View Article Online / Journal Homepage / Table of Contents for this issue
Dynamic Article Links

Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 7730

www.rsc.org/obc

PAPER

One-pot syntheses of novel pyrazole-containing bisphosphonate esters at room temperature†

Haoyue Xiang,[a] Xueyu Qi,[a,b] Yuyuan Xie,[a] Guangyu Xu[b] and Chunhao Yang*[a]

Received 9th May 2012, Accepted 29th July 2012
DOI: 10.1039/c2ob25889g

Published on 02 August 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25889G
Downloaded by University of Arizona on 19 December 2012

An efficient general synthetic approach has been developed to synthesize pyrazole-containing bisphosphonate (N-BPs) esters from chromenone derivatives *via* a sequential two-step reaction in one pot at ambient temperature in good to excellent yields. This protocol provides a new convenient method to prepare lipophilic bisphosphonate precursors with potential activities.

Introduction

Bisphosphonates (BPs) have been reported to exhibit important bioactive properties and are widely used in pharmaceuticals and agrochemicals, such as for the treatment of hypercalcemia[1] and chronic kidney disease,[2] as anti-cancer agents[3] and inhibitors of plant glutamine synthetase,[4] and especially as powerful inhibitors of bone resorption.[5] So far, most of the highly potent third-generation BP drugs against bone resorption contain a nitrogen heterocycle in the molecule, such as risedronate and zoledronate (Fig. 1).[6] These nitrogen-containing bisphosphonates are currently clinically applied widely to treat osteoporosis[6a,7] and Paget's disease,[8] and are the only clinically validated drugs targeting hFPPS.[9] More importantly, N-BPs also display direct anti-tumor activity *in vivo* by inhibiting cancer growth through anti-angiogenic, anti-invasive, and immunomodulatory actions.[10] Recently lipophilic bisphosphonates have attracted more attention because they display potent activities as γδ T cell stimulators,[11] anti-malarial agents,[12,13] anti-infective agents,[13] and anti-cancer agents[14] with improved cell penetration ability. Pyrazole is one important scaffold in medicinal chemistry due to its potential biological activity. Pyrazole derivatives are powerful inhibitors of COX-2,[15] CDK[16] and Hsp90.[17] For example, VER-49009 and CCT018159 (Fig. 1) are potent inhibitors of Hsp90. Therefore, a quick method to a larger number of hybrids containing both bisphosphonates and pyrazole groups would be very useful.

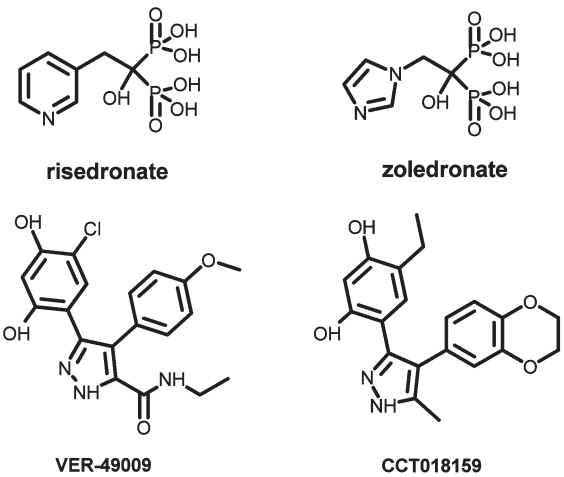


Fig. 1

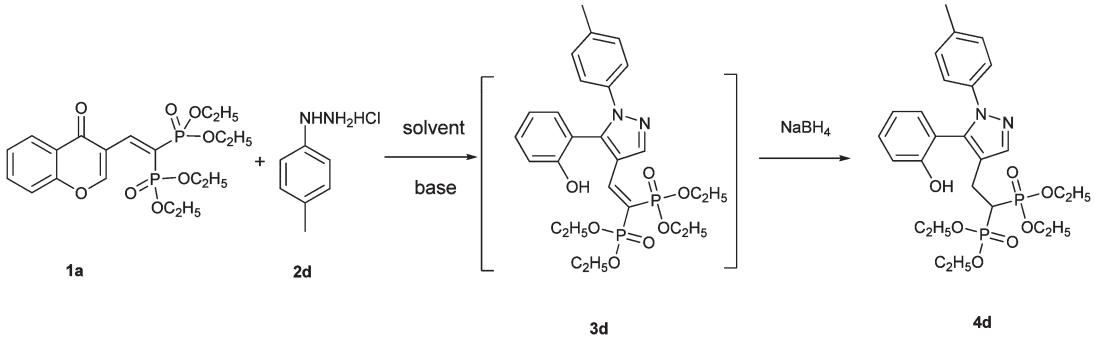
In addition, high throughput screening (HTS) plays an important role in medicinal chemistry, especially in the hit-to-lead process. HTS has seldom been used in bisphosphonate screening due to lack of diversified libraries.[12] Although many ways have been reported to construct bisphosphonates,[18] it is still an urgent task to develop a simple synthetic method for the facile generation of high-quality libraries of bisphosphonates or their precursors.

Recently, chromone-3-carboxaldehyde and chromen-4-one have attracted lots of interest due to their strong electrophilic centres.[19] Several papers have reported the synthesis of *o*-hydroxyphenyl pyrazole through a reaction between chromone and hydrazine.[17a,20] To the best of our knowledge, the synthetic chemistry and biochemistry of chromenone BPs have not been explored. Herein, this work provides a convenient method to prepare lipophilic pyrazole-containing bisphosphonate esters from chromenone derivatives with excellent yields in one pot at ambient temperature.

[a]*State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai, 201203, P. R. China. E-mail: chyang@mail.shcnc.ac.cn; Fax: +86-21-50806770; Tel: +86-21-50806770*
[b]*College of Chemistry and Chemical Engineering, Hunan Normal University, Changsha, 410081, China*

†Electronic supplementary information (ESI) available: The ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra for the final products. See DOI: 10.1039/c2ob25889g

This journal is © The Royal Society of Chemistry 2012



Scheme 1 Model reaction for optimization of reaction conditions.

Table 1 Optimization of reaction conditions[a]

Entry	Solvent	Base (equiv.)	Temperature	Yield[b] (%)
1	EtOH	NaOAc (2)	r.t	85
2	EtOH	K_2CO_3 (2)	r.t	73
3	EtOH	$NaHCO_3$ (2)	r.t	70
4	EtOH	Et_3N (2)	r.t	79
5	EtOH	NaOAc (1.2)	r.t	85
6	EtOH	None	r.t	Trace
7	CH_2Cl_2	NaOAc (2)	r.t	68
8	DMF	NaOAc (2)	r.t	71
9	DME	NaOAc (2)	r.t	75
10	EtOH	NaOAc (1.2)	45	85
11	EtOH	NaOAc (1.2)	Reflux	75

[a] Reaction conditions: **1a** (0.2 mmol), *p*-tolylhydrazine hydrochloride (**2d**) (0.2 mmol), solvent (5 mL), base, $NaBH_4$ (0.6 mmol). [b] Isolated yield.

