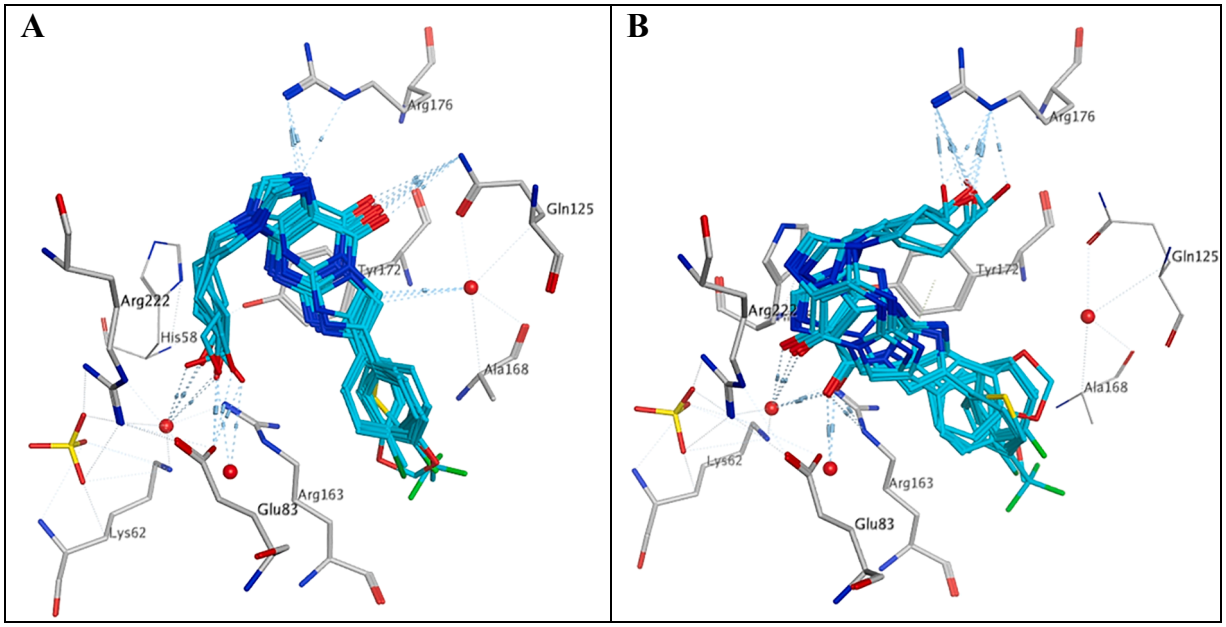


Fig. 5. Docking of HBG analogues **10a–h** showing two different orientations adopted by the compounds on binding within the HSV-1 TK active site.

Analysis of the docked HBG analogues **10a–h** compared with HBPG suggests that the ligand likely competes between two different binding orientations within the active site. In one orientation the tricyclic base moiety stacks with Tyr172 with the carbonyl group forming a H-bond with Gln125, while the acyclic hydroxyl group is situated 5.73–7.13 Å from the sulphate group (HPBG 5.66 Å) and donates a H-bond to Glu83 and/or accepts water bridged H-bonds from Arg163, Glu83, Arg222 and Lys62. Also, Arg176, in some derivatives, donates a H-bond to N-1 (Fig. 5A). In the other orientation the tricyclic structure is lying in a location that allows a stacking interaction with His58 and the carbonyl group is being upturned to accept a H-bond from Arg163 and/or water-bridged H-bonds from Arg163, Glu83, Arg222 and Lys62. In contrast, the same acyclic hydroxyl group in the second ligand orientation is 12.75 Å away from the sulphate compared with the former orientation

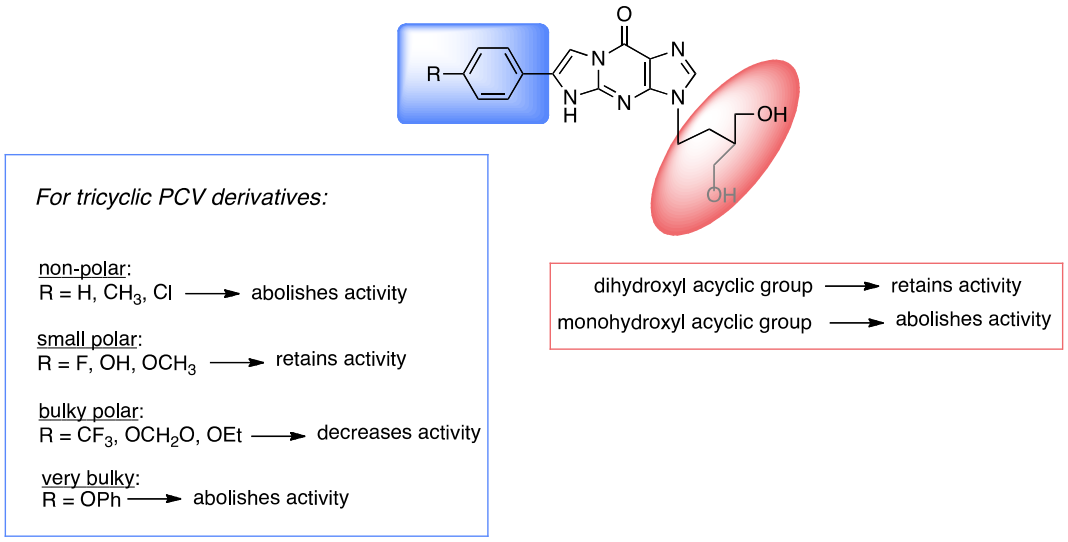


Fig. 6. Summary for SAR of the new tricyclic PCV compounds.

where it accepts a H-bond from Arg176 (Fig. 5B). In both orientations no contribution in ligand binding was observed for the 6-aryl group resulting in more flexibility and weaker binding of the whole compound within the active site.

3. Conclusion

Comparing antiviral activity to compound structure provides an insight into which functional groups may be beneficial towards HSV-1 inhibitory activity.

