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Phenyliodine(III) Bis(trifluoroacetate) Mediated Synthesis of 6-Piperidinylpurine Homo-*N*-nucleosides Modified with Isoxazolines or Isoxazoles[1]

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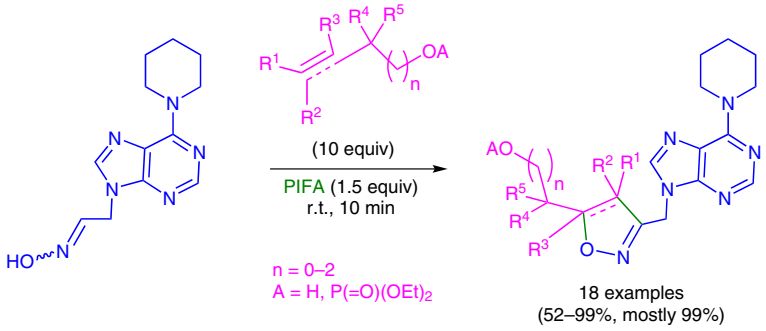

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Abstract The room temperature, 1,3-dipolar cycloaddition reactions of the nitrile oxide obtained from (6-piperidin-1-yl-9*H*-purin-9-yl)acetaldehyde oxime upon phenyliodine(III) bis(trifluoroacetate) treatment with excess unsaturated alcohols as solvent resulted in isoxazoline or isoxazole derivatives in almost quantitative yields. Analogous derivatives were prepared from the reactions of unsaturated phosphates. Preliminary biological tests indicated inhibition of lipid peroxidation for some of the examined compounds.

Key words modified homo-*N*-nucleosides, isoxazolines, isoxazoles, 1,3-dipolar cycloaddition reactions, phenyliodine(III) bis(trifluoroacetate), PIFA

Nucleosides and modified nucleosides represent classes of compounds that possess very interesting biological activities,[2] especially antiviral, anticancer and antimetabolic activities. Adenosine (**I**) (Figure 1), which is generated at an inflamed site, is receiving increasing interest as an endogenous anti-inflammatory agent. Thus, agents influencing the level of adenosine could act as possible drugs.[3] The modified derivative aristeromycin (**II**) is a natural product with antibiotic and antioncogenic activities,[4] whereas the synthetic derivative abacavir (**III**) is an HIV inhibitor.[5] Modified nucleosides with heterocyclic rings,[6] such as isoxazoline derivatives[7] **IVa**, **b**, have been studied for their anti-HIV and anticancer activities.

The homo-*N*-nucleosides, with a CH_2 group between adenine and a carbocyclic or heterocyclic ring, possess higher conformational flexibility[8] to combine with the bases DNA/RNA by a lowering of the electrostatic repulsion.[8b] Derivative **V** was prepared[9] in the search for agents active against the HIV and hepatitis B viruses. Isoxazolidinyl derivative **VI**[8b] is a special glucosidase inhibitor. Recently, we have reported reactions of 9-allyl-9*H*-purines with a nitrile oxide[10a] and nitrile imines[10b] for the preparation of purine derivatives **VIIa–c** and **VIIIa–c**, **IXa–c**, respectively. We have also studied these products as potential thrombin and lipid peroxidation inhibitors, and especially the latter derivatives for their antiproliferative and cytotoxic activity.

The isoxazoline moiety is a valuable synthon for subsequent modification to a variety of compounds, such as β-hydroxy ketones, γ-amino alcohols, α,β-unsaturated ketones and β-hydroxy nitriles.[7a–c,11] Isoxazolines are usually prepared by the 1,3-cycloaddition reaction of nitrile oxides to alkenes.[7a–c,10a] The nitrile oxides are prepared in situ from aldoximes through direct oxidation[12a–f] or halogenation and subsequent dehydrohalogenation in the presence of base in two steps,[12g–i] or from nitroalkanes and phenyl isocyanate through dehydration.[6,11e,f] However, these methods require the use of long reaction times or a complex combination of reagents.

Recently, hypervalent iodine reagents,[12a–d,13a] hypoiodite reagents[13b,c] or iodosobenzene[12e] has been employed for the one-pot synthesis of isoxazolines via the direct oxidation of aldoximes, and the 1,3-dipolar cycloaddition reactions of the resulting nitrile oxides to alkenes under mild conditions. In continuation of our studies on modified nucleosides,[10,14] we describe here the use of some hypervalent iodine reagents for the one-pot synthesis of modified homo-*N*-nucleosides, with isoxazoline or isoxazole moieties, via the in situ generation of the corresponding nitrile oxide. This nitrile oxide has been obtained for the first time, according to our knowledge, from the oxidation of (6-piperidin-1-yl-9*H*-purin-9-yl)acetaldehyde oxime. The reactions studied and the products obtained are outlined in Schemes 1–3.

The reaction of 6-piperidin-1-yl-9*H*-purine[14c] with 2-bromoacetaldehyde diethyl acetal and anhydrous potassium carbonate in anhydrous *N*,*N*-dimethylformamide at 140 °C under microwave irradiation for 45 minutes resulted

Table 1 Optimization of the Conditions for the 1,3-Dipolar Cycloaddition Reaction of Allyl Alcohol (**3a**) with the Nitrile Oxide Generated in situ from Oxime **2**

Entry	**3a** (equiv)	Method[a]	Conditions	Yield (%) of products
1	1	A	DMF, N_2, r.t., 22 h	**4a** (18), **5** (8), **2** (52)
2	1	B	MeOH, 0 °C, 1 h	**4a** (10), **5** (34), **6** (4), **2** (15)
3	1	B	MeOH, r.t., 1 h	**4a** (43), **5** (21), **6** (5), **2** (10)
4	1	B	CH_2Cl_2, r.t., 1 h	**4a** (50), **5** (24)
5	1	B	MeOH, reflux, 1 h	**4a** (58), **5** (12), **6** (5), **2** (12)
6	1	B	CH_2Cl_2, reflux, 1 h	**4a** (62), **5** (17)
7	1	B[b]	CH_2Cl_2, MW, 100 °C, 2 min	**4a** (50), **5** (25)
8	1	C	MeOH, reflux, 1 h	**4a** (40), **5** (24), **6** (5)
9	1	C	CH_2Cl_2, reflux, 1 h	**4a** (41), **5** (29)
10	2	B	MeOH, reflux, 1 h	**4a** (63), **5** (15), **6** (5)
11	2	B	CH_2Cl_2, reflux, 1 h	**4a** (67), **5** (15)
12	1	D	CH_2Cl_2, r.t., 5 min	**4a** (50), **5** (25)
13	2	D	CH_2Cl_2, r.t., 5 min	**4a** (71), **5** (14)
14	10	D	r.t., 5 min	**4a** (99)

[a] Method A: NCS (1-h addition), 1 h, then Et_3N; method B: PIDA (1.1 equiv), TFA (47 mol%) (2-h addition); method C: PIDA (1.1 equiv) (2-h addition); method D: PIFA (1.5 equiv) (5-min addition).
[b] In two parts, every 1 min.

in the formation of 9-(2,2-diethoxyethyl)-6-piperidin-1-yl-9*H*-purine in 83% yield, better than our former synthesis.[14c] Heating this acetal with hydrochloric acid led to (6-piperidin-1-yl-9*H*-purin-9-yl)acetaldehyde (**1**).[14c] Treatment of a solution of aldehyde **1** in aqueous ethanol with hydroxylamine hydrochloride in the presence of sodium acetate at