Table 2 Reaction of **1a** with various hydrazines[a]

Entry	Hydrazine	Product	Yield[b] (%)
1	**2a**	**4a**	60
2	**2b**	**4b**	72
3	**2c**	**4c**	84
4	**2d**	**4d**	85
5	**2e**	**4e**	89
6	**2f**	**4f**	80
7	**2g**	**4g**	94
8	**3h**	**4h**	92
9	**2i**	**4i**	83
10	**2j**	**4j**	90
11	**2k**	**4k**	88
12	**2l**	**4l**	76
13	**2m**	**4m**	85
14	**2n**	**4n**	89
15	**2o**	**4o**	90
16	**2p**	**4p**	80
17	**2q**	**4q**	61
18	**2r**	**4r**	79
19	**2s**	**4s**	81

[a] Reaction conditions: compound **1a** (0.2 mmol), hydrazine or hydrazine hydrochloride **2** (0.2 mmol), EtOH (5 mL), NaOAc (0.24 mmol) $NaBH_4$ (0.6 mmol) at room temperature. [b] Isolated yield.

Results and discussion

At the outset of our study, the reaction of tetraethyl 2-(4-oxo-4*H*-chromen-3-yl)ethene-1,1-diyldiphosphonate (**1a**) prepared according to the literature[21] and *p*-tolylhydrazine hydrochloride (**2d**) (Scheme 1) was used to optimize the reaction conditions (Table 1). Initially, the effect of base was taken into consideration.

We found that both organic base and inorganic base gave the desired product with moderate to good yield (entries 1–4). NaOAc was chosen as the best base for further reactions with consideration of the cost of base and yield of product. The amount of the base was also varied, which indicated that the reaction was not influenced by decreasing the amount of base to 1.2 equivalents (entry 5). Nevertheless, only a trace product was obtained without base (entry 6). After examining the solvents, we found that albeit the effect of solvents for this reaction is subtle, EtOH gave better yield than others (entries 5, 7–9).

Then, the effect of the reaction temperature was investigated. Raising the reaction temperature to 45 °C, the yield of product was almost equivalent to the output at room temperature. Even when the temperature was increased to boiling point, the yield decreased a little bit (entry 11).

Having the optimized reaction conditions (1.2 eq NaOAc, EtOH, r.t. entry 5), we investigated various hydrazines reacting with compound **1a** (Table 2) (Fig. 2). As illustrated in Table 2, aromatic hydrazines with electron-withdrawing or electron-donating substituents at the *ortho*-, *meta*-, or *para* position of the benzene ring were well tolerated. As a result, we found that hydrazine with electron-withdrawing or electron-donating substituents gave higher yields than hydrazinobenzene without any substituent (Table 2, entry 1). However, too strong electron-withdrawing (entries 16, 18) and electron-donating (entry 6) substituents decreased the yields of the desired products slightly. Obviously, the position of the substituents on the phenyl group of hydrazine had a considerable effect on the yield. Compared with the phenyl groups substituted at the *meta*-, or *para*-position, the *ortho*-position substituted phenylhydrazines gave lower yields (entry 2 *versus* 4; 9 *versus* 11; 12 *versus* 14 and 16 *versus* 17), which may be due to the steric hindrance effect of substituted group at the *ortho*-position. Heteroaryl hydrazines such as 5-bromo-2-hydrazinopyridine also reacted smoothly with compound **1a** in good yield (entry 19).

After that, the scope of compounds **1** was extended in this methodology by reaction with **2o**. The results are summarized in Table 3. Compared with entry 1, an electron-donating group (–Me) or withdrawing group (Cl) on the chromone moiety at the 6-position almost gave the same yield (entries 2–3). A hydroxyl group on the chromone provided a much lower yield (entry 4 *versus* 3).

Published on 02 August 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25889G
Downloaded by University of Arizona on 19 December 2012

Published on 02 August 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25889G
Downloaded by University of Arizona on 19 December 2012

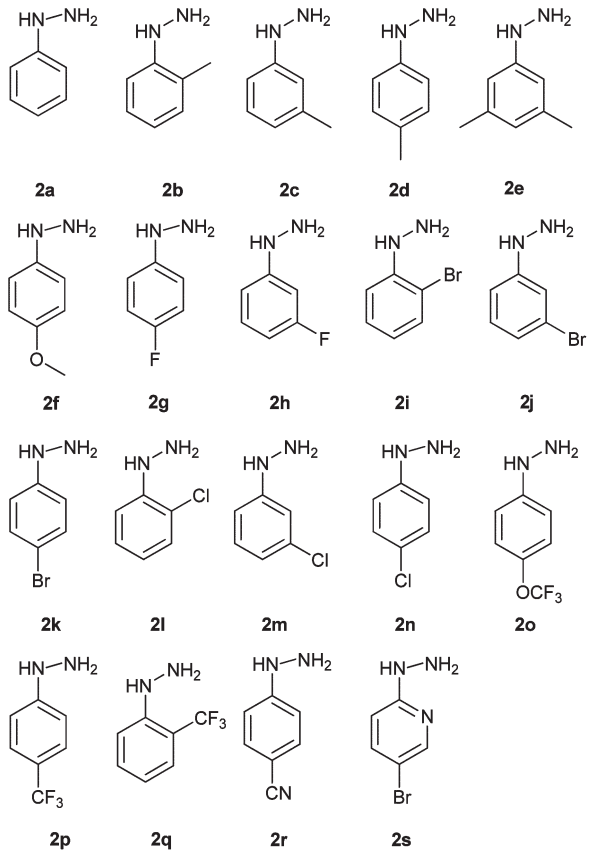
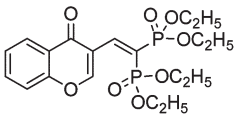
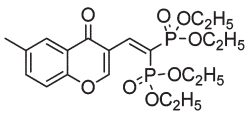
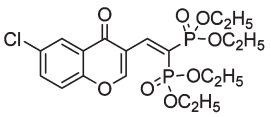
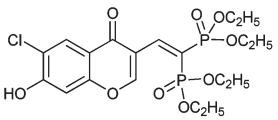


Fig. 2 The various hydrazines investigated.