The SAR study suggested that a di-hydroxyl acyclic sugar moiety was essential for the activity. For the PCV derivatives, activity was only retained in those that have a hydrogen bond forming group on the tricyclic ring, however the size of the hydrogen bond forming group is limited with larger groups inducing a steric effect that exhibits an apparent impact on activity, which was supported by molecular docking (Fig. 6).

The new tricyclic analogues of PCV and HBG are the carbocyclic analogues of the previously reported tricyclic analogues of GCV and ACV,[11,12] (Fig. 1). For both the tricyclic ACV and GCV derivatives, inhibitory activity against HSV-1 and HSV-2 were generally comparable, however this activity was not retained in HSV-1 TK⁻KOS ACV^r strain. Replacing oxygen in the acyclic chain of the tricyclic ACV analogues by carbon in the new tricyclic HBG derivatives abolished their activity, highlighting the preference of O rather than CH_2 in the acyclic chain of the tricyclic guanine derivative. In the case of the tricyclic PCV derivatives the activity generally decreased noticeably however activity was retained only in the tricyclic PCV derivatives with R = 6-(4-MeO-C_6H_4) and R = 6-(4-HO-C_6H_4) and R = 6-(4-F-C_6H_4) groups as discussed in the present study. Importantly, for two of the tricyclic PCV derivatives with R = 6-(4-MeO-C_6H_4) and R = 6-(4-F-C_6H_4) groups activity was retained in the ACV resistant HSV-1 TK⁻KOS strain, which was not observed for the tricyclic GCV compounds.[11,12]

This preliminary study provides useful data for further development of tricyclic acyclic nucleoside derivatives with improved lipophilicity and retention of activity in TK deficient strains.

4. Experimental

4.1. General experimental

All reagents and solvents were of general purpose or analytical grade and purchased from Sigma-Aldrich Ltd, Fisher Scientific, Fluka and Acros. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Bruker Avance DPX500 spectrometer operating at 500, 125 and 470 MHz respectively, with Me_4Si as internal standard. Elemental analysis was performed (for compounds **10e** and **10g**) by MEDAC Ltd (Chobham, Surrey, UK). High resolution mass spectra (HRMS) were determined (for compounds **9a–j**, **10a–d**, **10f**, and **10h**) at the EPSRC National Mass Spectrometry Facility at Swansea University and Medac Ltd (Chobham, Surrey, UK), using ESI (Electrospray Ionisation). Flash column chromatography was performed with silica gel 60 (230–400 mesh) (Merck) and TLC was carried out on precoated silica plates (kiesel gel 60 F_{254}, BDH). Compounds were visualised by illumination under UV light (254 nm). Melting points were determined on an electrothermal instrument and are uncorrected. All solvents were dried prior to use and stored over 4 Å molecular sieves, under nitrogen. All the compounds were ≥95% pure.

The following compounds were prepared as previously described: PCV (**6**),[16] HBG (**7**),[17] and the bromoketones (**8**).[21–25]

4.2. Chemistry

4.2.1. General method for the synthesis of tricyclic PCV and HBG derivatives *9* and *10*

To a suspension of penciclovir (**6**) or hydroxybutylguanine (**7**) (0.2 g, 0.8 mmol or 0.9 mmol, respectively) in dry dimethylformamide (16 mL), sodium hydride (60% suspension in mineral oil, 1.2 eq.) was added and the reaction stirred at room temperature (21 °C) for 1.5 h. Bromoketone (**8**) (1.3 eq.) was then added and the reaction stirred for 6 h. Aqueous ammonia (25% solution 5 mL) was added to quench the reaction, which was concentrated under reduced pressure and the residual oil purified by flash column chromatography using gradient elution (CH_2Cl_2-MeOH). The obtained products were recrystallised from a mixture of CH_2Cl_2 and MeOH.

*4.2.1.1. 3-(4-Hydroxy-3-(hydroxymethyl)butyl)-6-phenyl-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (**9a**).* Prepared from PCV (0.2 g, 0.8 mmol) and 2-bromo-1-(phenyl)ethan-1-one (**8a**) (0.21 g, 1.04 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 95:5 to 90:10 v/v to give the product as a white solid. Yield: 0.19 g (68%), m.p. 212–214 °C, TLC (CH_2Cl_2-MeOH 95:5 v/v) R*f* 0.26. ^{1}H NMR (DMSO-d_6): δ 1.51 (septet, 1H, J = 6.0 Hz, H-3′), 1.82 (q, 2H, J = 7.0 Hz, H-2′), 3.40 and 3.47 (two quint, 4H, J = 5.4 Hz, H-4′), 4.17 (t, 2H, J = 7.5 Hz, H-1′), 4.48 (t, 2H, J = 5.3 Hz, 2 × OH), 7.39 (t, 1H, J = 7.0 Hz, H-4″), 7.49 (t, 2H, J = 7.7 Hz, H-3″ and H-5″), 7.91 (d, 2H, J = 7.4 Hz, H-2″ and H-6″), 7.95 (s, 1H, H-2), 8.21 (s, 1H, H- 7), 13.07 (br.s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 29.1 (C-2′), 41.3 (C-3′), 42.0 (C-

1′), 61.8 (C-4′), 103.6 (C-7), 115.9 (C-9a), 125.4 (C-4″), 128.4 (C-6), 129.2 (C-2″ and C-6″), 129.4 (C-1″), 129.5 (C-3″ and C-5″), 139.0 (C-2), 146.9 (C-4a), 150.6 (C-3a), 151.7 (C-9). [ESI-HRMS] calculated for $C_{18}H_{20}N_5O_3$: 354.1561 $[M+H]^+$. Found: 354.1562 $[M+H]^+$.