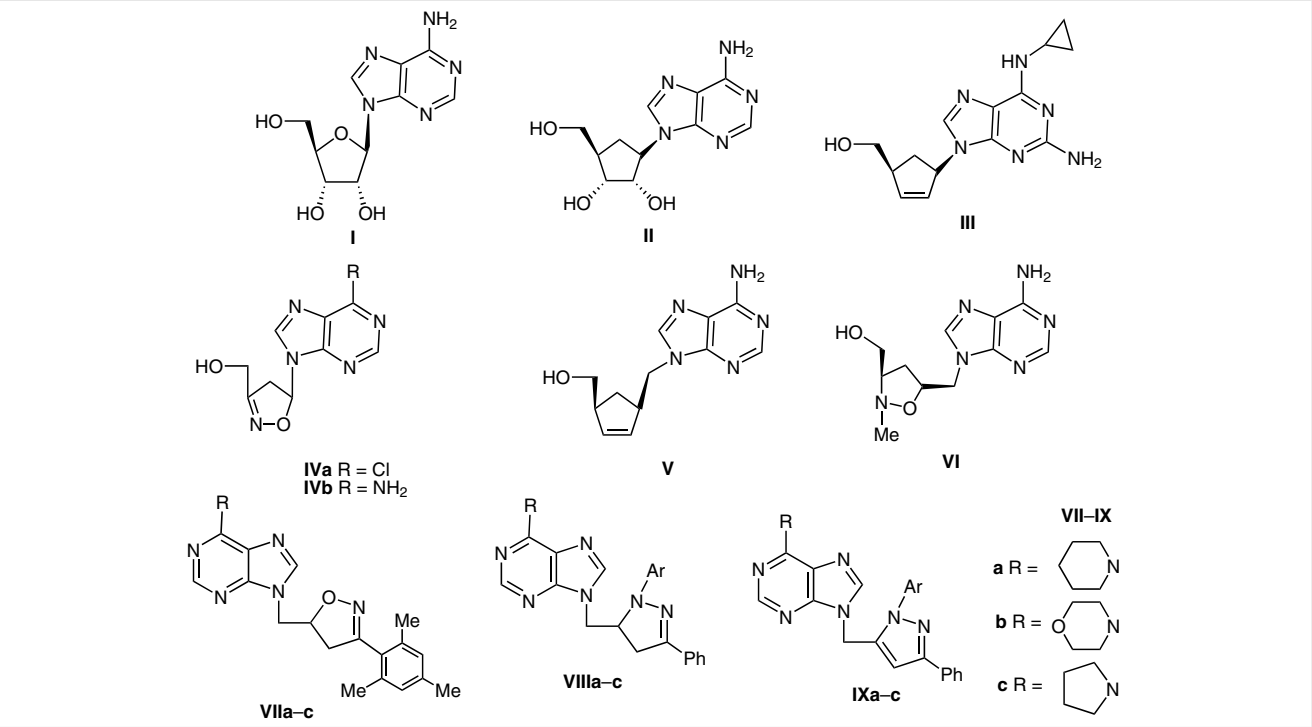
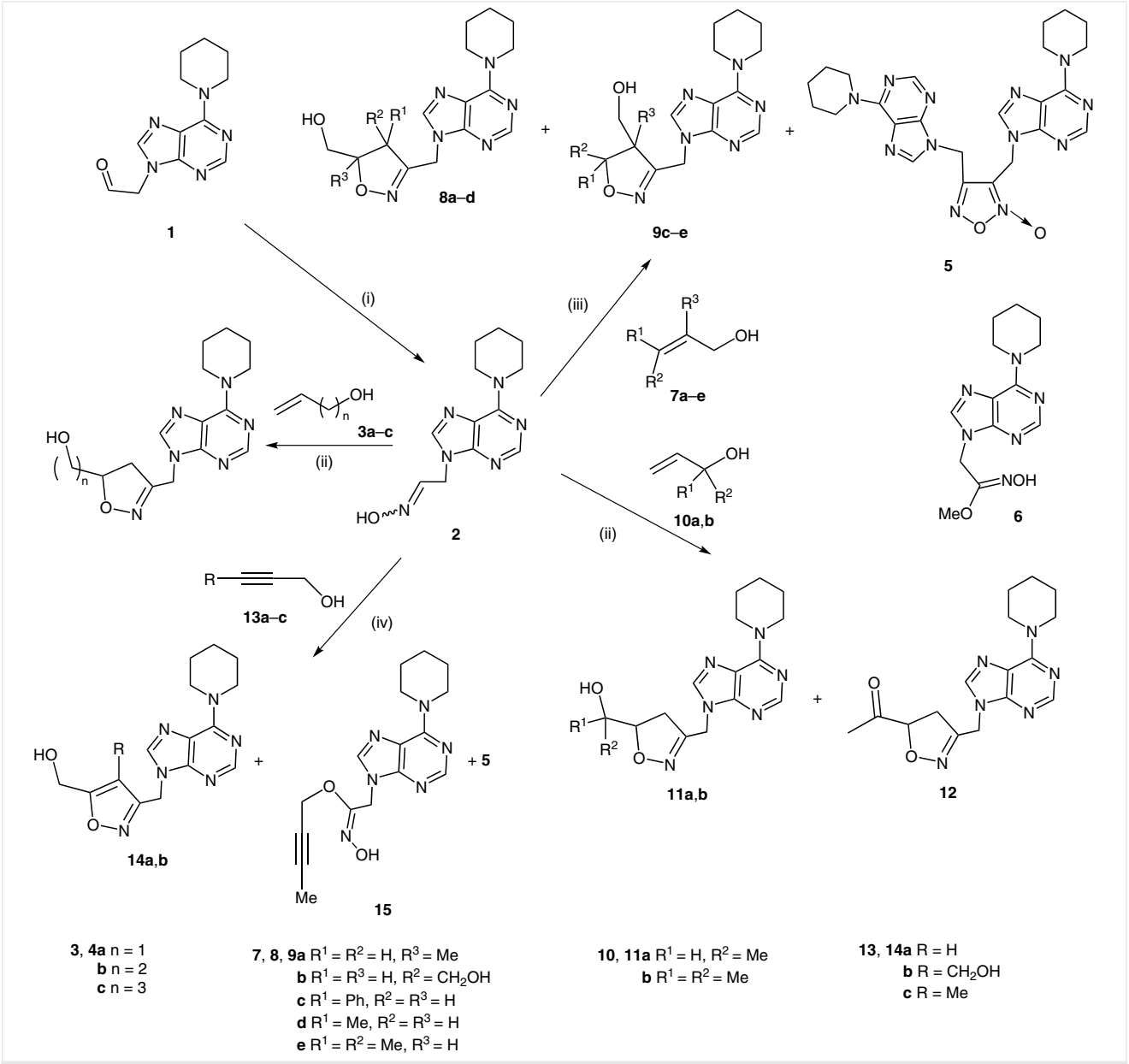


Figure 1 Nucleosides and modified nucleosides with important biological activities

80 °C for 2 hours resulted in the formation of oxime **2** (Scheme 1) in 86% yield as a 1:1 mixture of *E*- and *Z*-isomers, as indicated by ^{1}H NMR spectroscopy.

We investigated suitable conditions for the 1,3-dipolar cycloaddition reaction of the nitrile oxide, generated from oxime **2**, with unsaturated alcohols by using allyl alcohol (**3a**) as the representative reactant. Different oxidants and solvents were screened under different temperature conditions (Table 1).

First, the classical[7a,b] method by chlorination of oxime **2** with *N*-chlorosuccinimide in *N*,*N*-dimethylformamide solution, followed by addition of alkene **3a** and triethylamine (method A; Table 1, entry 1), in a one-pot procedure resulted in the new isoxazoline derivative **4a** (Scheme 1) in only 18% yield. The dimerization product, furoxan **5** (8%), was also obtained, along with recovered starting oxime **2** (52%). Isoxazoline **4a** had the expected[15] regiochemistry, as indicated by HMBC measurements. Thus, the protons of the



Scheme 1 *Reagents and conditions*: (i) $NH_2OH{\cdot}HCl$ (1.5 equiv), NaOAc (2 equiv), H_2O, EtOH, 80 °C, 2 h; (ii) **3a–c** (10 equiv) (for **4a–c**) or **10a**, **b** (10 equiv) (for **11a**, **b**, **12**), PIFA (1.5 equiv), r.t., 10 min; (iii) **7a–e** (10 equiv), PIFA (1.5 equiv), r.t. (40 °C for **7c**), 10 min; (iv) **13a–c** (10 equiv), PIFA (1.5 equiv), r.t. (60 °C for **13b**), 10 min.

NCH_2 group [5.07 ppm (s, 2 H)] correlate to 4-CH_2 (40.0 ppm in the ^{13}C NMR spectrum) and not to 5-CH (81.8 ppm) of the isoxazoline.

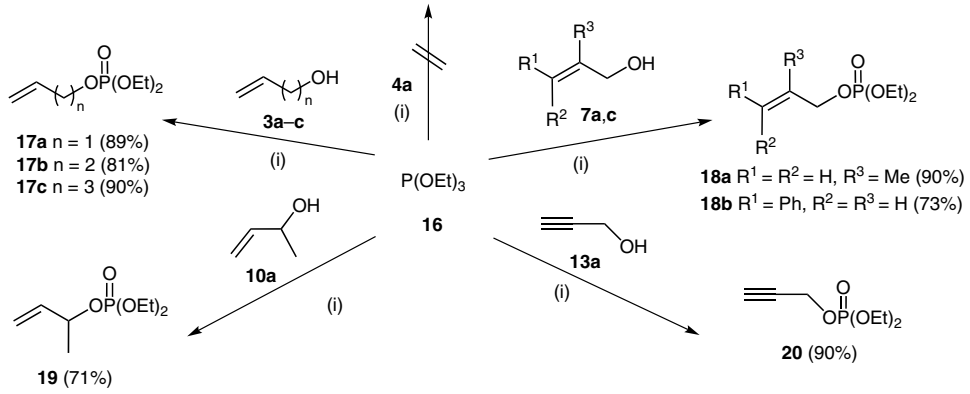
Then, oxidation of oxime **2** with phenyliodine(III) diacetate (PIDA) in the presence of a catalytic amount (47 mol%) of trifluoroacetic acid in methanol was performed at 0 °C (method B; Table 1, entry 2). This reaction led only to a 10% yield of isoxazoline **4a** and a higher amount of furoxan (34%), while the methoxy oxime derivative **6** (4%) was isolated. Increasing the temperature to room temperature or reflux provided a 43% or 58% yield of **4a** (Table 1, entries 3 and 5) and a decreased amount of furoxan **5** (21% or 12%, respectively). When dichloromethane was used as a solvent at room temperature or at 40 °C, **4a** was isolated in slightly better yields (50% or 62%, respectively) (Table 1, entries 4 and 6). The use of microwave irradiation with dichloromethane as solvent did not improve the yield of **4a** (50%) (Table 1, entry 7). Without catalysis by trifluoroacetic acid (method C; Table 1, entries 8 and 9), the yield of **4a** in methanol or dichloromethane decreased to 40% or 41%, respectively, while the furoxan yield increased (24% or 29%) (Table 1, entries 8 and 9). With 2 equivalents of allyl alcohol (**3a**), under method B, in boiling methanol or dichloromethane, isoxazoline **4a** was obtained in 63% or 67% yield, respectively (Table 1, entries 10 and 11). It seemed from these results that increasing the amount of allyl alcohol in boiling dichloromethane resulted in a relatively better yield of isoxazoline **4a** and a lower yield of furoxan **5**.