Table 3 The scope of compounds **1**[a]

Entry	Compounds **1**	Product	Yield[b] (%)
1	 **1a**	**4o**	85
2	 **1b**	**4t**	87
3	 **1c**	**4u**	84
4	 **1d**	**4v**	60

[a] Reaction conditions: compound **1** (0.2 mmol), 4-(trifluoromethoxy)-phenylhydrazine hydrochloride **2o** (0.2 mmol), EtOH (5 mL), NaOAc (0.24 mmol), $NaBH_4$ (0.6 mmol) at room temperature. [b] Isolated yield.

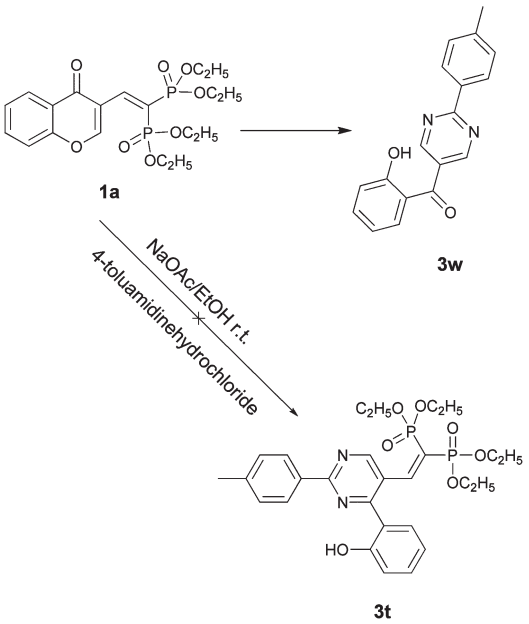


Fig. 3 Reaction with amidine.

To our surprise, when we treated compound **1a** with 4-toluamidine hydrochloride under the optimized conditions, compound **3w** without a bisphosphonate group was detected instead of the expected compound **3t** (Fig. 3), which may be due to the difference of nucleophilic ability of amidine and hydrazine or the preferred attack of amidine to the olefin carbon rather than the carbonyl carbon for steric reasons after attacking the α-carbon.

Conclusions

In summary, we have developed an efficient and useful synthetic method *via* a sequential two-step one-pot reaction to construct various pyrazole-bisphosphonate esters in good to excellent yields. Moreover, the reaction occurred in green solvent under mild conditions with wide scope and high functional tolerance, and the starting materials are readily commercially available and cheap. Further studies of biological activities of these compounds are in progress.

Experimental

General information

Unless otherwise noted, all solvents and other reagents are commercially available and used without further purification. ^{1}H ^{13}C and ^{31}P NMR spectra were recorded on Varian Mercury-300/400 and Varian Mercury-400/500 spectrometers. MS and HRMS spectra were performed on a Finnigan MAT 95 spectrometer. Melting points were measured by Büchi 510 melting point apparatus without further correction.

Preparation of the starting material substituted 3-formyl-4-chromenones[22]

Dimethylformamide (6.0 mL) was cooled in an ice-cold water bath and 2-hydroxyacetophenone (0.01 mmol) was added to this

 This journal is © The Royal Society of Chemistry 2012

Published on 02 August 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25889G
Downloaded by University of Arizona on 19 December 2012

with vigorous stirring; phosphorus oxychloride (2.0 mL) was slowly added into the solution. The pink colour thick mass was kept overnight at room temperature. The mixture was then decomposed by cold water and extracted by EtOAc (3 × 100 mL). Concentrated under reduced pressure, the crude product was further purified by column chromatography (PE : EtOAc 10 : 1).

6-Methyl-4-oxo-4*H*-chromene-3-carbaldehyde

Yellow solid (64%). Mp 164–166 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.38 (s, 1H), 8.52 (s, 1H), 8.07 (s, 1H), 7.55 (d, 1H, J = 8.6 Hz), 7.42 (d, 1H, J = 8.6 Hz), 2.48 (s, 3H). IR (KBr) 3082, 2856, 1695, 1655, 1616, 1485, 949, 891, 825, 773, 545, 486 cm^{-1}.

6-Chloro-4-oxo-4*H*-chromene-3-carbaldehyde

Yellow solid (89%). Mp 94–96 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.36 (s, 1H), 8.54 (s, 1H), 8.25 (d, 1H, J = 2.6 Hz), 7.70 (dd, 1H, J = 8.9, 2.6 Hz), 7.51 (d, 1H, J = 8.9 Hz). IR (KBr) 3074, 2977, 2881, 1651, 1623, 1604, 1568, 1463, 1443, 1388, 1338, 1307, 1089, 1049, 997, 923, 842, 636, 543 cm^{-1}.

6-Chloro-7-hydroxy-4-oxo-4*H*-chromene-3-carbaldehyde

Yellow solid (86%). Mp > 300 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 11.69 (s, 1H), 8.18 (s, 1H), 7.93 (s, 1H), 7.04 (s, 1H), 5.55 (s, 1H). IR (KBr) 3116, 2974, 1635, 1585, 1567, 1388, 1307, 1253, 1097, 1049, 921, 842, 642 cm^{-1}.

General procedure for the syntheses of compounds 1a–1d

Firstly, 100 mL of dry THF was placed in a 250 mL flask and cooled to 0 °C under nitrogen and 3-formylchromone (4 mmol), titanium tetrachloride (1.97 g, 10.4 mmol), tetraethyl methylene-bisphosphonate (1.16 g, 10.4 mmol) and *N*-methylmorpholine (2.1 g, 20.8 mmol) were added successively. Then the mixture was partitioned between EtOAc (100 mL) and H_2O and extracted by EtOAc (100 mL) twice after stirring for 3–4 h at room temperature. The combined the organic layers were washed with aqueous $NaHCO_3$ to neutral, dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure, and then the crude product was further purified by column chromatography (CH_2Cl_2 : MeOH 100 : 0–40 : 1).

General procedure for the syntheses of compounds 4a–4v

Compound **1** (0.2 mmol), NaOAc (0.24 mmol), and hydrazine hydrochloride **2** (0.2 mmol, when free hydrazine used, NaOAc was not necessary) were dissolved in EtOH (5 mL) and the mixture was stirred at room temperature for 2–12 hours until the starting materials disappeared, (monitored by TLC). $NaBH_4$ (0.6 mmol) was added, after compound **1** was completely converted to the intermediate. Then, the ethanol was evaporated under reduced pressure after stirring at room temperature for another 3 hours. The residue was partitioned between 1 N HCl and EtOAc (20 mL). HCl layer was extracted with ethyl acetate (20 mL) twice. The combined the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, the crude product was obtained and further purified by column chromatography (CH_2Cl_2 : MeOH 100 : 0–30 : 1).