*4.2.1.2. 6-(4-Fluorophenyl)-3-(4-hydroxy-3-(hydroxymethyl)butyl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (**9b**)*. Prepared from PCV (0.2 g, 0.8 mmol) and 2-bromo-1-(4-fluorophenyl)ethanone (**8b**) (0.23 g, 1.04 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 98:2 to 91:9 v/v to give the product as a white solid. Yield: 0.19 g (65%), m.p. > 300 °C, TLC (CH_2Cl_2-MeOH 9:1 v/v) R*f* 0.49. ^{1}H NMR (DMSO-d_6): δ 1.50 (septet, 1H, J = 6.0 Hz, H-3′), 1.81 (q, 2H, J = 7.0 Hz, H-2′), 3.38 and 3.46 (two quint, 4H, J = 5.4 Hz, H-4′), 4.17 (t, 2H, J = 7.5 Hz, H-1′), 4.48 (t, 2H, J = 5.25 Hz, 2 × OH), 7.34 (t, 2H, J_{HF} = 8.8 Hz, H-3″ and H-5″), 7.97 (s, 1H, H-2), 7.98 (dd, 2H, J_{HH},J_{HF} = 6.0, 8.5 Hz, H-2″ and H-6″), 8.21 (s, 1H, H-7), 13.10 (br.s, 1H, H-5). ^{13}C NMR(DMSO-d_6): δ 29.1 (C-2′), 41.3 (C-3′), 42.0 (C-1′), 61.8 (C-4′), 103.6 (C-7), 116.1 (C-9a), 116.6 (d, 2C, J_{CF} = 22 Hz, C-3″ and C-5″), 125.1 (C-1″), 127.7 (d, 2C, J_{CF} = 8.0 Hz, C-2″ and C-6″), 128.5 (C-6), 139.6 (C-2), 146.8 (C-4a), 150.6 (C-3a), 151.8 (C-9), 162.6 (d, 1C, J_{CF} = 245 Hz, C-4″). ^{19}F NMR(DMSO-d_6): δ-112.40. [ESI-HRMS] calculated for $C_{18}H_{19}N_5O_3F$: 372.1472 $[M+H]^+$. Found: 372.1483 $[M+H]^+$.

*4.2.1.3. 6-(4-Chlorophenyl)-3-(4-hydroxy-3-(hydroxymethyl)butyl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one, (**9c**)*. Prepared from PCV (0.2 g, 0.8 mmol) and 2-bromo-1-(4-chlorophenyl)ethanone (**8c**) (0.24 g, 1.04 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 95:5 to 90:10 v/v to give the product as a white solid. Yield: 0.19 g (62%), m.p. 258–260 °C, TLC (CH_2Cl_2-MeOH 95:5 v/v) R*f* 0.29. ^{1}H NMR (DMSO-d_6): δ 1.50 (septet, 1H, J = 6.0 Hz, H-3′), 1.81 (q, 2H, J = 7.0 Hz, H-2′), 3.38 and 3.46 (two quint, 4H, J = 5.5 Hz, H-4′), 4.17 (t, 2H, J = 7.5 Hz, H-1′), 4.48 (t, 2H, J = 5.2 Hz, 2 × OH), 7.56 (d, 2H, J = 8.6 Hz, H-2″ and H-6″), 7.94 (s, 1H, H-2), 7.95 (d, 2H, J = 8.6 Hz, H-3″ and H-5″), 8.29 (s, 1H, H-7), 13.13 (br.s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 29.1 (C-2′), 41.3 (C-3′), 42.0 (C-1′), 61.8 (C-4′), 104.3 (C-7), 116.0 (C-9a), 127.2 (C-2″ and C-6″), 127.5 (C-1″), 128.4 (C-6), 129.6 (C-3″ and C-5″), 133.7 (C-4″), 139.5 (C-2), 146.9 (C-4a), 150.7 (C-3a), 151.8 (C-9). [ESI-HRMS] calculated for $C_{18}H_{19}N_5O_3Cl$: 388.1176 $[M+H]^+$. Found: 388.1187 $[M+H]^+$.

*4.2.1.4. 3-(4-Hydroxy-3-(hydroxymethyl)butyl)-6-(p-tolyl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (**9d**)*. Prepared from PCV (0.2 g, 0.8 mmol) and 2-bromo-1-(*p*-tolyl)ethanone (**8d**) (0.22 g, 1.04 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 100:0 to 85:15 v/v to give the product as a white solid. Yield: 0.18 g (61%), m.p. 112–114 °C, TLC (CH_2Cl_2-MeOH 95:5 v/v) R*f* 0.47. ^{1}H NMR (DMSO-d_6): δ 1.50 (septet, 1H, J = 6.0 Hz, H-3′), 1.82 (q, 2H, J = 7.0 Hz, H-2′), 2.34 (s, 3H, CH_3), 3.39 and 3.46 (two quint, 4H, J = 5.4 Hz, H-4′), 4.17 (t, 2H, J = 7.5 Hz, H-1′), 4.48 (t, 2H, J = 5.3 Hz, 2 × OH), 7.28 (d, 2H, J = 8.0 Hz, H-3″ and H-5″), 7.79 (d, 2H, J = 8.0 Hz, H-2″ and H-6″), 7.95 (s, 1H, H-2), 8.13 (s, 1H, H-7), 13.01 (br.s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 21.3 (CH_3), 29.1 (C-2′), 41.3 (C-3′), 44.0 (C-1′), 61.8 (C-4′), 103.0 (C-7), 116.0 (C-9a), 125.4 (C-3″ and C-5″), 125.7 (C-1″), 129.5 (C-6), 130.0 (C-2″ and C-6″), 138.8 (C-4″), 139.5 (C-2), 146.8 (C-4a), 150.6 (C-3a), 151.8 (C-9). [ESI-HRMS] calculated for $C_{19}H_{21}N_5O_3Na$: 390.1537$[M+Na]^+$. Found: 390.1533$[M+Na]^+$.