When phenyliodine(III) bis(trifluoroacetate) (PIFA, method D; Table 1, entry 12) in dichloromethane was used at room temperature, isoxazoline **4a** was obtained in 50% yield in a total time of 10 minutes (5-min addition, 5-min stirring). The dimerization product **5** was obtained in 25% yield. When 2 equivalents of **3a** in dichloromethane was used, the yield of **4a** increased to 71% while the yield of furoxan **5** decreased to 14% (Table 1, entry 13). Use of 10 equivalents of **3a**, as a solvent, afforded isoxazoline **4a** almost quantitatively at room temperature in only 10 minutes total time (Table 1, entry 14), while furoxan **5** was not isolated. Crucially, the oxidation of oxime **2**,[12c] followed by trapping of the nitrile oxide formed with the excess alkene **3a** used, is so fast that the side reaction can no longer compete.

Table 2 1,3-Dipolar Cycloaddition Reactions of Unsaturated Alcohols with the Nitrile Oxide Generated from Oxime **2**

Entry	Alcohol	Method[a]	Conditions	Yield (%) of products
1	**3b**	B	CH_2Cl_2, reflux, 1 h	**4b** (48), **5** (22), **2** (8)
2	**3b**	D	r.t., 5 min	**4b** (99)
3	**3c**	B	MeOH, reflux, 1 h	**4c** (50), **5** (18), **6** (5), **2** (8)
4	**3c**	B	CH_2Cl_2, reflux, 1 h	**4c** (53), **5** (26), **2** (5)
5	**3c**	D	r.t., 5 min	**4c** (99)
6	**7a**	B	MeOH, reflux, 1 h	**8a** (11), **5** (32), **6** (5), **2** (20)
7	**7a**	B	CH_2Cl_2, reflux, 1 h	**8a** (12), **5** (38), **2** (12)
8	**7a**	D	r.t., 5 min	**8a** (99)
9	**7b**	B	MeOH, reflux, 1 h	**8b** (6), **5** (27), **6** (5), **2** (35)
10	**7b**	D	r.t., 5 min	**8b** (99)
11	**7c**	B	MeOH, reflux, 1 h	**5** (32), **6** (5), **2** (30)
12	**7c**	D	40 °C, 5 min	**8c** (21), **9c** (42), **5** (15)
13	**7d**	B	MeOH, reflux, 1 h	**5** (22), **6** (5), **2** (50)
14	**7d**	D	r.t., 5 min	**8d** (33), **9d** (66)
15	**7e**	B	MeOH, reflux, 1 h	**5** (26), **6** (5), **2** (42)
16	**7e**	D	r.t., 5 min	**9e** (52), **5** (18), **2** (12)
17	**10a**	D	r.t., 5 min	**11a** (70), **12** (30)
18	**10b**	D	r.t., 5 min	**11b** (99)
19	**13a**	B	MeOH, reflux, 1 h	**14a** (50), **5** (16), **6** (5), **2** (12)
20	**13a**	B	CH_2Cl_2, reflux, 1 h	**14a** (75), **5** (12)
21	**13a**	D	r.t., 5 min	**14a** (99)
22	**13b**	D	60 °C, 5 min	**14b** (56), **5** (22)
23	**13c**	D	r.t., 5 min	**15** (48), **5** (12)

[a] Method B: PIDA (1.1 equiv), TFA (47 mol%) (2-h addition); method D: alcohol (10 equiv), PIFA (1.5 equiv) (5-min addition).



Scheme 2 *Reagents and conditions*: (i) I_2 (5-min addition), anhydrous CH_2Cl_2, 0 °C, then r.t., 5 min; unsaturated alcohol, pyridine (excess), anhydrous CH_2Cl_2, 0 °C (5-min addition), then r.t., 5 min.

After the examination of suitable reaction conditions, different alkenols, substituted allyl alcohols and substituted propargyl alcohols were reacted with the nitrile oxide generated from oxime **2** (Scheme 1 and Table 2). Most of the alkenols and allyl alcohols reacted almost quantitatively in the presence of PIFA (method D; Table 2, entries 2, 5, 8, 10 and 18), while in the presence of PIDA and trifluoroacetic acid the yields of isoxazolines were moderate (method B; Table 2, entries 1, 3 and 4) or low (Table 2, entries 6, 7 and 9) with increased amounts of furoxan **5**.

In the case of cinnamyl alcohol (**7c**), crotyl alcohol (**7d**) and 3-methyl-2-buten-1-ol (**7e**), method B gave only furoxan **5**, along with some methoxy oxime **6**, while oxime **2** was recovered (Table 2, entries 11, 13 and 15). Oxidation of **2** in the presence of **7c** with PIFA (method D) resulted in the regioisomers **8c** and **9c** (Table 2, entry 12) without regioselectivity.[16] HMBC experiments with **8c** revealed correlation of the NC*H*$_2$ group [4.91 (d, *J* = 16.0 Hz, 1 H) and 4.99 ppm (d, *J* = 16.0 Hz, 1 H)] with 4-*C*H–Ph of the isoxazoline [55.9 ppm in the ^{13}C NMR spectrum and 4.19 ppm (d, *J* = 6.2 Hz, 1

Table 3 Summarized Biological Results[a]

Entry	Compound	RA (%) 100 μM		LOX (%) 100 μM	AAPH (%) 100 μM
		20 min	60 min		
1	**4a**	3	56	8	91
2	**4b**	No	No	44	34
3	**4c**	9	No	30	92
4	**8a**	62	No	43	32
5	**8b**	No	17	9	47
6	**11a**	Nt	Nt	No	No
7	**11b**	Nt	Nt	No	No
8	**14a**	1	12	44	30
9	**15**	No	No	0.2	No
10	**21a**	Nt	Nt	5	1
11	**21b**	Nt	Nt	No	14
12	**21c**	Nt	Nt	2	38
13	**22a**	Nt	Nt	No	4
14	**24**	Nt	Nt	4	2.5
15	**25**	Nt	Nt	41	68
16	NDGA	86	95	84	–
17	Trolox	–	–	–	63

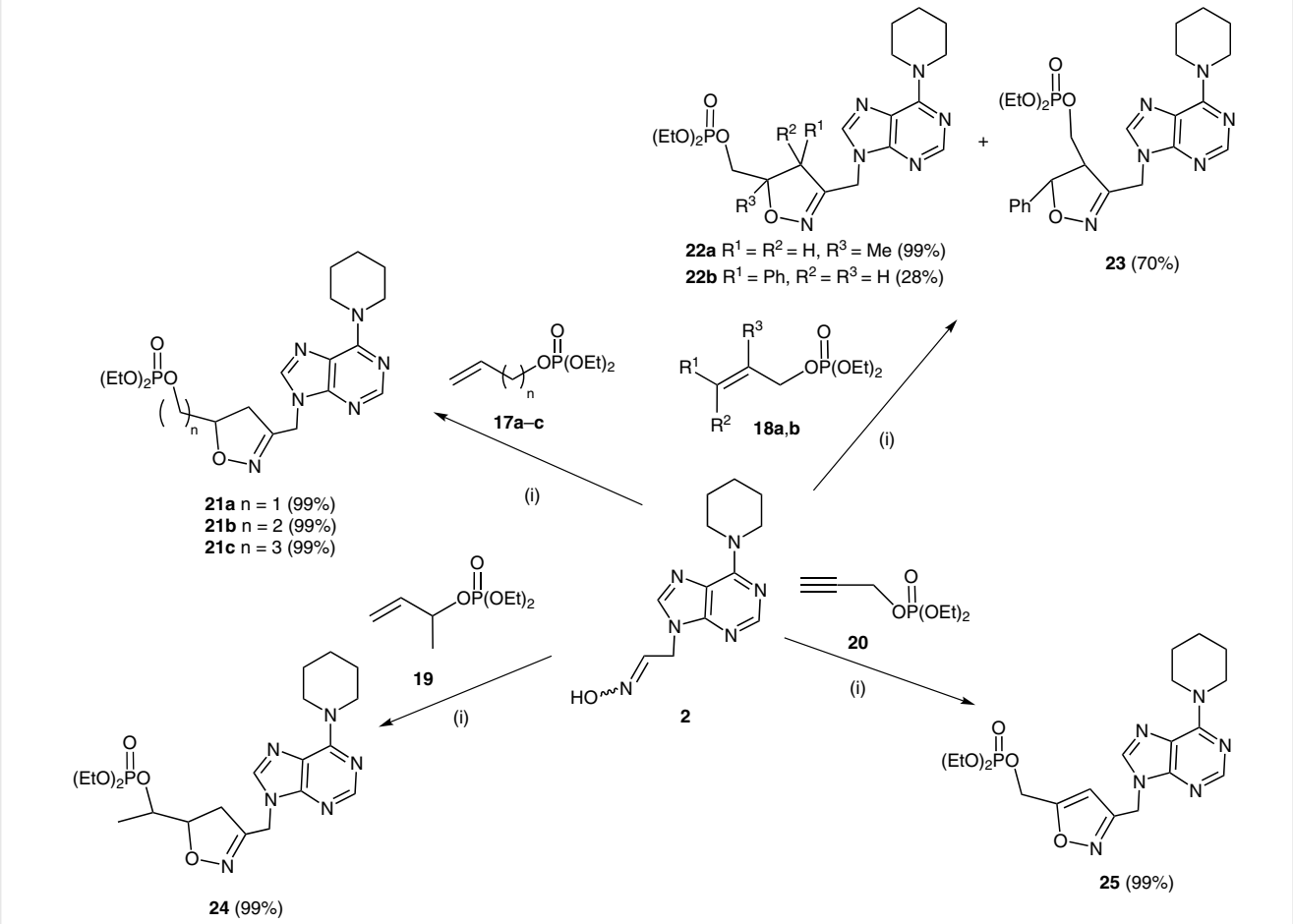
[a] RA (%): % interaction with DPPH (reducing ability); LOX (%): % *in vitro* inhibition of soybean lipoxygenase; LOX: lipoxygenase; AAPH (%): % inhibition of lipid peroxidation; NDGA: nordihydroguaiaretic acid; No: no activity under the experimental conditions; Nt: not tested.