Tetraethyl 2-(4-oxo-4*H*-chromen-3-yl)ethene-1,1-diyldiphosphonate (1a)

Yellow solid (56%). Mp 75–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.42–8.13 (m, 2H), 7.71 (ddd, 1H, J = 8.6, 7.2, 1.7 Hz), 7.55–7.38 (m, 2H), 4.26–4.05 (m, 8H), 1.38 (t, 6H, J = 7.1 Hz), 1.25 (t, 6H, J = 7.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.59, 157.80, 156.07, 151.16 (d, J = 3.0 Hz, PC*CH*), 134.24, 126.07, 125.88, 123.78, 122.95 (t, J = 166.8 Hz, P*C*), 119.74 (dd, J = 21.2, 8.4 Hz, PCCH*C*), 118.40, 62.91 (d, J = 5.7 Hz PO*CH*$_2$), 62.88 (d, J = 5.5 Hz PO*CH*$_2$), 16.35 (d, J = 6.5 Hz, POCH$_2$*CH*$_3$), 16.21 (d, J = 6.4 Hz, POCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 32.86 (d, J = 50.1 Hz), 29.72 (t, J = 50.1 Hz). IR (KBr) 3068, 2983, 2904, 1651, 1616, 1581, 1568, 1463, 1245, 1033, 956, 846, 769, 659, 528 cm^{-1}. *m*/*z* (EI): 444 (M$^+$, 4), 307 (100), 171 (22). calcd for $C_{19}H_{26}O_8P_2$, 444.1103; found 444.1103.

Tetraethyl 2-(6-methyl-4-oxo-4*H*-chromen-3-yl)ethene-1,1-diyldiphosphonate (1b)

Yellow solid (52%). Mp 88–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.28 (dd, 1H, J = 47.8, 28.4 Hz), 8.01 (s, 1H), 7.50 (dd, 1H, J = 8.5, 1.7 Hz), 7.38 (d, 1H, J = 8.6 Hz), 4.28–4.14 (m, 4H), 4.16–4.04 (m, 4H), 2.46 (s, 3H), 1.38 (t, 6H, J = 7.1 Hz), 1.24 (t, 6H, J = 7.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.64, 157.76, 154.35, 151.41 (d, J = 3.0 Hz, PC*CH*), 135.98, 135.44, 125.38, 122.56 (t, J = 167.3 Hz, P*C*), 123.44, 119.55 (dd, J = 21.2, 8.4 Hz, PCCH*C*), 118.13, 62.87 (d, J = 6.0 Hz, PO*CH*$_2$), 62.85 (d, J = 5.8 Hz, PO*CH*$_2$), 21.00, 16.35 (d, J = 6.6 Hz, POCH$_2$*CH*$_3$), 16.20 (d, J = 6.0 Hz, POCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 32.98 (d, J = 50.4 Hz), 29.82 (d, J = 50.4 Hz). IR (KBr) 3060, 2981, 2900, 1651, 1618, 1579, 1568, 1481, 1230, 1059, 964, 794, 669, 560 cm^{-1}. *m*/*z* (EI): 458 (M$^+$, 4), 321 (100), 247 (22) 185(23). calcd for $C_{20}H_{28}O_8P_2$, 458.1259; found 458.1265.

Tetraethyl 2-(6-chloro-4-oxo-4*H*-chromen-3-yl)ethene-1,1-diyldiphosphonate (1c)

Yellow solid (52%). Mp 64–65 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.23 (ddd, 1H, J = 48, 30, 0.9 Hz), 8.19 (d, 1H, J = 2.6 Hz) 7.64 (dd, 1H, J = 8.9, 2.6 Hz), 7.46 (d, 1H, J = 8.9 Hz), 4.28–4.04 (m, 8H), 1.38 (t, 6H, J = 7.1 Hz), 1.26 (t, 6H, J = 7.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.47, 157.73, 154.39, 150.62 (d, J = 3.0 Hz, PC*CH*), 134.45, 131.92, 125.49, 124.70, 123.84 (t, J = 166.7 Hz, *PC*), 120.15, 119.82 (dd, J = 21.4, 8.4 Hz, PCCH*C*), 62.95 (t, J = 6.6 Hz, PO*CH*$_2$), 16.36 (d, J = 6.5 Hz, POCH$_2$*CH*$_3$), 16.23 (d, J = 6.4 Hz, POCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 32.57 (d, J = 49.0 Hz), 29.49 (d, J = 49.0 Hz). IR (KBr) 2987, 2906, 1651, 1614, 1589, 1566, 1465, 1439, 1247, 1028, 980, 665 544 cm^{-1}.

Published on 02 August 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25889G
Downloaded by University of Arizona on 19 December 2012

m/z (EI): 478 (M^+, 4), 341 (100), 343 (36) 267 (12) 205 (18). calcd for $C_{19}H_{25}ClO_8P_2$, 478.0713; found 478.0710.

Tetraethyl 2-(6-chloro-7-hydroxy-4-oxo-4*H*-chromen-3-yl)-ethene-1,1-diyldiphosphonate (1d)

Yellow solid (47%). Mp 184–185 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.99 (br s, 1H), 8.62 (s, 1H), 8.26 (dd, 1H, J = 48.9, 27.5 Hz), 8.12 (s, 1H), 6.99 (s, 1H), 4.32–4.08 (m, 8H), 1.40 (t, 6H, J = 7.1 Hz), 1.31 (t, 6H, J = 7.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.75, 158.54, 156.31, 155.79, 152.82 (d, J = 2.4 Hz, PC*CH*), 126.75, 119.47 (dd, J = 20.8, 8.3 Hz, PCCH*C*), 116.88, 103.68, 63.68 (d, J = 6.4 Hz, PO*CH*$_2$), 63.14 (d, J = 6.0 Hz, PO*CH*$_2$), 16.31 (d, J = 6.4 Hz, POCH$_2$*CH*$_3$), 16.14 (d, J = 6.6 Hz, POCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 32.15 (d, J = 50.5 Hz), 29.91 (d, J = 50.5 Hz). IR (KBr) 3068, 2989, 2941, 1645, 1625, 1604, 1587, 1496, 1456, 1251, 1214, 1010, 787, 677, 538 cm^{-1}. *m/z* (EI): 494 (M^+, 4), 385 (44), 387(16) 357(100) 359(100) 221 (22). calcd for $C_{19}H_{25}ClO_9P_2$, 494.0662; found 494.0667.