*4.2.1.5. 3-(4-Hydroxy-3-(hydroxymethyl)butyl)-6-(4-(trifluoromethyl) phenyl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (**9e**)*. Prepared from PCV (0.2 g, 0.8 mmol) and 2-bromo-1-(4-(trifluoromethyl)phenyl) ethanone (**8e**) (0.28 g, 1.04 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 95:5 to 92:8 v/v to give the product as a white solid. Yield: 0.18 g (55%), m.p. > 300 °C, TLC (CH_2Cl_2-MeOH 95:5 v/v) R*f* 0.43. ^{1}H NMR (DMSO-d_6): δ 1.51 (septet, 1H, J = 6.0 Hz, H-3′), 1.82 (q, 2H, J = 7.0 Hz, H-2′), 3.39 and 3.46 (two quint, 4H, J = 5.4 Hz, H-4′), 4.18 (t, 2H, J = 7.0 Hz, H-1′), 4.45 (br s, 2H, 2 × OH), 7.85 (d, 2H, J = 7.8 Hz, H-2″ and H-6″), 7.98 (s, 1H, H-2), 8.15 (d, 2H, J = 7.7 Hz, H-3″ and H-5″), 8.42 (s, 1H, H-7), 13.24 (br.s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 29.2 (C-2′), 42.0 (C-3′), 42.3 (C-1′), 61.8 (C-4′), 105.7 (C-7), 116.1 (C-9a), 124.5 (d, 1C, J_{CF} = 272 Hz, CF_3), 126.1(C-2″ and C-6″), 126.4 (d, 2C, J_{CF} = 3.8 Hz, C-3″ and C-5″), 128.0 (C-6), 128.5 (q, 1C, J_{CF} = 31.8 Hz, C-4″), 132.6 (C-1″), 139.7 (C-2), 147.0 (C-4a), 150.8 (C-3a), 151.7 (C-9). ^{19}F NMR(DMSO-d_6): δ-61.11.[ESI-HRMS] calculated for $C_{19}H_{19}N_5O_3F_3$: 422.1440 $[M+H]^+$, Found: 422.1430 $[M+H]^+$.

*4.2.1.6. 3-(4-Hydroxy-3-(hydroxymethyl)butyl)-6-(4-hydroxyphenyl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (**9f**)*. Prepared from PCV (0.2 g, 0.8 mmol) and 2-bromo-1-(4-hydroxyphenyl)ethanone (**8f**) (0.22 g, 1.04 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 95:5 to 90:10 v/v to give the product as a pale yellow solid. Yield: 0.11 g (38%), m.p. > 300 °C, TLC (CH_2Cl_2-MeOH 9:1 v/v) R*f* 0.25. ^{1}H NMR (DMSO-d_6): δ 1.51 (septet, 1H, J = 6.0 Hz, H-3′), 1.81 (q, 2H, J = 7.0 Hz, H-2′), 3.38 and 3.45 (two quint, 4H, J = 5.4 Hz, H-4′), 4.17 (t, 2H, J = 7.0 Hz, H-1′), 4.47 (br s, 2H, 2 × OH), 6.86 (d, 2H, J = 8.7 Hz, H-3″ and H-5″), 7.72 (d, 2H, J = 8.7 Hz, H-2″ and H-6″), 7.95 (br s, 2H, H-2 and H-7) 9.87 (br s, 1H, phenolic OH), 12.89 (br.s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 29.1 (C-2′), 41.3 (C-3′), 42.0 (C-1′), 61.8 (C-4′), 101.4 (C-7), 116.0 (C-9a), 116.3 (C-3″ and C-5″), 119.2 (C-1″), 127.1 (C-2″ and C-6″), 129.9 (C-6), 139.6 (C-2), 146.6 (C-4a), 150.5 (C-3a) 151.8 (C-9), 158.6 (C- 4″). [ESI-HRMS] calculated for $C_{18}H_{18}N_5O_4$: 368.1359 $[M-H]^+$. Found: 368.1349 $[M-H]^+$.

*4.2.1.7. 3-(4-Hydroxy-3-(hydroxymethyl)butyl)-6-(4-methoxyphenyl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (**9g**)*. Prepared from PCV (0.2 g, 0.8 mmol) and 2-bromo-1-(4-methoxyphenyl)ethanone (**8g**) (0.24 g, 1.04 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 97.5:2.5 to 87:13 v/v to give the product as a white solid. Yield: 0.24 g (79%), m.p. 202–203 °C, TLC (CH_2Cl_2-MeOH 9:1 v/v) R*f* 0.45. ^{1}H NMR (DMSO-d_6): δ 1.51 (septet, 1H, J = 6.0 Hz, H-3′), 1.81 (q, 2H, J = 7.0 Hz, H-2′), 3.39 and 3.46 (two quint, 4H, J = 5.5 Hz, H-4′), 3.81 (s, 3H, OCH_3), 4.17 (t, 2H, J = 7.5 Hz, H-1′), 4.47 (t, 2H, J = 5.2 Hz, 2 × OH), 7.04 (d, 2H, J = 8.0 Hz, H-3″ and H-5″), 7.85 (d, 2H, J = 8.0 Hz, H-2″ and H-6″), 7.95 (s, 1H, H-2), 8.07 (s, 1H, H-7), 12.97 (br.s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 29.1 (C-2′), 41.3 (C-3′), 42.0 (C-1′), 55.8 (OCH_3), 61.8 (C-4′), 102.2 (C-7), 115.0 (C-3″ and C-5″), 116.1 (C-9a), 120.9 (C-1″), 127.0 (C-2″ and C-6″), 129.4 (C-6), 139.5 (C-2), 146.7 (C-4a), 150.5 (C-3a), 151.8 (C-9), 160.1 (C-4″). [ESI-HRMS] calculated for $C_{19}H_{22}N_5O_4$: 384.1666 $[M+H]^+$. Found: 384.1666 $[M+H]^+$.