H) for the corresponding proton in the ^{1}H NMR spectrum]. The analogous HMBC experiments with **9c** indicated correlation of the NCH_2 group [5.13 (d, J = 16.4 Hz, 1 H) and 5.17 ppm (d, J = 16.4 Hz, 1 H)] with 4-C*H*–CH_2OH of the isoxazoline [59.4 ppm in the ^{13}C NMR spectrum and 3.33 ppm (ddd, J = 4.1, 7.2, 7.4 Hz, 1 H) for the corresponding proton in the ^{1}H NMR spectrum]. Reaction of crotyl alcohol (**7d**) under method D led to a mixture (1:2) of the regioisomers **8d** and **9d** (Table 2, entry 14). HMBC correlation of the NCH_2 group for **8d** and **9d** was analogous to that described for **8c** and **9c**. Reaction of alkenol **7e** under PIFA conditions gave only regioisomer **9e** (Table 2, entry 16), probably due to steric reasons; the isoxazolines **9c**, **d** were also obtained in higher yield than their regioisomers **8c**, **d**.

1-Methyl-2-propen-1-ol (**10a**) reacted under the optimized conditions to give isoxazoline **11a**, along with the oxidation product **12** (Table 2, entry 17). Isoxazoline **11a** was obtained as a mixture (1:1) of diastereomers, as indicated by HSQC and HMBC experiments. The ethanol group of **11a** is in a pseudoequatorial position, while the 5-H of the isoxazoline ring is in a pseudoaxial position [4.45 ppm (ddd, J = 5.0, 7.6, 10.9 Hz, 1 H) for one diastereomer, 4.52 ppm (ddd, J = 3.2, 8.6, 11.5 Hz, 1 H) for the other]. The reaction of 1,1-dimethyl-2-propen-1-ol (**10b**) gave isoxazoline **11b** quantitatively (Table 2, entry 18).

1,3-Dipolar cycloaddition reactions with propargyl alcohols **13a–c** were tested next. Isoxazole **14a** was isolated quantitatively upon in situ trapping of the nitrile oxide generated from PIFA oxidation of oxime **2** with propargyl alcohol (**13a**) (Table 2, entry 21). Oxidation with PIDA and trifluoroacetic acid gave lower yields (Table 2, entries 19 and 20). 2-Butyne-1,4-diol (**13b**) reacted at its melting point to give isoxazole **14b**, along with furoxan **5** (Table 2, entry 22). Reaction of 2-butyn-1-ol (**13c**) only led to the oxime derivative **15** (Table 2, entry 23), analogous to the formation of methoxy derivative **6**.

Nucleosides or modified nucleosides containing a phosphate group present very interesting antiviral activities.[2,17] Taking this into consideration, we tried to prepare phosphate derivatives of the above hydroxy-substituted isoxazolines and isoxazoles. Efforts for the phosphorylation of **4a** proved unsuccessful (Scheme 2). For that reason, the unsat-



Scheme 3 *Reagents and conditions*: (i) unsaturated phosphate (10 equiv), PIFA (1.5 equiv), r.t., 10 min.

urated diethyl phosphates were prepared first by extending the mild, rapid and easy method[18a] for the synthesis of phosphates from phenols or primary and secondary alcohols. Thus, treatment of triethyl phosphite (**16**) with iodine and unsaturated alcohols and pyridine in dichloromethane at 0 °C resulted in **17a–c**, **18a**, **b**, **19** and **20** in very good yields (Scheme 2), comparable or better than the yields obtained from preparations with diethyl chlorophosphate[18b–f] as starting material.

The above-prepared unsaturated phosphates **17a–c**, **18a**, **b**, **19** and **20** trapped the in situ formed nitrile oxide from oxime **2** in the presence of PIFA (Scheme 3). The product isoxazolines **21a–c**, **22a**, **24** and the isoxazole **25** were isolated almost quantitatively. Isoxazoline **24** was obtained as a mixture (1:1) of diastereomers, as indicated by ^{1}H NMR spectroscopy. With phosphate **18b** derived from cinnamyl alcohol, the regioisomers **22b** and **23** were obtained as a mixture after PTLC in 28% and 70% yield, respectively (as indicated by ^{1}H NMR spectroscopy).

Preliminary biological tests have revealed that the antioxidant activity of the examined isoxazolines and isoxazoles is low to moderate (12–62%), as measured by interaction with the stable free radical 1,1-diphenyl-2-picrylhydrazyl (DPPH) (Table 3). Compounds **4a**, **4c** and **25** displayed 91%, 92% and 68% inhibition respectively (better results than the standard) of lipid peroxidation at 0.1 mM, as tested by the 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH) protocol (Table 3). Compounds **4b**, **8a**, **14a** and **25** gave 41–44% inhibition of soybean lipoxygenase (Table 3). None of the compounds exhibited significant antiviral effects in tests for anti-herpes simplex virus (anti-HSV) activity.

In conclusion, an efficient synthesis of 6-piperidinylpurine homo-*N*-nucleosides modified with isoxazolines or isoxazoles in excellent yields is reported. This method involves the 1,3-cycloaddition reaction of unsaturated alcohols or phosphates with the nitrile oxide resulting from oxidation of (6-piperidin-1-yl-9*H*-purin-9-yl)acetaldehyde oxime with PIFA at room temperature. Some compounds display interesting inhibition of lipid peroxidation.

All chemicals were procured from either Sigma-Aldrich or Merck. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained as Nujol mulls with a Perkin Elmer 1310 spectrophotometer. NMR spectra were recorded on an Agilent 500/54 (DD2) spectrometer (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR, 202 MHz for ^{31}P NMR) using $CDCl_3$ as solvent and TMS as an internal standard; *J* values are reported in Hz. Mass spectra were determined on a Shimadzu LCMS-2010 EV instrument under electrospray ionization (ESI) conditions. Microanalyses were performed on a Perkin Elmer 2400-II elemental analyzer. Silica gel 60 (Merck) was used for column chromatography. Microwave experiments were performed in a scientific focused microwave reactor (Biotage Initiator 2.0). (6-Piperidin-1-yl-9*H*-purin-9-yl)acetaldehyde (**1**) has been reported previously.[14c]

9-(2,2-Diethoxyethyl)-6-piperidin-1-yl-9*H*-purine[14c]

6-Piperidin-1-yl-9*H*-purine (0.5 g, 2.46 mmol), anhydrous DMF (10 mL), anhydrous K_2CO_3 (0.374 g, 2.71 mmol) and 2-bromoacetaldehyde diethyl acetal (0.42 mL, 0.55 g, 2.71 mmol) were added with a magnetic stirrer bar to a vial suitable for microwave irradiation. The mixture was irradiated (45–55 W) at 140 °C for 45 min, and then was filtered. The filtrate was concentrated (heptane was added to remove the DMF as an azeotropic mixture). The residue was chromatographed (silica gel; EtOAc–hexane, 1:1) to give the 9-(2,2-diethoxyethyl)-6-piperidin-1-yl-9*H*-purine; yield: 0.651 g (83%); mp 46–48 °C (hexane) (Lit.[14c] 46–48 °C).

(6-Piperidin-1-yl-9*H*-purin-9-yl)acetaldehyde Oxime (2)

A solution of aldehyde **1** (0.457 g, 1.87 mmol) in H_2O (10 mL) and EtOH (4 mL) was heated at 80 °C. NH_2OH·HCl (0.13 g, 1.87 mmol) and NaOAc (0.205 g, 2.5 mmol) were added and the mixture was heated for 1 h. Then, NH_2OH·HCl (65 mg, 0.93 mmol) and NaOAc (0.102 g, 1.24 mmol) were added again, and the mixture was heated for a further 1 h. After cooling, the aqueous solution was extracted with EtOAc (10 × 20 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated to give **2** (*E*/*Z* = 1:1) as a white solid; yield: 0.417 g (86%); mp 168–170 °C (EtOAc).

IR (KBr): 3431, 3084, 2928, 2851, 1598, 1569, 1481 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.60–1.91 (m, 12 H), 4.17–4.45 (m, 8 H), 4.95 (d, *J* = 8.7 Hz, 2 H), 5.10 (d, *J* = 7.5 Hz, 2 H), 6.88 (t, *J* = 7.5 Hz, 1 H), 7.58 (t, *J* = 8.7 Hz, 1 H), 7.82 (s, 1 H), 7.86 (s, 1 H), 8.34 (s, 1 H), 8.35 (s, 1 H), 10.8 (br s, 1 H), 11.2 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.3, 25.9, 41.8, 42.1, 46.7, 119.2, 138.1, 138.5, 143.4, 144.0, 150.1, 150.2, 151.0, 151.1, 152.4, 152.5.

MS (ESI): *m*/*z* = 261 [M + H]$^+$.

Anal. Calcd for $C_{12}H_{16}N_6O$: C, 55.37; H, 6.20; N, 32.29. Found: C, 55.26; H, 6.44; N, 32.07.