Tetraethyl 2-(5-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-ethane-1,1-diyldiphosphonate (4a)

Yellow solid (60%). Mp 90–92 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.69 (s, 1H), 7.30–7.25 (m, 2H), 7.25–7.23 (m, 1H), 7.22–7.11 (m, 3H), 7.00–6.89 (m, 2H), 6.83 (t, 1H, J = 7.4 Hz), 4.22–3.84 (m, 8H), 3.28–2.80 (m, 2H), 2.77–2.41 (tt, 1H, J = 24.1, 7.4 Hz), 1.33–1.15 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.45, 140.18, 140.05, 137.19, 131.66, 130.92, 128.60, 126.89, 123.83, 120.39, 119.44 (t, J = 8.8 Hz, PCHCH$_2$*C*), 118.20 (d, J = 6.3 Hz, PCHCH$_2$C*CH*), 118.10 (d, J = 2.5 Hz, PCHCH$_2$C*C*), 62.86 (dd, J = 20.2, 6.1 Hz, PO*CH*$_2$), 62.66 (dd, J = 20.2, 6.1 Hz, PO*CH*$_2$), 37.25 (t, J = 132.3 Hz, P*CH*), 20.59, 16.25 (m, PCH*CH*$_2$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.14. IR (KBr) 3151, 2981, 1612, 1599, 1502, 1446, 1392, 1244, 1219, 1019, 985, 761, 524 cm^{-1}. *m/z* (EI): 536 (M^+, 19), 399 (100), 247 (12). calcd for $C_{25}H_{34}N_2O_7P_2$, 536.1841; found 536.1857.

Tetraethyl 2-(5-(2-hydroxyphenyl)-1-*o*-tolyl-1*H*-pyrazol-4-yl)-ethane-1,1-diyldiphosphonate (4b)

Colorless oil (72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.70 (s, 1H), 7.17–7.10 (m, 4H), 7.07–6.98 (m, 1H), 6.90 (dd, 1H, J = 7.6, 1.6 Hz), 6.85 (d, 1H, J = 8.2 Hz), 6.75 (td, 1H, J = 7.4, 0.8 Hz), 4.20–3.94 (m, 8H), 3.28–2.85 (m, 2H), 2.65 (tt, 1H, J = 23.5, 7.6 Hz), 2.09 (s, 3H), 1.40–1.13 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.26, 139.59, 138.84, 138.54, 135.74, 131.54, 130.68, 130.60, 128.50, 127.73, 125.77, 119.99, 118.23, 118.05–117.74 (m, PCHCH$_2$*C*), 117.53, 62.78 (t, J = 14.4 Hz, PO*CH*$_2$), 37.29 (t, J = 132.9 Hz, P*CH*), 20.69 (t, J = 4.3 Hz, PCH*CH*$_2$), 17.59, 16.57–15.97 (m, POCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.25. IR (KBr) 3394, 3187, 2919, 2740, 2601, 1645, 1614, 1500, 1446, 1386, 1259, 1022, 798, 532 cm^{-1}. *m/z* (EI): 550 (M^+, 10), 413 (100). calcd for $C_{26}H_{36}N_2O_7P_2$, 550.1998; found 550.2007.

Tetraethyl 2-(5-(2-hydroxyphenyl)-1-*m*-tolyl-1*H*-pyrazol-4-yl) ethane-1,1-diyldiphosphonate (4c)

White solid (84%). Mp 92–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.68 (s, 1H), 7.29–7.20 (m, 1H), 7.17 (s, 1H), 7.08–7.03 (m, 1H), 7.01–6.90 (m, 4H), 6.83 (td, 1H, J = 7.4, 1.1 Hz), 4.18–3.92 (m, 8H), 3.24–2.84 (m, 2H), 2.73–2.49 (m, 1H), 2.23 (s, 3H), 1.35–1.15 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.32, 139.97, 139.82, 138.55, 137.02, 128.21, 127.62, 124.49, 120.62, 120.33, 119.30 (dd, J = 10.2, 7.8 Hz, PCHCH$_2$*C*), 118.12, 118.06, 63.01–62.36 (m, PO*CH*$_2$), 37.14 (t, J = 132.7 Hz, P*CH*), 21.20, 20.54 (t, J = 4.3 Hz, PCH*CH*$_2$), 16.21 (dd, J = 9.9, 5.1 Hz, POCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.17, 40.13.

IR (KBr) 3417, 3155, 2981, 1612, 1592, 1496, 1446, 1369, 1261, 1027, 971, 760, 526 cm^{-1}. *m/z* (EI): 550 (M^+, 12), 413 (100), 261(14). calcd for $C_{26}H_{36}N_2O_7P_2$, 550.1998; found 550.1985.

Tetraethyl 2-(5-(2-hydroxyphenyl)-1-*p*-tolyl-1*H*-pyrazol-4-yl) ethane-1,1-diyldiphosphonate (4d)

Yellow solid (85%). Mp 101–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.68 (s, 1H), 7.24 (m, 1H), 7.15 (d, 2H, J = 8.3 Hz), 7.01 (d, 2H, J = 8.2 Hz), 6.94 (m, 2H), 6.85 (t, 1H, J = 7.4 Hz), 4.19–3.95 (m, 8H), 3.22–3.04 (m, 1H), 2.94 (tt, 1H, J = 23.8, 11.9 Hz), 2.61 (tt, 1H, J = 24.4, 7.4 Hz), 2.26 (s, 3H), 1.34–1.19 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.35, 139.86, 137.59, 136.95, 136.75, 131.68, 130.92, 129.23, 123.71, 120.51, 118.44, 119.22–119.37 (m, PCHCH$_2$*C*), 118.28, 63.16–62.31 (m, PO*CH*$_2$), 37.26 (t, J = 133.1 Hz, P*CH*), 20.99, 20.62 (t, J = 4.3 Hz, PCH*CH*$_2$), 16.58–15.89 (m, POCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.14, 40.09. IR (KBr) 3145, 2981, 2929, 1614, 1590, 1519, 1471, 1444, 1392, 1255, 1018, 966, 823, 532 cm^{-1}. *m/z* (EI): 550 (M^+, 12), 413 (100). calcd for $C_{26}H_{36}N_2O_7P_2$, 550.1998; found 550.1995.