*4.2.1.8. 6-(4-Ethoxyphenyl)-3-(4-hydroxy-3-(hydroxymethyl)butyl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (**9h**)*. Prepared from PCV (0.2 g, 0.8 mmol) and 2-bromo-1-(4-ethoxyphenyl)ethanone (**8h**) (0.25 g, 1.04 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 95:5 to 91:9 v/v to give the product as a pale yellow solid. Yield: 0.24 g (77%), m.p. 276–278 °C, TLC (CH_2Cl_2-MeOH 9:1 v/v) R*f* 0.5. ^{1}H NMR (DMSO-d_6): δ 1.35 (t, 3H, J = 7.0 Hz, CH_3), 1.51 (septet, 1H, J = 6.0 Hz, H-3′), 1.82 (q, 2H, J = 7.0 Hz, H-2′), 3.39 and 3.46 (two quint, 4H, J = 5.5 Hz, H-4′), 4.08 (q, 2H, J = 7.0 Hz, OCH_2), 4.17 (t, 2H, J = 7.0 Hz, H-1′), 4.44 (br s, 2H, 2 × OH), 7.02 (d, 2H, J = 8.3 Hz, H-3″ and H-5″), 7.83 (d, 2H, J = 8.3 Hz, H-2″ and H-6″), 7.94 (s, 1H, H-2), 8.05 (s, 1H, H-7), 12.93 (br.s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 15.1 (CH_3), 29.2 (C-2′), 41.4 (C-3′), 42.0 (C-1′), 61.8 (C-4′), 63.7 (OCH_2), 102.1 (C-7), 115.4 (C-3″ and C-5″), 116.1 (C-9a), 120.8 (C-1″), 127.0 (C-2″ and C-6″), 129.4 (C-6), 140.0 (C-2), 146.7 (C-4a), 150.5 (C-3a), 151.8 (C-9), 159.4 (C-4″). [ESI-HRMS] calculated for $C_{20}H_{22}N_5O_4$: 396.1672 $[M-H]^+$, Found: 396.1668 $[M-H]^+$.

*4.2.1.9. 6-(Benzo[d][1,3]dioxol-5-yl)-3-(4-hydroxy-3-(hydroxymethyl) butyl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (**9i**)*. Prepared from PCV (0.2 g, 0.8 mmol) and 1-(benzo[*d*][1,3]dioxol-5-yl)-2-bromoethanone (**8i**) (0.25 g, 1.04 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH-acetone 80:10:10 v/v/v to give the product as a pale yellow solid. Yield: 0.21 g (68%), m.p. 259–260 °C, TLC (CH_2Cl_2-MeOH 9:1 v/v) R*f* 026. ^{1}H NMR (DMSO-d_6): δ 1.51 (septet, 1H, J = 6.0 Hz, H-3′), 1.82 (q, 2H, J = 7.0 Hz, H-2′), 3.38 and 3.46 (two quint, 4H, J = 5.5 Hz, H-4′), 4.17 (t, 2H, J = 7.5 Hz, H-1′) 4.45 (t, 2H, J = 5.2 Hz, 2 × OH), 6.09 (s, 2H, H-2″), 7.03 (d, 1H, J = 8.1 Hz, H-7″), 7.41 (dd, 1H, J = 1.8, 8.1 Hz, H-6″), 7.53 (d, 1H, J = 1.7 Hz, H-4″), 7.94 (s, 1H, H-2), 8.11 (s, 1H, H-7), 12.92 (br.s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 29.2 (C-2′), 41.4 (C-3′), 42.0 (C-1′), 61.8 (C-4′), 101.9 (C-2″), 102.8 (C-7), 106.0 (C-4″), 109.2 (C-7″), 116.1 (C-9a), 119.5 (C-6″), 122.4 (C-5″), 129.3 (C-6), 139.6 (C-2), 146.7 (C-4a), 148.2 (C-7a"), 148.5 (C-3a"), 150.6 (C-3a) 151.8 (C-9). [ESI-HRMS] calculated for $C_{19}H_{20}N_5O_5$: 398.1459 $[M+H]^+$. Found: 398.1460 $[M+H]^+$.

*4.2.1.10. 3-(4-Hydroxy-3-(hydroxymethyl)butyl)-6-(4-phenoxyphenyl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (**9j**)*. Prepared from PCV (0.2 g, 0.8 mmol) and 2-bromo-1-(4-phenoxyphenyl)ethanone (**8j**) (0.3 g, 1.04 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 100:0 to 92:8 v/v to give the product as a white solid. Yield: 0.26 g (75%), m.p. 278–280 °C, TLC (CH_2Cl_2-MeOH 9:1 v/v) R*f* 0.53. ^{1}H NMR (DMSO-d_6): δ 1.52 (septet, 1H, J = 6.0 Hz, H-3′), 1.82 (q, 2H, J = 7.0 Hz, H-2′), 3.38 and 3.46 (two quint, 4H, J = 5.5 Hz, H-4′), 4.18 (t, 2H, J = 7.5 Hz, H-1′), 4.44 (br s, 2H, 2 × OH), 7.09 (d, 4H, J = 8.1 Hz, H-3″, H-5″, H-2‴ and H-6‴), 7.20 (t, 1H, J = 7.4 Hz, H-4‴), 7.44 (t, 2H, J = 8.0 Hz, H-3‴ and H-5‴), 7.93 (d, 2H, J = 8.8 Hz, H- 2″ and H-6″), 7.98 (s, 1H, H-2), 8.14 (s, 1H, H-7), 13.04 (br.s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 29.1 (C-2′), 41.4 (C-3′), 42.0 (C-1′), 61.8 (C-4′), 103.1 (C-7), 115.9 (C-9a), 119.2 and 119.6 (C-3″, C-5″, C-2‴ and C-6‴), 123.6 (C-1″), 124.5 (C-4‴), 127.4 and 130.7 (C-2″, C-6″, C-3‴ and C-5‴), 129.0 (C-6), 139.5 (C-2), 146.8 (C-4a), 150.6 (C-3a), 151.7 (C-9), 156.5 and 157.7 (C- 4″ and C-1‴). [ESI-HRMS] calculated for $C_{24}H_{22}N_5O_4$:444.1672 $[M-H]^+$, Found: 444.1675 $[M-H]^+$.