{3-[(6-Piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-5-yl}methanol (4a); Typical Procedures

Method A

NCS (0.348 g, 2.6 mmol) was added gradually over 1 h to a solution of oxime **2** (0.378 g, 1.45 mmol) in DMF (5 mL) at r.t. under N_2. Stirring was continued for a further 1 h. Allyl alcohol (**3a**) (0.11 mL, 94 mg, 1.6 mmol) and Et_3N (0.28 mL, 0.2 g, 2.03 mmol) were then added, and stirring was continued for 22 h. After filtration, the filtrate was concentrated and the residue was separated by column chromatography (silica gel; EtOAc–hexane, 1:1, then EtOAc, and finally EtOAc–MeOH, 9:1) to give at first furoxan **5** (40 mg, 8%), followed by recovered oxime **2** (0.197 g, 52%) and isoxazoline **4a** (0.106 g, 18%).

Method B

A solution of oxime **2** (50 mg, 0.19 mmol) in MeOH (10 mL) was added dropwise at r.t. over 2 h to a solution of PIDA (68 mg, 0.21 mmol) in MeOH (1 mL), in which allyl alcohol (**3a**) (14 μL, 12 mg, 0.21 mmol) and TFA (7 μL, 10.4 mg, 0.09 mmol) had been added. The mixture was stirred for a further 1 h, then concentrated, and the residue was separated by column chromatography (silica gel; EtOAc, then EtOAc–MeOH, 9:1) to give furoxan **5** (11 mg, 21%), followed by recovered oxime **2** (5 mg, 10%), oxime **6** (3 mg, 5%) and isoxazoline **4a** (26 mg, 43%).

Method C

A solution of oxime **2** (50 mg, 0.19 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 2 h to a solution of PIDA (68 mg, 0.21 mmol) in CH_2Cl_2 (1 mL) under reflux, in which allyl alcohol (**3a**) (14 µL, 12 mg, 0.21 mmol) had been added. The mixture was stirred for a further 1 h, then cooled and concentrated, and the residue was separated by column chromatography (silica gel; EtOAc, then EtOAc–MeOH, 9:1) to give furoxan **5** (15 mg, 29%), followed by isoxazoline **4a** (24.5 mg, 41%).

Method D

Oxime **2** (25 mg, 0.095 mmol) was added gradually at r.t. to a solution of PIFA (81.7 mg, 0.19 mmol) in allyl alcohol (**3a**) (0.129 mL, 0.11 g, 1.9 mmol). Then, further PIFA (40.8 mg, 0.095 mmol) was added, followed by the gradual addition of oxime **2** (25 mg, 0.095 mmol). All of the above additions lasted 5 min in total. Stirring was continued for 5 min. Then, hexane was added for the removal of **3a** by evaporation (5 cycles). The residue was purified by column chromatography (silica gel; EtOAc, then EtOAc–MeOH, 9:1) to give **4a** as a white solid; yield: 59.5 mg (99%); mp 127–129 °C (EtOAc).

IR (KBr): 3350, 3104, 2938, 2853, 1586, 1564, 1480 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.62–1.80 (m, 6 H), 2.87 (dd, *J* = 7.8, 17.4 Hz, 1 H), 2.95 (dd, *J* = 10.9, 17.4 Hz, 1 H), 3.23 (br s, 1 H), 3.54 (dd, *J* = 4.1, 12.3 Hz, 1 H), 3.77 (dd, *J* = 2.8, 12.3 Hz, 1 H), 4.09–4.39 (m, 4 H), 4.66–4.76 (m, 1 H), 5.10 (s, 2 H), 7.80 (s, 1 H), 8.31 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8, 26.2, 36.6, 39.9, 46.5, 63.3, 81.8, 119.5, 137.7, 150.6, 152.7, 153.9, 154.8.

MS (ESI): *m*/*z* = 317 $[M + H]^{+\cdot}$, 339 $[M + Na]^{+\cdot}$, 355 $[M + K]^{+\cdot}$.

Anal. Calcd for $C_{15}H_{20}N_6O_2$: C, 56.95; H, 6.37; N, 26.56. Found: C, 56.86; H, 6.42; N, 26.45.

3,4-Bis[(6-piperidin-1-yl-9*H*-purin-9-yl)methyl]-1,2,5-oxadiazole 2-Oxide (5)

Yield: 40 mg (8%) (method A); white solid; mp 60–62 °C (EtOAc–hexane).

IR (KBr): 3018, 2926, 2854, 1590 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.71–1.85 (m, 12 H), 4.24–4.43 (m, 8 H), 5.55 (s, 2 H), 6.01 (s, 2 H), 7.95 (s, 1 H), 8.03 (s, 1 H), 8.31 (s, 1 H), 8.34 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.6, 24.7, 26.2, 35.5, 38.7, 47.0, 47.1, 111.9, 119.5, 119.6, 138.0, 138.1, 150.2, 151.8, 152.2, 152.3, 153.3.

MS (ESI): *m*/*z* = 517 $[M + H]^{+\cdot}$, 539 $[M + Na]^{+\cdot}$.

Anal. Calcd for $C_{24}H_{28}N_{12}O_2$: C, 55.80; H, 5.46; N, 32.54. Found: C, 55.71; H, 5.53; N, 32.39.

Methyl *N*-Hydroxy-2-(6-piperidin-1-yl-9*H*-purin-9-yl)ethanimidoate (6)

Yield: 3 mg (5%) (method B); white solid; mp 102–104 °C (EtOAc–hexane).

IR (KBr): 3420, 3026, 2927, 2854, 1637, 1587, 1567 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.67–1.79 (m, 6 H), 3.80 (s, 3 H), 4.21–4.33 (m, 4 H), 4.98 (s, 2 H), 7.79 (s, 1 H), 8.34 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8, 26.2, 44.1, 46.7, 53.0, 119.2, 138.3, 150.7, 152.4, 153.2, 167.9.

MS (ESI): *m*/*z* = 291 $[M + H]^{+\cdot}$.

Anal. Calcd for $C_{13}H_{18}N_6O_2$: C, 53.78; H, 6.25; N, 28.95. Found: C, 54.03; H, 6.35; N, 28.76.

2-{3-[(6-Piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-5-yl}ethanol (4b)

Yield: 62 mg (99%) (method D); light yellow oil.

IR (KBr): 3240, 3028, 2936, 2851, 1592 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.68–1.81 (m, 7 H), 1.89 (dt, *J* = 6.4, 13.1 Hz, 1 H), 2.72 (dd, *J* = 7.7, 17.2 Hz, 1 H), 3.04 (dd, *J* = 10.6, 17.2 Hz, 1 H), 3.69 (t, *J* = 6.4 Hz, 2 H), 4.14–4.29 (m, 4 H), 4.76–4.85 (m, 1 H), 5.10 (s, 2 H), 7.84 (s, 1 H), 8.28 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.6, 26.0, 37.3, 40.1, 40.4, 46.5, 58.4, 79.4, 119.3, 137.9, 150.2, 152.4, 153.8, 154.8.

MS (ESI): *m*/*z* = 331 $[M + H]^{+\cdot}$, 353 $[M + Na]^{+\cdot}$, 369 $[M + K]^{+\cdot}$.

Anal. Calcd for $C_{16}H_{22}N_6O_2$: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.31; H, 6.53; N, 25.35.

3-{3-[(6-Piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-5-yl}propan-1-ol (4c)

Yield: 65 mg (99%) (method D); light yellow oil.

IR (KBr): 3241, 3029, 2937, 2857, 1590, 1568 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.53–1.67 (m, 2 H), 1.67–1.80 (m, 8 H), 2.56 (dd, *J* = 8.3, 17.4 Hz, 1 H), 2.97 (dd, *J* = 10.4, 17.4 Hz, 1 H), 3.64 (t, *J* = 5.9 Hz, 2 H), 4.18–4.30 (m, 4 H), 4.60–4.69 (m, 1 H), 5.10 (s, 2 H), 7.78 (s, 1 H), 8.32 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8, 26.2, 28.6, 31.6, 40.0, 40.4, 46.5, 62.2, 81.7, 119.5, 137.6, 150.6, 152.7, 153.9, 154.4.

MS (ESI): *m*/*z* = 345 $[M + H]^{+\cdot}$, 367 $[M + Na]^{+\cdot}$, 383 $[M + K]^{+\cdot}$.

Anal. Calcd for $C_{17}H_{24}N_6O_2$: C, 59.28; H, 7.02; N, 24.40. Found: C, 59.20; H, 6.86; N, 24.29.

{5-Methyl-3-[(6-piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-5-yl}methanol (8a)

Yield: 62 mg (99%) (method D); white solid; mp 183–185 °C (EtOAc).

IR (KBr): 3234, 3017, 2925, 2853, 1592, 1562 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.30 (s, 3 H), 1.68–1.78 (m, 6 H), 2.57 (d, *J* = 17.4 Hz, 1 H), 3.03 (d, *J* = 17.4 Hz, 1 H), 3.42 (d, *J* = 12.1 Hz, 1 H), 3.63 (d, *J* = 12.1 Hz, 1 H), 4.15–4.30 (m, 4 H), 5.07 (s, 2 H), 7.79 (s, 1 H), 8.31 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5, 24.8, 26.2, 40.2, 42.2, 46.4, 67.2, 88.3, 119.5, 137.6, 150.6, 152.8, 153.9, 154.9.

MS (ESI): *m*/*z* = 331 $[M + H]^{+\cdot}$, 353 $[M + Na]^{+\cdot}$, 369 $[M + K]^{+\cdot}$.

Anal. Calcd for $C_{16}H_{22}N_6O_2$: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.11; H, 6.65; N, 25.38.

{3-[(6-Piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazole-4,5-diyl}dimethanol (8b)

Yield: 65 mg (99%) (method D); yellow oil.