Tetraethyl 2-(1-(3,5-dimethylphenyl)-5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4e)

White solid (90%). Mp 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.74 (s, 1H), 7.35–7.29 (m, 1H), 7.04–7.02 (m, 2H), 6.95 (s, 2H), 6.91 (td, 1H, J = 8.1, 0.9 Hz), 6.86 (s, 1H), 4.27–3.98 (m, 8H), 3.30–2.98 (m, 2H), 2.70 (tt, 1H, J = 23.1, 7.5 Hz), 2.23 (s, 6H), 1.41–1.25 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.42, 139.92, 139.82, 138.23, 137.03, 131.70, 130.91, 128.62, 121.52, 120.42, 119.29 (dd, J = 10.1, 8.0 Hz, PCHCH$_2$*C*), 118.24, 118.17, 63.18–62.49 (m, PO*CH*$_2$), 37.26 (t, J = 132.8 Hz, P*CH*), 21.20, 20.66 (t, J = 4.2 Hz, PCH*CH*$_2$), 16.32 (dd, J = 10.0, 5.3 Hz, POCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.19, 40.14. IR (KBr) 3154, 2983, 2943, 1616, 1597, 1510, 1444, 1373, 1251, 1221, 1000, 972, 848, 755, 528 cm^{-1}. *m/z* (EI): 564 (M^+, 12), 427 (100), 275 (8). calcd for $C_{27}H_{38}N_2O_7P_2$, 564.2154; found 564.2153.

Tetraethyl 2-(5-(2-hydroxyphenyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4f)

Yellow solid (80%). Mp 120–122.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.67 (s, 1H), 7.27 (m, 1H), 7.22–7.17

This journal is © The Royal Society of Chemistry 2012

Published on 02 August 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25889G
Downloaded by University of Arizona on 19 December 2012

(m, 2H), 6.96–6.93 (m, 2H), 6.85 (t, 1H, J = 7.4 Hz), 6.77–6.69 (m, 2H), 4.18–3.96 (m, 8H), 3.74 (s, 3H), 3.23–3.05 (m, 1H), 3.00–2.84 (m, 1H), 2.62 (tt, 1H, J = 25.6, 7.6 Hz), 1.36–1.18 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.40, 155.39, 139.61, 137.04, 133.33, 131.70, 130.94, 125.36, 120.53, 119.32–118.83 (m, PCHCH$_2$*C*), 118.59, 118.33, 113.75, 63.08–62.31 (m, PO*CH*$_2$), 55.33, 37.32 (J = 133.6 Hz, P*CH*), 20.63 (t, J = 4.1 Hz, PCH*CH*$_2$), 16.27 (m, POCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.15, 40.09. IR (KBr) 3141, 2981, 2931, 2738, 1730, 1614, 1589, 1518, 1468, 1446, 1369, 1251, 1016, 966, 850, 777, 659, 532 cm^{-1}. m/z (EI): 566 (M$^+$, 12), 429 (100), 167 (26), 149 (68). calcd for $C_{26}H_{36}N_2O_8P_2$, 566.1947; found 566.1952.

Tetraethyl 2-(1-(4-fluorophenyl)-5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4g)

Yellow solid (94%). Mp 64–65 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (br s, 1H), 7.68 (s, 1H), 7.30–7.21 (m, 3H), 6.99–6.83 (m, 5H), 4.20–3.94 (m, 8H), 3.26–2.81 (m, 2H), 2.73–2.47 (m, 1H), 1.32–1.18 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.36 (d, J = 246.7 Hz, F*ArC*), 155.45, 140.05, 137.4, 136.17, 131.61, 131.14, 125.70 (d, J = 8.6 Hz, ArCCH*CH*), 120.63, 119.47 (dd, J = 10.7, 7.6 Hz, PCHCH2*C*), 118.78, 118.16, 115.47 (d, J = 22.8 Hz, ArC*CH*), 63.22–62.37 (m, PO*CH*$_2$), 37.31 (t, J = 133.2 Hz, P*CH*), 16.45–16.05 (m, POCH2*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.05, 40.00. IR (KBr) 3138, 2923, 2850, 1616, 1517, 1467, 1446, 1396, 1365, 1245, 1219, 1029, 966, 850, 760, 532 cm^{-1}. m/z (EI): 554 (M$^+$, 9), 417 (100), 265 (11). calcd for $C_{25}H_{33}FN_2O_7P_2$, 554.1747; found 554.1743.

Tetraethyl 2-(1-(3-fluorophenyl)-5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4h)

Yellow solid (92%). Mp 92–93 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.70 (s, 1H), 7.39–7.27 (m, 1H), 7.22–6.94 (m, 5H), 6.91–6.84 (m, 2H), 4.20–3.91 (m, 8H), 3.26–2.81 (m, 2H), 2.69–2.49 (m, 1H), 1.35–1.15 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.34 (d, J = 246.3 Hz, F*C*), 155.34, 141.30 (d, J = 10.3 Hz, FCCH*C*), 140.46, 137.31, 131.44, 131.18, 129.67 (d, J = 9.0 Hz, FCCH*CH*), 120.63, 120.00–119.70 (m, PCHCH2*CH*), 118.99 (d, J = 2.8 Hz, FCCH*CH*), 118.63, 117.95, 113.67 (d, J = 21.0 Hz, FC*CH*), 111.07 (d, J = 25.3 Hz, FC*CH*), 64.94–60.29 (m, PO*CH*$_2$), 37.15 (t, J = 133.0 Hz, P*CH*), 20.45 (t, J = 4.1 Hz, PCH*CH*$_2$), 16.20 (dd, J = 11.1, 5.3 Hz, POCH2*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.02, 39.96. IR (KBr) 3133, 2985, 2910, 1610, 1600, 1508, 1496, 1496, 1441, 1388, 1367, 1246, 1029, 972, 873, 798, 762, 534 cm^{-1}. m/z (EI): 554(M$^+$, 10), 417 (100), 265 (10). calcd for $C_{25}H_{33}FN_2O_7P_2$, 554.1747; found 554.1763.

Tetraethyl 2-(1-(2-bromophenyl)-5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4i)

Colorless oil (83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.74 (s, 1H), 7.50 (dd, 1H, J = 7.8, 1.5 Hz), 7.36 (dd, 1H, J = 7.7, 1.6 Hz), 7.16 (m, 3H), 7.01 (dd, 1H, J = 7.6, 1.6 Hz), 6.86 (d, 1H, J = 7.3 Hz), 6.76 (td, 1H, J = 7.5, 1.1 Hz), 4.17–3.95 (m, 8H), 3.31–2.86 (m, 2H), 2.66 (tt, 1H, J = 23.6, 7.5 Hz), 1.36–1.17 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.24, 140.24, 139.07, 138.79, 133.06, 131.63, 130.95, 130.24, 129.93, 127.62, 122.2, 120.11, 118.56–118.27 (m, PCHCH$_2$*C*), 118.24, 117.11, 62.84, 37.28 (t, J = 132.9 Hz, PCH), 20.67 (t, J = 4.2 Hz, PCH*CH*$_2$), 16.40. ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.14. IR (KBr) 3417, 3157, 2983, 2931, 2740, 1614, 1589, 1493, 1444, 1390, 1259, 1018, 758, 524 cm^{-1}. m/z (EI): 616 (M$^+$, (Br^{81}), 12), 616 (M$^+$, (Br^{79}), 12), 479 (100), 477(100), 327 (10). 325 (10). calcd for $C_{25}H_{33}BrN_2O_7P_2$, 614.0946; found 614.0940.