*4.2.1.11. 3-(4-Hydroxybutyl)-6-phenyl-3,5-dihydro-9H-imidazo[1,2-a] purin-9-one (**10a**)*. Prepared from HBG (0.2 g, 0.9 mmol) and 2-bromo-1-(phenyl)ethan-1-one (**8a**) (0.23 g, 1.17 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 95:5 to 93:7 v/v to give the product as a white solid. Yield: 0.18 g (61%), m.p. 248–250 °C, TLC (CH_2Cl_2-MeOH 95:5 v/v) R*f* 0.32. ^{1}H NMR (DMSO-d_6): δ 1.43 (quint., 2H, J = 7.0 Hz, H-3′), 1.85 (quint, 2H, J = 7.0 Hz, H- 2′), 3.42 (q, 2H, J = 5.5 Hz, H-4′), 4.11 (t, 2H, J = 7.2 Hz, H-1′), 4.49 (t, 1H, J = 4.8 Hz, OH), 7.39 (t, 1H, J = 7.4 Hz, H-4″), 7.48 (t, 2H, J = 7.7 Hz, H-3″ and H-5″), 7.91 (d, 2H, J = 7.6 Hz, H-2″ and H-6″), 7.95 (s, 1H, H-2), 8.22 (s, 1H, H-7), 13.07 (br.s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 26.7 (C-2′), 30.0 (C-3′), 43.5 (C-1′), 60.6 (C-4′), 103.6 (C-7), 116.1 (C-9a), 125.4 (C-4″), 128.5 (C-6), 129.2 (C-2″ and C-6″), 129.4 (C-1″), 129.5 (C-3″ and C-5″), 139.7 (C-2), 146.9 (C-4a), 150.9 (C-3a), 151.8 (C-9). [ESI-HRMS] calculated for $C_{17}H_{28}N_5O_2$: 322.1309 $[M+H]^+$. Found: 322.1302 $[M+H]^+$.

*4.2.1.12. 6-(4-Fluorophenyl)-3-(4-hydroxybutyl)-3,5-dihydro-9H-imidazo [1,2-a]purin-9-one (**10b**)*. Prepared from HBG (0.2 g, 0.9 mmol) and 2-bromo-1-(4-fluorophenyl)ethanone (**8b**) (0.25 g, 1.17 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 100:0 to 94:6 v/v to give the product as a white solid. Yield: 0.19 g (62%), m.p. 288–290 °C, TLC (CH_2Cl_2-MeOH 95:5 v/v) R*f* 0.31. ^{1}H NMR (DMSO-d_6): δ 1.43 (quint, 2H, J = 7.5 Hz, H-3′), 1.85 (quint, 2H, J = 7.5 Hz, H-2′), 3.42 (q, 2H, J = 5.4 Hz, H-4′), 4.11 (t, 2H, J = 7.0 Hz, H-1′), 4.49 (t, 1H, J = 5.0 Hz, OH), 7.34 (t, 2H, J_{HF} = 8.9 Hz, H-3″ and H-5″), 7.96 (dd, 2H, J_{HF} = 5.0, 9.0 Hz, H-2″ and H-6″), 7.96 (s, 1H, H-2), 8.22 (d, 1H, J = 2.0 Hz, H-7), 13.09 (br.s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 26.7 (C-2′), 30.0 (C-3′), 43.5 (C-1′), 60.6 (C-4′), 103.6 (C-7), 116.1 (C-9a), 116.6 (d, 2C, J_{CF} = 22.6 Hz, C-3″ and C-5″), 125.1 (d, 1C, J = 3.8 Hz, C-1″), 127.7 (d, 2C, J = 7.5 Hz, C-2″ and C-6″), 128.5 (C-6), 139.7 (C- 2), 146.8 (C-4a), 150.7 (C-3a), 151.8 (C-9), 162.6 (d, 1C, J = 246.5 Hz, C-4″). ^{19}F NMR(DMSO-d_6): δ-112.40.[ESI-HRMS] calculated for $C_{17}H_{17}N_5O_2F$: 342.1366 $[M+H]^+$. Found: 342.1373 $[M+H]^+$.

*4.2.1.13. 6-(4-Chlorophenyl)-3-(4-hydroxybutyl)-3,5-dihydro-9H-imidazo [1,2-a]purin-9-one (**10c**)*. Prepared from HBG (0.2 g, 0.9 mmol) and 2-bromo-1-(4-chlorophenyl)ethanone (**8c**) (0.27 g, 1.17 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 95:5 to 92:8 v/v to give the product as a white solid. Yield: 0.2 g (62%), m.p. 280–282 °C, TLC (CH_2Cl_2-MeOH 95:5 v/v) R*f* 0.36. ^{1}H NMR (DMSO-d_6): δ 1.43 (quint, 2H, J = 7.0 Hz, H-3′), 1.85 (quint, 2H, J = 7.5 Hz; H-2′), 3.42 (q, 2H, J = 5.5 Hz, H-4′), 4.10 (t, 2H, J = 7.0 Hz, H-1′), 4.48 (t, 1H, J = 5.0 Hz, OH), 7.53 (d, 2H, J = 8.4 Hz, H-2″ and H-6″), 7.92 (d, 2H, J = 8.4 Hz, H-3″ and H-5″), 7.94 (s, 1H, H-2), 8.27 (s, 1H, H-7), 14.00 (br.s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 26.7 (C-2′), 30.0 (C-3′), 43.5 (C-1′), 60.6 (C-4′), 104.3 (C-7), 116.1 (C-9a), 127.1 (C-2″ and 6″), 127.4 (C-1″), 128.3 (C-6), 129.5 (C-3″ and C-5″), 133.6 (C-4″), 139.7 (C-2), 146.9 (C-4a), 150.7 (C-3a), 151.7 (C-9).[ESI-HRMS] calculated for $C_{17}H_{17}N_5O_2Cl$: 358.1071 $[M+H]^+$. Found: 358.1075 $[M+H]^+$.