IR (KBr): 3239, 3031, 2935, 2854, 1591, 1567, 1482 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.66–1.77 (m, 6 H), 3.41 (dt, *J* = 4.3, 11.0 Hz, 1 H), 3.84–4.04 (m, 4 H), 4.17–4.29 (m, 4 H), 4.65 (dt, *J* = 3.5, 11.0 Hz, 1 H), 5.11 (d, *J* = 16.1 Hz, 1 H), 5.19 (d, *J* = 16.1 Hz, 1 H), 7.85 (s, 1 H), 8.28 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8, 26.2, 39.6, 46.5, 51.7, 57.7, 59.7, 83.4, 119.5, 138.3, 150.0, 152.3, 153.8, 156.6.

MS (ESI): *m*/*z* = 347 $[M + H]^{+\cdot}$, 369 $[M + Na]^{+\cdot}$, 385 $[M + K]^{+\cdot}$.

Anal. Calcd for $C_{16}H_{22}N_6O_3$: C, 55.48; H, 6.40; N, 24.26. Found: C, 55.43; H, 6.49; N, 24.18.

{4-Phenyl-3-[(6-piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-5-yl}methanol (8c)

Yield: 16 mg (21%) (method D); white oil.

IR (KBr): 3227, 3015, 2923, 2854, 1590, 1566 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.65–1.76 (m, 6 H), 3.61 (dd, *J* = 4.0, 12.4 Hz, 1 H), 3.81 (dd, *J* = 5.2, 12.4 Hz, 1 H), 4.19 (d, *J* = 6.2 Hz, 1 H), 4.15–4.28 (m, 5 H), 4.59 (ddd, *J* = 4.0, 5.2, 6.2 Hz, 1 H), 4.91 (d, *J* = 16.0 Hz, 1 H), 4.99 (d, *J* = 16.0 Hz, 1 H), 7.18–7.35 (m, 5 H), 7.54 (s, 1 H), 8.22 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8, 26.2, 39.0, 46.5, 55.8, 62.9, 90.5, 119.3, 127.4, 128.5, 129.1, 136.8, 140.0, 150.3, 152.3, 153.6, 156.6.

MS (ESI): *m*/*z* = 393 $[M + H]^+$, 415 $[M + Na]^+$, 431 $[M + K]^+$.

Anal. Calcd for $C_{21}H_{24}N_6O_2$: C, 64.27; H, 6.16; N, 21.41. Found: C, 64.32; H, 6.22; N, 21.34.

{5-Phenyl-3-[(6-piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-4-yl}methanol (9c)

Yield: 32 mg (42%) (method D); white solid; mp 158–159 °C (MeOH).

IR (KBr): 3227, 3085, 3015, 2923, 2854, 1590, 1566, 1478 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.65–1.76 (m, 6 H), 3.33 (ddd, *J* = 4.5, 7.1, 7.4 Hz, 1 H), 3.83 (dd, *J* = 7.1, 11.6 Hz, 1 H), 4.09 (dd, *J* = 4.5, 11.6 Hz, 1 H), 4.15–4.29 (m, 5 H), 5.13 (d, *J* = 16.4 Hz, 1 H), 5.17 (d, *J* = 16.4 Hz, 1 H), 5.34 (d, *J* = 7.4 Hz, 1 H), 7.18–7.37 (m, 5 H), 7.84 (s, 1 H), 8.25 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.7, 26.2, 39.7, 46.4, 59.4, 61.7, 85.6, 119.6, 125.5, 128.4, 128.9, 137.7, 138.1, 149.7, 152.2, 153.8, 155.4.

MS (ESI): *m*/*z* = 393 $[M + H]^+$, 415 $[M + Na]^+$, 431 $[M + K]^+$.

Anal. Calcd for $C_{21}H_{24}N_6O_2$: C, 64.27; H, 6.16; N, 21.41. Found: C, 64.16; H, 6.11; N, 21.28.

{4-Methyl-3-[(6-piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-5-yl}methanol (8d) and {5-Methyl-3-[(6-piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-4-yl}methanol (9d)

Yield of **8d** + **9d**: 21 mg (33%) + 42 mg (66%) (method D); yellow oil.

IR (KBr): 3240, 3028, 2936, 2854, 1593, 1568 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 7.2 Hz, 1.5 H), 1.27 (d, *J* = 6.4 Hz, 3 H), 1.64–1.77 (m, 9 H), 2.98 (ddd, *J* = 4.7, 8.2, 12.8 Hz, 1 H), 3.08 (ddd, *J* = 3.2, 4.4, 7.2 Hz, 0.5 H), 3.55 (dd, *J* = 4.4, 12.3 Hz, 0.5 H), 3.72 (dd, *J* = 8.2, 11.4 Hz, 1 H), 3.76 (dd, *J* = 3.2, 12.3 Hz, 0.5 H), 3.93 (dd, *J* = 4.7, 11.4 Hz, 1 H), 4.16–4.32 (m, 7.5 H), 4.43 (dq, *J* = 6.4, 12.8 Hz, 1 H), 5.03 (d, *J* = 15.7 Hz, 0.5 H), 5.14 (d, *J* = 15.7 Hz, 1 H), 5.15 (d, *J* = 15.7 Hz, 0.5 H), 5.19 (d, *J* = 15.7 Hz, 1 H), 7.80 (s, 0.5 H), 7.83 (s, 1 H), 8.27 (s, 1 H), 8.33 (s, 0.5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1, 20.3, 24.8, 24.9, 26.2, 38.3, 40.1, 43.6, 46.5, 57.3, 62.2, 62.7, 80.7, 89.0, 119.4, 119.7, 137.6, 138.1, 149.8, 150.6, 152.3, 152.8, 153.9, 156.0, 158.5.

MS (ESI): *m*/*z* = 331 $[M + H]^+$, 353 $[M + Na]^+$, 369 $[M + K]^+$.

Anal. Calcd for $C_{16}H_{22}N_6O_2$: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.06; H, 6.63; N, 25.40.

{5,5-Dimethyl-3-[(6-piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-4-yl}methanol (9e)

Yield: 35 mg (52%) (method D); yellow oil.

IR (KBr): 3229, 3025, 2925, 2854, 1589 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.23 (s, 3 H), 1.30 (s, 3 H), 1.64–1.77 (m, 6 H), 2.90 (dd, *J* = 4.7, 9.1 Hz, 1 H), 3.76 (dd, *J* = 9.1, 11.4 Hz, 1 H), 3.89 (dd, *J* = 4.7, 11.4 Hz, 1 H), 4.15–4.34 (m, 4 H), 5.16 (d, *J* = 15.7 Hz, 1 H), 5.24 (d, *J* = 15.7 Hz, 1 H), 7.83 (s, 1 H), 8.28 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.3, 24.8, 26.2, 28.1, 40.9, 46.5, 57.2, 60.1, 86.8, 119.8, 138.1, 149.9, 152.3, 154.0, 157.4.

MS (ESI): *m*/*z* = 345 $[M + H]^+$, 383 $[M + K]^+$.

Anal. Calcd for $C_{17}H_{24}N_6O_2$: C, 59.28; H, 7.02; N, 24.40. Found: C, 59.35; H, 6.96; N, 24.29.

1-{3-[(6-Piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-5-yl}ethanol (11a)

Yield: 44 mg (70%) (method D); yellow oil.

IR (KBr): 3244, 3104, 2940, 2854, 1592, 1567 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 6.5 Hz, 3 H), 1.19 (d, *J* = 6.5 Hz, 3 H), 1.67–1.78 (m, 12 H), 2.76 (dd, *J* = 7.6, 17.6 Hz, 1 H), 2.80 (dd, *J* = 11.5, 17.3 Hz, 1 H), 2.94 (dd, *J* = 10.9, 17.6 Hz, 1 H), 2.97 (dd, *J* = 8.6, 17.3 Hz, 1 H), 3.66 (dq, *J* = 5.0, 6.5 Hz, 1 H), 4.03 (dq, *J* = 3.2, 6.5 Hz, 1 H), 4.17–4.34 (m, 8 H), 4.46 (ddd, *J* = 5.0, 7.6, 10.9 Hz, 1 H), 4.53 (ddd, *J* = 3.2, 8.6, 11.5 Hz, 1 H), 5.10 (s, 4 H), 7.78 (s, 2 H), 8.33 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.0, 19.1, 24.8, 26.2, 34.5, 37.5, 39.9, 40.0, 46.4, 67.0, 69.2, 85.1, 85.6, 119.5, 137.6, 137.7, 150.6, 152.8, 152.9, 153.9, 154.9, 155.0.

MS (ESI): *m*/*z* = 331 $[M + H]^+$, 353 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{22}N_6O_2$: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.13; H, 6.64; N, 25.31.

1-{3-[(6-Piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-5-yl}ethanone (12)

Yield: 19 mg (30%) (method D); yellow oil.

IR (KBr): 3229, 3019, 2925, 2854, 1723, 1589 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.66–1.78 (m, 6 H), 2.28 (s, 3 H), 3.08 (dd, *J* = 12.0, 17.8 Hz, 1 H), 3.20 (dd, *J* = 6.7, 17.8 Hz, 1 H), 4.17–4.31 (m, 4 H), 4.90 (dd, *J* = 6.7, 12.0 Hz, 1 H), 5.11 (s, 2 H), 7.75 (s, 1 H), 8.32 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.9, 26.2, 26.5, 37.5, 39.6, 46.5, 84.5, 119.5, 137.3, 150.7, 153.0, 154.0, 154.7, 206.1.

MS (ESI): *m*/*z* = 329 $[M + H]^+$, 351 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{20}N_6O_2$: C, 58.52; H, 6.14; N, 25.59. Found: C, 58.47; H, 6.11; N, 25.45.