Tetraethyl 2-(1-(3-bromophenyl)-5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4j)

White solid (90%). Mp 107–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (br s, 1H), 7.70 (s, 1H), 7.55 (t, 1H, J = 1.9 Hz), 7.33–7.27 (m, 2H), 7.16–7.09 (m, 1H), 7.04 (t, 1H, J = 8.0 Hz), 7.0–6.95 (m, 2H), 6.93–6.85 (m, 1H), 4.19–3.94 (m, 8H), 3.04 (m, 2H), 2.72–2.47 (m, 1H), 1.36–1.15 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.34, 140.99, 140.48, 137.33, 131.47, 131.25, 129.79, 129.72, 126.79, 122.08, 121.85, 120.70, 120.05–119.52 (m, PCHCH$_2$*C*), 118.79, 117.96, 62.77 (m, PO*CH*2), 37.18 (t, J = 133.1 Hz, P*CH*), 20.47 (t, J = 4.1 Hz, PCH*CH*$_2$), 16.22 (dd, J = 11.5, 5.3 Hz, POCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.01, 39.95. IR (KBr) 3133, 2981, 1591, 1579, 1491, 1444, 1387, 1263, 1223, 1028, 970, 850, 789, 526 cm^{-1}. m/z (EI): 616 (M$^+$, (Br^{81}), 12), 616 (M$^+$, (Br^{79}), 12), 479 (100), 477(100), 327 (9). 325 (9). calcd for $C_{25}H_{33}BrN_2O_7P_2$, 614.0946; found, 614.0944 [M$^+$].

Tetraethyl 2-(1-(4-bromophenyl)-5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4k)

Yellow solid (88%). Mp 123–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.69 (s, 1H), 7.36–7.29 (m, 2H), 7.28–7.25 (m, 1H), 7.18–7.11 (m, 2H), 7.00–6.91 (m, 2H), 6.87 (td, 1H, J = 7.4, 1.1 Hz), 4.21–3.89 (m, 8H), 3.25–2.79 (m, 2H), 2.72–2.46 (m, 1H), 1.33–1.17 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.41, 140.44, 139.10, 137.30, 131.74, 131.55, 131.22, 125.18, 120.72, 120.52, 119.87 (dd, J = 10.5, 7.3 Hz, PCHCH$_2$*C*), 118.77, 118.08, 62.82 (m, PO*CH*2), 37.25 (t, J = 133.1 Hz, P*CH*), 20.53 (t, J = 4.2 Hz, PCH*CH*$_2$), 16.66–16.01 (m, POCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.02, 39.97. IR (KBr) 3143, 2980, 1614, 1591, 1495, 1467, 1444, 1390, 1257, 1226, 1045, 1014, 964, 852, 764, 532 cm^{-1}. m/z (EI): 616 (M$^+$, (Br^{81}), 14), 616 (M$^+$, (Br^{79}), 14), 479 (100), 477(100), 327 (10), 325 (10). calcd for $C_{25}H_{33}BrN_2O_7P_2$, 614.0946; found 614.0952.

Tetraethyl 2-(1-(2-chlorophenyl)-5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4l)

Colorless oil (76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.75 (s, 1H), 7.35 (m, 2H), 7.25–7.10 (m, 3H), 7.03–6.94 (m, 1H), 6.86 (d, 1H, J = 8.2 Hz), 6.77 (td, 1H, J = 7.5, 1.1 Hz), 4.22–3.93 (m, 8H), 3.03 (m, 2H), 2.78–2.52 (tt, 1H, J = 23.4,

Published on 02 August 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25889G
Downloaded by University of Arizona on 19 December 2012

7.5 Hz), 1.38–1.15 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.21, 140.37, 138.93, 137.49, 132.27, 131.49, 130.92, 129.94, 129.89, 129.74, 126.94, 120.09, 118.40–118.33 (m, PCHCH$_2$*C*), 118.23, 117.11, 62.82 (t, J = 15.6 Hz, PO*CH*2), 37.26 (t, J = 133.0 Hz, P*CH*), 20.63 (t, J = 4.3 Hz, PCH*CH*$_2$), 16.32. ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.13. IR (KBr) 3392, 3165, 2983, 2931, 2740, 1614, 1591, 1495, 1446, 1390, 1249, 1163, 1028, 966, 758, 532 cm^{-1}. *m/z* (EI): 572 (M^+, (Cl^{37}), 5), 570 (M^+, (Cl^{35}) 17), 435 (34), 433 (100), 281 (11). calcd for $C_{25}H_{33}ClN_2O_7P_2$, 570.1452; found, 570.1444.

Tetraethyl 2-(1-(3-chlorophenyl)-5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4m)

White solid (85%). Mp 104–106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.70 (s, 1H), 7.39–7.38 (m, 1H), 7.35–7.26 (m, 1H), 7.18–7.05 (m, 3H), 7.0–6.95 (m, 2H), 6.89 (td, 1H, J = 7.4, 1.0 Hz), 4.21–3.93 (m, 8H), 3.24–2.85 (m, 2H), 2.71–2.48 (m, 1H), 1.36–1.16 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.43, 141.02, 140.53, 137.40, 134.27, 131.55, 131.31, 129.52, 126.96, 124.02, 121.51, 120.77, 119.97 (dd, J = 10.8, 7.1 Hz, PCHCH$_2$*C*), 118.89, 118.09, 63.37–62.27 (m, PO*CH*$_2$), 37.28 (t, J = 133.2 Hz, P*CH*), 20.54 (t, J = 4.3 Hz, PCH*CH*2), 16.28 (m, POCH$_2$*CH*3). ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.02, 39.94. IR (KBr) 3158, 2981, 1614, 1595, 1487, 1446, 1369, 1251, 1220, 1022, 970, 842, 783, 757, 522 cm^{-1}. *m/z* (EI): 572 (M^+, (Cl^{37}), 5), 570 (M^+, (Cl^{35}) 13), 435 (36), 433 (100), 281 (12). calcd for $C_{25}H_{33}ClN_2O_7P_2$, 570.1452; found 570.1451.