*4.2.1.14. 3-(4-Hydroxybutyl)-6-(p-tolyl)-3,5-dihydro-9H-imidazo[1,2-a] purin-9-one (**10d**)*. Prepared from HBG (0.2 g, 0.9 mmol) and 2-bromo-1-(*p*-tolyl)ethanone (**8d**) (0.25 g, 1.17 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 100:0 to 94:6 v/v to give the product as a white solid. Yield: 0.2 g (67%), m.p. 260–261 °C, TLC (CH_2Cl_2-MeOH 95:5 v/v) R*f* 0.63. ^{1}H NMR (DMSO-d_6): δ 1.43 (quint, 2H, J = 7.0 Hz, H-3′), 1.85 (quint, 2H, J = 7.5 Hz, H-2′), 2.34 (s, 3H, CH_3), 3.42 (q, 2H, J = 5.5 Hz, H-4′), 4.11 (t, 2H, J = 7.2 Hz, H-1′), 4.49 (t, 1H, J = 5 Hz, OH), 7.28 (d, 2H, J = 8.0 Hz, H-3″ and H-5″), 7.79 (d, 2H, J = 8.2 Hz, H-2″ and H-6″), 7.95 (s, 1H, H-2), 8.14 (s, 1H, H-7), 13.01 (br.s, 1H, H- 5). ^{13}C NMR (DMSO-d_6): δ 21.3 (CH_3), 26.7 (C-2′), 30.0 (C-3′), 43.5 (C-1′), 60.6 (C-4′), 103.0 (C-7), 116.0 (C-9a), 125.4 (C-3″ and 5″), 125.6 (C-1″), 129.5 (C- 6), 130.1 (C-2″ and C-6″), 138.8 (C-4″), 139.6 (C-2), 146.8 (C-4a), 150.6 (C- 3a), 151.8 (C-9). [ESI-HRMS] calculated for $C_{18}H_{20}N_5O_2$: 338.1617 $[M+H]^+$. Found: 338.1626 $[M+H]^+$.

*4.2.1.15. 3-(4-Hydroxybutyl)-6-(4-(trifluoromethyl)phenyl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (**10e**)*. Prepared from HBG (0.2 g, 0.9 mmol) and 2-bromo-1-(4-(trifluoromethyl)phenyl)ethanone (**8e**) (0.3 g, 1.17 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 97.5:2.5 to 92:8 v/v to give the product as a white solid. Yield: 0.25 g (71%), m.p. 292–293 °C, TLC (CH_2Cl_2-MeOH 95:5 v/v) R*f* 0.58. ^{1}H NMR (DMSO-d_6): δ 1.44 (quint, 2H, J = 7.0 Hz, H-3′), 1.86 (quint, 2H, J = 7.5 Hz, H-2′), 3.43 (q, 2H, J = 5.5 Hz, H-4′), 4.12 (t, 2H, J = 7.0 Hz, H-1′), 4.45 (t, 1H, J = 5.0 Hz, OH), 7.84 (d, 2H, J = 8.0 Hz, H-2″ and H-6″), 7.96 (s, 1H, H-2), 8.14 (d, 2H, J = 8.0 Hz, H-3″ and H-5″), 8.42 (s, 1H, H-7), 13.23 (br.s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 26.7 (C-2′), 30.0 (C-3′), 43.5 (C-1′), 60.6 (C-4′), 105.7 (C-7), 116.1 (C-9a), 124.5 (d, 1C, J = 272.0 Hz, CF_3), 126.0 (C-2″ and C-6″), 126.4 (d, 2C, J = 3.6 Hz, C-3″ and C-5″), 128.0 (C-6), 128.5 (q, 1C, J_{CF} = 32.0 Hz, C-4″), 132.6 (C-1″), 139.8 (C-2), 147.1 (C-4a), 150.8 (C-3a), 151.7 (C-9). ^{19}F NMR(DMSO-d_6): δ −61.14. Anal. Calcd for $C_{18}H_{16}F_3N_5O_2{\cdot}0.5H_2O$ (400.1309): C, 54.00; H, 2.38; N, 17.49. Found: C, 53.56; H, 3.84; N, 17.33.

*4.2.1.16. 3-(4-Hydroxybutyl)-6-(4-methoxyphenyl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (**10f**)*. Prepared from HBG (0.2 g, 0.9 mmol) and 2-bromo-1-(4-methoxyphenyl)ethanone (**8g**) (0.27 g, 1.17 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 95:5 to 93:7 v/v to give the product as a white solid. Yield:

0.19 g (61%), m.p. 252–254 °C, TLC (CH_2Cl_2-MeOH 95:5 v/v) R*f* 0.23. ^{1}H NMR (DMSO-d_6): δ 1.43 (quint, 2H, J = 7.0 Hz, H-3′), 1.85 (quint, 2H, J = 7.5 Hz; H-2′), 3.42 (q, 2H, J = 5.4 Hz, H-4′), 3.81 (s, 3H, OCH_3) 4.11 (t, 2H, J = 7.0 Hz, H-1′), 4.48 (t, 1H, J = 5.0 Hz, OH), 7.04 (d, 2H, J = 8.8 Hz, H-3″ and 5″), 7.84 (d, 2H, J = 8.8 Hz, H-2″ and H-6″), 7.94 (s, 1H, H-2), 8.08 (s, 1H, H-7), 12.97 (br.s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 26.7 (C-2′), 30.1 (C-3′), 43.5 (C-1′), 55.7 (OCH_3), 60.6 (C-4′), 102.2 (C-7), 115.0 (C-3″ and C-5″), 116.0 (C-9a), 120.9 (C-1″), 126.9 (C-2″ and C-6″), 129.4 (C-6), 139.6 (C-2), 146.7 (C-4a), 150.5 (C-3a), 151.8 (C-9), 160.1 (C-4″).[ESI-HRMS] calculated for $C_{18}H_{20}N_5O_3$: 354.1566 $[M+H]^+$. Found: 354.1563 $[M+H]^+$.