2-{3-[(6-Piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-5-yl}propan-2-ol (11b)

Yield: 65 mg (99%) (method D); yellow oil.

IR (KBr): 3243, 3031, 2939, 2854, 1592 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.08 (s, 3 H), 1.26 (s, 3 H), 1.67–1.79 (m, 6 H), 2.83 (dd, *J* = 11.0, 17.5 Hz, 1 H), 2.93 (dd, *J* = 9.0, 17.5 Hz, 1 H), 4.20–4.28 (m, 4 H), 4.44 (dd, *J* = 9.0, 11.0 Hz, 1 H), 5.09 (s, 2 H), 7.77 (s, 1 H), 8.33 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.6, 24.9, 26.2, 26.3, 35.9, 39.9, 46.5, 71.1, 88.1, 119.5, 137.5, 150.7, 152.9, 154.0, 155.2.

MS (ESI): *m*/*z* = 345 $[M + H]^+$, 367 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{24}N_6O_2$: C, 59.28; H, 7.02; N, 24.40. Found: C, 59.36; H, 6.92; N, 24.32.

{3-[(6-Piperidin-1-yl-9*H*-purin-9-yl)methyl]isoxazol-5-yl}methanol (14a)

Yield: 59 mg (99%) (method D); white solid; mp 131–133 °C (EtOAc).

IR (KBr): 3144, 3018, 2938, 2854, 1595, 1566, 1452 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.67–1.79 (m, 6 H), 4.15–4.31 (m, 4 H), 4.64 (s, 2 H), 5.42 (s, 2 H), 6.25 (s, 1 H), 7.86 (s, 1 H), 8.30 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.5, 26.0, 38.6, 46.6, 55.7, 100.9, 119.4, 138.1, 150.1, 152.2, 153.6, 159.2, 173.8.

MS (ESI): *m*/*z* = 315 $[M + H]^{+\cdot}$, 337 $[M + Na]^{+\cdot}$.

Anal. Calcd for $C_{15}H_{18}N_6O_2$: C, 57.31; H, 5.77; N, 26.74. Found: C, 57.12; H, 5.91; N, 26.56.

{3-[(6-Piperidin-1-yl-9*H*-purin-9-yl)methyl]isoxazole-4,5-diyl}dimethanol (14b)

Yield: 37 mg (56%) (method D); yellow oil.

IR (KBr): 3240, 3015, 2937, 2863, 1594, 1441 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.68–1.80 (m, 6 H), 4.16–4.33 (m, 4 H), 4.53 (s, 2 H), 4.68 (s, 2 H), 5.48 (s, 2 H), 7.86 (s, 1 H), 8.26 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.5, 26.0, 37.5, 46.7, 51.9, 54.2, 114.9, 119.1, 139.3, 149.9, 151.9, 153.6, 158.3, 169.2.

MS (ESI): *m*/*z* = 345 $[M + H]^{+\cdot}$.

Anal. Calcd for $C_{16}H_{20}N_6O_3$: C, 55.80; H, 5.85; N, 24.40. Found: C, 55.89; H, 5.34; N, 24.27.

But-2-ynyl *N*-Hydroxy-2-(6-piperidin-1-yl-9*H*-purin-9-yl)ethanimidoate (15)

Yield: 30 mg (48%) (method D); pale yellow oil.

IR (KBr): 3451, 3025, 2925, 2854, 1588, 1458 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.68–1.76 (m, 6 H), 1.86 (t, *J* = 2.4 Hz, 3 H), 4.22–4.31 (m, 4 H), 4.76 (d, *J* = 2.4 Hz, 2 H), 4.99 (s, 2 H), 7.80 (s, 1 H), 8.37 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 3.7, 24.8, 26.2, 44.1, 46.8, 54.4, 72.3, 84.5, 119.3, 138.3, 150.7, 150.8, 152.5, 166.9.

MS (ESI): *m*/*z* = 329 $[M + H]^{+\cdot}$, 351 $[M + Na]^{+\cdot}$.

Anal. Calcd for $C_{16}H_{20}N_6O_2$: C, 58.52; H, 6.14; N, 25.59. Found: C, 58.41; H, 6.23; N, 25.48.

Allyl Diethyl Phosphate (17a); Typical Procedure

I_2 (2.05 g, 8.07 mmol) was added gradually over 5 min to a solution of $P(OEt)_3$ (**16**) (1.51 mL, 1.463 g, 8.82 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C. This mixture was stirred at r.t. for 5 min, then added dropwise over 5 min to a solution of allyl alcohol (**3a**) (0.5 mL, 0.427 g, 7.36 mmol) and pyridine (2.37 mL, 29.41 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C. Then, the mixture was stirred at r.t. for 5 min. Et_2O (50 mL) was added and the mixture was washed with 20% v/v $NaHSO_4$ (3 × 20 mL) and 0.1 M Na_3PO_4 as buffer (2 × 10 mL). The organic layer was dried and concentrated, and the residue was separated by column chromatography (silica gel; EtOAc–hexane, 1:1) to give **17a** as an oil;[18b] yield: 1.271 g (89%).

But-3-enyl Diethyl Phosphate (17b)

Yield: 1.24 g (81%); oil.[18c]

Diethyl Pent-4-enyl Phosphate (17c)

Yield: 1.471 g (90%); oil.[18d]

IR (KBr): 3076, 2939, 1642, 1265, 1036, 978 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.1 Hz, 6 H), 1.78 (quint, *J* = 6.6 Hz, 2 H), 2.16 (q, *J* = 6.6 Hz, 2 H), 3.99–4.16 (m, 6 H), 4.99 (d, *J* = 10.2 Hz, 1 H), 5.04 (d, *J* = 16.9 Hz, 1 H), 5.80 (ddt, *J* = 6.6, 10.2, 16.9 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1 (d, *J* = 6.0 Hz), 29.5, 29.6 (d, *J* = 5.7 Hz), 63.7 (d, *J* = 5.9 Hz), 66.9 (d, *J* = 6.0 Hz), 115.5, 137.3.

^{31}P NMR (202 MHz, $CDCl_3$): δ = –0.88.

MS (ESI): *m*/*z* = 223 $[M + H]^{+\cdot}$, 245 $[M + Na]^{+\cdot}$.

Diethyl 2-Methylprop-2-enyl Phosphate (18a)

Yield: 1.378 g (90%); oil.[18b]

Cinnamyl Diethyl Phosphate (18b)

Yield: 1.451 g (73%); oil.[18f]

Diethyl 1-Methylprop-2-enyl Phosphate (19)

Yield: 1.087 g (71%); oil.[18b]

Diethyl Propargyl Phosphate (20)

Yield: 1.272 g (90%); oil.[18b]

Diethyl {3-[(6-Piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-5-yl}methyl Phosphate (21a); Typical Procedure

The above method D was followed for the reaction of allyl diethyl phosphate (**17a**) (0.184 g, 0.95 mmol) with oxime **2**. After the 5 minutes of stirring, MeOH was added for the removal of excess **17a** by evaporation (5 cycles). The residue was separated by PTLC (EtOAc) to give **21a** as an orange oil; yield: 85 mg (99%).

IR (KBr): 3042, 2943, 2860, 1593, 1211, 1138, 1038 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.32 (dt, *J* = 0.9, 7.1 Hz, 3 H), 1.33 (dt, *J* = 0.9, 7.1 Hz, 3 H), 1.68–1.78 (m, 6 H), 2.87 (dd, *J* = 7.3, 17.6 Hz, 1 H), 3.03 (dd, *J* = 11.1, 17.6 Hz, 1 H), 3.98–4.13 (m, 6 H), 4.20–4.30 (m, 4 H), 4.79–4.87 (m, 1 H), 5.12 (s, 2 H), 7.78 (s, 1 H), 8.33 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1 (d, *J* = 6.7 Hz), 24.8, 26.2, 37.2, 39.8, 46.5, 64.2 (d, *J* = 6.0 Hz), 67.1 (d, *J* = 5.5 Hz), 79.2 (d, *J* = 7.8 Hz), 119.5, 137.6, 150.5, 152.7, 153.9, 154.2.

^{31}P NMR (202 MHz, $CDCl_3$): δ = –2.0.

MS (ESI): *m*/*z* = 453 $[M + H]^{+\cdot}$, 475 $[M + Na]^{+\cdot}$.

Anal. Calcd for $C_{19}H_{29}N_6O_5P$: C, 50.44; H, 6.46; N, 18.57. Found: C, 50.32; H, 6.52; N, 18.48.

Diethyl 2-{3-[(6-Piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-5-yl}ethyl Phosphate (21b)

Yield: 88 mg (99%); orange oil.

IR (KBr): 3079, 2930, 2857, 1642, 1591, 1210, 1138, 1039 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.0 Hz, 6 H), 1.68–1.83 (m, 6 H), 1.87–1.94 (m, 1 H), 1.94–2.01 (m, 1 H), 2.63 (dd, *J* = 7.9, 17.3 Hz, 1 H), 3.03 (dd, *J* = 10.5, 17.3 Hz, 1 H), 4.05–4.18 (m, 6 H), 4.18–4.28 (m, 4 H), 4.78 (ddt, *J* = 5.3, 7.9, 10.5 Hz, 1 H), 5.12 (s, 2 H), 7.78 (s, 1 H), 8.33 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.2 (d, *J* = 6.5 Hz), 24.8, 26.2, 35.8 (d, *J* = 6.7 Hz), 40.0, 40.6, 46.7, 63.9 (d, *J* = 2.4 Hz), 64.0 (d, *J* = 2.4 Hz), 78.1, 119.5, 137.6, 150.6, 152.7, 153.9, 154.6.

^{31}P NMR (202 MHz, $CDCl_3$): δ = –1.14.

MS (ESI): *m*/*z* = 467 $[M + H]^{+\cdot}$, 489 $[M + Na]^{+\cdot}$.

Anal. Calcd for $C_{20}H_{31}N_6O_5P$: C, 51.50; H, 6.70; N, 18.02. Found: C, 51.63; H, 6.75; N, 17.94.

Diethyl 3-{3-[(6-Piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-5-yl}propyl Phosphate (21c)

Yield: 90 mg (99%); orange oil.

IR (KBr): 3063, 2931, 2853, 1589, 1565, 1062, 1024, 993 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.0 Hz, 6 H), 1.63–1.83 (m, 8 H), 1.97–2.20 (m, 2 H), 2.58 (dd, *J* = 8.2, 17.3 Hz, 1 H), 2.99 (dd, *J* = 10.5, 17.3 Hz, 1 H), 3.97–4.21 (m, 6 H), 4.22–4.32 (m, 4 H), 4.50–4.57 (m, 1 H), 5.13 (s, 2 H), 7.80 (s, 1 H), 8.36 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.2 (d, *J* = 5.8 Hz), 24.7, 26.2, 29.8, 31.3, 40.3, 40.4, 46.9, 63.9 (d, *J* = 6.2 Hz), 67.0 (d, *J* = 5.5 Hz), 81.2, 119.5, 137.9, 149.9, 151.9, 153.4, 154.3.

^{31}P NMR (202 MHz, $CDCl_3$): δ = –1.08.

MS (ESI): *m*/*z* = 481 $[M + H]^{+\cdot}$, 503 $[M + Na]^{+\cdot}$.

Anal. Calcd for $C_{21}H_{33}N_6O_5P$: C, 52.49; H, 6.92; N, 17.49. Found: C, 52.41; H, 6.74; N, 17.28.

Diethyl {5-Methyl-3-[(6-piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-5-yl}methyl Phosphate (22a)

Yield: 88 mg (99%); orange oil.

IR (KBr): 3030, 2930, 2857, 1642, 1589, 1482, 1214, 1132, 1036 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.23–1.37 (m, 6 H), 1.38 (s, 3 H), 1.60–1.81 (m, 6 H), 2.64 (d, *J* = 17.6 Hz, 1 H), 3.02 (d, *J* = 17.6 Hz, 1 H), 3.89 (dd, *J* = 5.8, 10.8 Hz, 1 H), 3.98 (dd, *J* = 5.8, 10.8 Hz, 1 H), 4.09 (dq, *J* = 6.9, 7.4 Hz, 4 H), 4.22–4.28 (m, 4 H), 5.08 (s, 2 H), 7.78 (s, 1 H), 8.33 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1 (d, *J* = 5.9 Hz), 22.6, 24.9, 26.2, 40.1, 43.0, 46.6, 64.2 (d, *J* = 5.8 Hz), 70.3 (d, *J* = 5.3 Hz), 86.1 (d, *J* = 8.2 Hz), 119.7, 137.6, 150.8, 152.8, 154.1, 154.2.

^{31}P NMR (202 MHz, $CDCl_3$): δ = –1.29.

MS (ESI): *m*/*z* = 467 $[M + H]^{+\cdot}$, 489 $[M + Na]^{+\cdot}$.

Anal. Calcd for $C_{20}H_{31}N_6O_5P$: C, 51.50; H, 6.70; N, 18.02. Found: C, 51.56; H, 6.57; N, 17.91.

Diethyl {4-Phenyl-3-[(6-piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-5-yl}methyl Phosphate (22b) and Diethyl {5-Phenyl-3-[(6-piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-4-yl}methyl Phosphate (23)

Yield of **22b** + **23**: 28 mg (28%) + 70 mg (70%); orange oil.

IR (KBr): 3085, 2983, 2908, 2836, 1638, 1588, 1480 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.28–1.36 (m, 8.4 H), 1.66–1.83 (m, 8.4 H), 3.28–3.34 (m, 1 H), 4.02–4.18 (m, 8.4 H), 4.18–4.33 (m, 5.6 H), 4.50 (d, *J* = 6.4 Hz, 0.4 H), 4.69–4.73 (m, 0.4 H), 4.95 (d, *J* = 15.4 Hz, 0.4 H), 5.03 (d, *J* = 15.4 Hz, 0.4 H), 5.17 (d, *J* = 15.8 Hz, 1 H), 5.27 (d, *J* = 15.8 Hz, 1 H), 5.54 (d, *J* = 7.6 Hz, 1 H), 7.29–7.37 (m, 7 H), 7.57 (s, 0.4 H), 7.84 (s, 1 H), 8.26 (s, 0.4 H), 8.29 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.3 (d, *J* = 6.5 Hz), 16.5 (d, *J* = 3.9 Hz), 24.6, 24.8, 26.2, 26.3, 38.8, 38.9, 46.6, 47.2, 56.6, 57.5 (d, *J* = 6.8 Hz), 64.2 (d, *J* = 4.9 Hz), 64.5 (d, *J* = 3.3 Hz), 85.5, 87.7 (d, *J* = 2.0 Hz), 119.4, 119.5, 125.8, 127.5, 128.3, 128.7, 129.0, 129.2, 137.6, 137.8, 139.4, 139.7, 150.4, 150.6, 152.3, 152.6, 153.1, 153.2, 153.5, 153.8.

^{31}P NMR (202 MHz, $CDCl_3$): δ = –0.97, –1.15.

MS (ESI): *m*/*z* = 529 $[M + H]^{+\cdot}$, 551 $[M + Na]^{+\cdot}$.

Anal. Calcd for $C_{25}H_{33}N_6O_5P$: C, 56.81; H, 6.29; N, 15.90. Found: C, 56.65; H, 6.24; N, 15.76.

Diethyl 1-{3-[(6-Piperidin-1-yl-9*H*-purin-9-yl)methyl]-4,5-dihydroisoxazol-5-yl}ethyl Phosphate (24)

Yield: 88 mg (99%); orange oil.

IR (KBr): 3035, 2927, 2854, 1642, 1587, 1211, 1132, 1033 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.15–1.37 (m, 18 H), 1.65–1.81 (m, 12 H), 2.92 (dd, *J* = 8.1, 18.4 Hz, 2 H), 2.97 (dd, *J* = 6.5, 18.4 Hz, 2 H), 4.01–4.15 (m, 10 H), 4.16–4.29 (m, 8 H), 4.46–4.52 (m, 1 H), 4.52–4.67 (m, 2 H), 5.10 (s, 4 H), 7.77 (s, 1 H), 7.78 (s, 1 H), 8.33 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1 (d, *J* = 1.5 Hz), 16.2 (d, *J* = 2.2 Hz), 17.7 (d, *J* = 2.1 Hz), 22.7 (d, *J* = 2.2 Hz), 24.9, 26.2, 36.4, 36.8, 39.8, 39.9, 46.7, 63.9 (d, *J* = 3.6 Hz), 64.1 (d, *J* = 3.9 Hz), 74.7 (d, *J* = 6.1 Hz), 82.6 (d, *J* = 7.0 Hz), 83.5 (d, *J* = 7.5 Hz), 118.1, 119.6, 137.7, 150.6, 152.6, 153.9, 154.2, 154.3.

^{31}P NMR (202 MHz, $CDCl_3$): δ = –1.61, –1.80.

MS (ESI): *m*/*z* = 467 $[M + H]^{+\cdot}$, 489 $[M + Na]^{+\cdot}$.

Anal. Calcd for $C_{20}H_{31}N_6O_5P$: C, 51.50; H, 6.70; N, 18.02. Found: C, 51.62; H, 6.74; N, 17.98.

Diethyl {3-[(6-Piperidin-1-yl-9*H*-purin-9-yl)methyl]isoxazol-5-yl}methyl Phosphate (25)

Yield: 85 mg (99%); orange oil.

IR (KBr): 3018, 2931, 2851, 1592, 1480, 1210, 1184, 1139, 1034 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.30 (dt, *J* = 0.9, 7.1 Hz, 6 H), 1.69–1.77 (m, 6 H), 4.04–4.15 (m, 4 H), 4.18–4.30 (m, 4 H), 5.06 (d, *J* = 8.9 Hz, 2 H), 5.44 (s, 2 H), 6.39 (s, 1 H), 7.79 (s, 1 H), 8.35 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1 (d, *J* = 6.6 Hz), 24.8, 26.2, 38.5, 46.6, 59.1 (d, *J* = 4.8 Hz), 64.4 (d, *J* = 6.0 Hz), 103.5, 119.6, 137.5, 150.6, 152.8, 153.9, 159.8, 168.1 (d, *J* = 7.7 Hz).

^{31}P NMR (202 MHz, $CDCl_3$): δ = –1.40.

MS (ESI): *m*/*z* = 451 $[M + H]^{+\cdot}$, 473 $[M + Na]^{+\cdot}$.

Anal. Calcd for $C_{19}H_{27}N_6O_5P$: C, 50.66; H, 6.04; N, 18.66. Found: C, 50.59; H, 6.12; N, 18.57.

Biological Experiments

For the *in vitro* biological assays, test compounds were dissolved in DMSO.

1) RA (%) measurements: interaction with the stable free radical DPPH (final concentration: 0.05 mM) in absolute EtOH (final concentration: 0.1 mM).[14b–d]

2) Lipoxygenase inhibition: the soybean lipoxygenase/linoleic sodium protocol was used.[14b–d]

3) Antilipid peroxidation: the AAPH protocol was performed.[14b–d]

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