*4.2.1.17. 6-(Benzo[d][1,3]dioxol-5-yl)-3-(4-hydroxybutyl)-3,5-dihydro-9H-imidazo[1,2-a]purin-9-one (**10g**)*. Prepared from HBG (0.2 g, 0.9 mmol) and 1-(benzo[*d*][1,3]dioxol-5-yl)-2-bromoethanone (**8i**) (0.28 g, 1.17 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 97.5:2.5 to 92:8 v/v to give the product as a pale yellow solid. Yield: 0.23 g (69%), m.p. 272–274 °C, TLC (CH_2Cl_2-MeOH 95:5 v/v) R*f* 0.38. ^{1}H NMR (DMSO-d_6): δ 1.43 (quint, 2H, J = 7.5 Hz, H-3′), 1.85 (quint, 2H, J = 7.5 Hz; H-2′), 3.42 (q, 2H, J = 5.5 Hz, H-4′), 4.11 (t, 2H, J = 7 Hz, H-1′), 4.45 (t, 1H, J = 5 Hz, OH), 6.09 (s, 1H, H-2″), 7.03 (d, 1H, J = 8.2 Hz, H-7″), 7.41 (d, 1H, J = 8.1 Hz, H-6″), 7.53 (s, 1H, H-4″), 7.93 (s, 1H, H-2), 8.12 (s, 1H, H-7), 12.92 (br.s, 1H, H- 5). ^{13}C NMR (DMSO-d_6): δ 26.7 (C-2′), 30.1 (C-3′), 43.5 (C-1′), 60.7 (C- 4′), 101.9 (C-2″), 102.8 (C-7), 106.0 (C-4″), 109.2 (C-7″), 116.0 (C-9a), 119.4 (C-6″), 122.5 (C-5″), 129.4 (C-6), 139.9 (C-2), 146.7 (C-4a), 148.2 (C-7a"), 148.5 (C-3a"), 150.6 (C-3a), 151.8 (C-9). Anal. Calcd for $C_{18}H_{17}N_5O_4{\cdot}0.3H_2O$ (372.5312): C, 58.00; H, 4.76; N, 18.79. Found: C, 57.60; H, 4.37; N, 18.56.

*4.2.1.18. 3-(4-Hydroxybutyl)-6-(thiophen-2-yl)-3,5-dihydro-9H-imidazo [1,2-a]purin-9-one (**10h**)*. Prepared from HBG (0.2 g, 0.9 mmol) and 2-bromo-1-(thiophen-2-yl)ethanone (**8 k**) (0.24 g, 1.17 mmol) and purified by flash column chromatography eluting with CH_2Cl_2-MeOH 95:5 to 92:8 v/v to give the product as a pale yellow solid. Yield: 0.19 g (64%), m.p. 246–247 °C, TLC (CH_2Cl_2-MeOH 9:1 v/v) R*f* 0.67. ^{1}H NMR (DMSO-d_6): δ 1.43 (quint., 2H, J = 7.0 Hz, H-3′), 1.85 (quint, 2H, J = 7.5 Hz; H-2′), 3.42 (q, 2H, J = 5.5 Hz, H-4′), 4.11 (t, 2H, J = 7.0 Hz, H-1′), 4.45 (t, 1H, J = 5.0 Hz, OH), 7.18 (t, 1H, J = 4.2 Hz, H-4″), 7.61 (d, 1H, J = 3.3 Hz, H-3″), 7.66 (d, 1H, J = 4.9 Hz, H-5″), 7.91 (s, 1H, H-2), 7.95 (s, 1H, H-7), 13.14 (br.s, 1H, H-5). ^{13}C NMR (DMSO-d_6): δ 26.6 (C-2′), 30.0 (C-3′), 43.5 (C-1′), 60.6 (C-4′), 102.7 (C-7), 116.1 (C-9a), 124.6 (C-6), 126.6 (C-3″), 127.5 (C-4″), 128.6 (C-5″), 139.7 (C-2), 146.5 (C-4a), 150.6 (C-3a), 151.7 (C-9). [ESI-HRMS] calculated for $C_{15}H_{16}N_5O_2S$: 330.1019 $[M+H]^+$. Found: 330.1021 $[M+H]^+$.

4.3. Antiviral and cytotoxicity assays

The antiviral assays were based on inhibition of virus-induced cytopathicity or plaque formation in HEL [herpes simplex virus 1 (HSV-1) (KOS), HSV-2 (G), vaccínia virus, vesicular stomatitis virus, cytomegalovirus (HCMV), varicella-zoster virus (VZV), adenovirus-2, and human corona virus (299E)], Vero (*para*-influenza-3, reovirus-1, Sindbisvirus, and Coxsackie B4), HeLa (vesicular stomatitis virus, Coxsackie virus B4, and respiratorysyncytial virus), or MDCK [influenza A (H1N1; H3N2) and influenza B] cell cultures. Confluent cell cultures (or nearly confluent for MDCK cells) in microtiter 96-well plates were inoculated with 100 $CCID_{50}$of virus (1 $CCID_{50}$ being the virus dose to infect 50% of the cell cultures) or with 20 plaque- forming units (PFU). After 1–2 h virus adsorption period, residual virus was removed, and the cell cultures were incubated in the presence of varying concentrations (200, 40, 8, 1.6, 0.32 μM) of the test compounds. Viral cytopathicity was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. Antiviral activity was expressed as the EC_{50} (50% effective concentration) or compound concentration required to reduce virus-induced cytopathogenicity or viral plaque formation by 50%. The MCC (minimal cytotoxic concentration) values were determined as the compound concentration required to afford a microscopically visible alteration of cell morphology. The new compounds were screened for their potential cytostatic activity against eight human cancer cell lines. The 50% cytostatic inhibitory concentration (IC_{50}) causing a 50% decrease in cell proliferationrelative to the number of cells in the untreated controls was determined against retina (non cancerous) hTERT RPE-1, pancreatic adenocarcinomaCapan-1, chronic myeloid leukaemia Hap1, lung carcinoma NCI-H460, acute lymphoblastic leukaemia DND-41, acute myeloid leukaemia HL-60, chronic myeloid leukaemia K-562 and non-Hodgkin lymphoma Z-138.

4.4 Molecular modelling

Docking studies were performed using the MOE[18] crystal structure of HSV-1 thymidine kinase co-crystallised with PCV (PDB 1KI3)[19] and 9-(4-hydroxybutyl)-N2-phenylguanine (HBPG) (PDB 1QHI).[20] All minimisations were performed with MOE until a RMSD gradient of 0.01 Kcal/mol/A with the MMFF94 forcefield and partial charges were automatically calculated. The Alpha Triangle placement, which derives poses by random superposition of ligand atom triplets through alpha sphere dummies in the receptor site, was chosen to determine the poses. The London ΔG scoring function estimates the free energy of binding of the ligand from a given pose. Refinement of the results was done using the MMFF94 forcefield, and rescoring of the refined results using the London ΔG scoring function was applied. The output database dock file was created with different poses for each ligand and arranged according to the final score function (S), which is the score of the last stage that was not set to zero.

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Appendix A. Supplementary data

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