Tetraethyl 2-(1-(4-chlorophenyl)-5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4n)

Yellow solid (89%). Mp 105–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.69 (s, 1H), 7.28 (t, 1H, J = 7.2 Hz), 7.25–7.13 (m, 4H), 7.01–6.92 (m, 2H), 6.87 (t, 1H, J = 7.4 Hz), 4.05 (m, 8H), 3.26–2.81 (m, 2H), 2.59 (tt, 1H, J = 7.4 Hz), 1.36–1.14 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.43, 140.37, 138.60, 137.34, 132.53, 131.56, 131.20, 128.77, 124.91, 120.69, 119.80 (dd, J = 10.7, 7.3 Hz, PCHCH$_2$*C*), 118.76, 118.10, 62.81 (m, PO*CH*2), 37.28 (t, J = 133.6 Hz, P*CH*), 20.54 (t, J = 4.4 Hz, PCH*CH*2), 16.63–16.02 (m, POCH2*CH*3). ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.02, 39.97. IR (KBr) 3143, 2981, 2734, 1616, 1593, 1498, 1469, 1444, 1390, 1369, 1257, 1226, 1167, 1016, 964, 852, 764, 532 cm^{-1}. *m/z* (EI): 572 (M^+, (Cl^{37}) 5), 570 (M^+, (Cl^{35}), 13), 435 (37), 433 (100), 281 (12). calcd for $C_{25}H_{33}ClN_2O_7P_2$, 570.1452; found 570.1448.

Tetraethyl 2-(5-(2-hydroxyphenyl)-1-(4-(trifluoromethoxy)-phenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4o)

White solid (90%). Mp 102–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.70 (s, 1H), 7.37–7.26 (m, 3H), 7.06 (d, 2H, J = 8.5 Hz), 6.96 (dd, 2H, J = 7.3, 2.2 Hz), 6.88 (t, 1H, J = 7.2 Hz), 4.21–3.92 (m, 8H), 3.26–2.80 (m, 2H), 2.60 (tdd, 1H, J = 23.4, 8.4, 6.1 Hz), 1.37–1.15 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.39, 147.52, 140.39, 138.46, 137.34, 131.52, 131.23, 124.88, 121.02, 120.70, 120.28 (q, J = 258.6 Hz, CF3), 120.16–119.40 (m, PCHCH$_2$*C*), 118.81, 118.04, 62.78 (m, PO*CH*$_2$), 37.21 (t, J = 133.1 Hz, P*CH*), 20.50 (t, J = 4.2 Hz, PCH*CH*$_2$), 16.23 (dd, J = 11.5, 5.2 Hz, POCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.01, 39.96. IR (KBr) 3133, 2987, 1616, 1593, 1516, 1467, 1449, 1394, 1371, 1267, 1222, 1165, 1020, 964, 860, 750, 530 cm^{-1}. *m/z* (EI): 620 (M^+, 11), 483 (100), 331 (11). calcd for $C_{26}H_{33}F_3N_2O_8P_2$, 620.1664; found 620.1668.

Tetraethyl 2-(5-(2-hydroxyphenyl)-1-(4-(trifluoromethyl)-phenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4p)

White solid (80%). Mp 142–142.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.73 (s, 1H), 7.47 (d, 2H, J = 8.7 Hz), 7.39 (d, 2H, J = 8.5 Hz), 7.29 (ddd, 1H, J = 8.2, 7.2, 1.9 Hz), 7.02–6.94 (m, 2H), 6.89 (td, 1H, J = 7.4, 1.1 Hz), 4.20–3.91 (m, 8H), 3.18–2.85 (m, 2H), 2.73–2.45 (m, 1H), 1.32–1.13 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.42, 142.80, 140.97, 137.53, 131.49, 131.36, 128.47 (q, J = 32.8 Hz, CF_3ArC), 125.87–125.82 (m, CF_3Ar*CH*), 123.88 (q, J = 272.1 Hz, *CF*$_3$), 123.30, 120.82 (s, 19H), 120.36 (dd, J = 10.6, 7.3 Hz, PCHCH$_2$*C*), 118.83, 118.03, 63.20–62.23 (m, PO*CH*$_2$), 38.27, 37.21, 36.15, 20.49 (t, J = 4.3 Hz, PCH*CH*$_2$), 16.62–16.05 (m, POCH2*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 39.97, 39.92. IR (KBr) 3100, 2987, 1616, 1593, 1523, 1448, 1390, 1326, 1251, 1226, 1201, 1163, 1066, 1024, 962, 845, 754, 532 cm^{-1}. *m/z* (EI): 604 (M^+, 9), 467 (100), 315 (14). calcd for $C_{26}H_{33}F_3N_2O_7P_2$, 604.1715; found 604.1715.

Tetraethyl 2-(5-(2-hydroxyphenyl)-1-(2-(trifluoromethyl)-phenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4q)

White solid (61%). Mp 125–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.72 (s, 1H), 7.69–7.61 (m, 1H), 7.44–7.35 (m, 3H), 7.22–7.12 (m, 1H), 6.95–6.84 (m, 2H), 6.77 (t, 1H, J = 7.4 Hz), 4.23–3.94 (m, 8H), 3.30–2.83 (m, 2H), 2.78–2.53 (m, 1H), 1.41–1.17 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.36, 140.08, 138.88, 137.28, 131.93, 131.61, 130.92, 129.70, 128.81, 127.18, 120.28, 119.00–118.61 (m, PCHCH$_2$*C*), 118.54, 117.36, 62.78 (t, J = 16.5 Hz, PO*CH*2), 37.17 (t, J = 133.4 Hz, P*CH*), 20.55 (t, J = 4.2 Hz, PCH*CH*$_2$), 16.26. ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.11. IR (KBr) 3165, 2985, 1608, 1589, 1510, 1458, 1389, 1321, 1233, 1159, 1036, 964, 860, 754, 536 cm^{-1}. *m/z* (EI): 604 (M^+, 11), 467 (100), 315 (10). calcd for $C_{26}H_{33}F_3N_2O_7P_2$, 604.1715; found 604.1720.

Tetraethyl 2-(1-(4-cyanophenyl)-5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4r)

Yellow solid (79%). Mp 121–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (br, 1H), 7.75 (s, 1H), 7.56–7.46 (m, 2H), 7.42–7.36 (m, 2H), 7.36–7.28 (m, 1H), 6.98 (m, 2H), 6.93 (m, 1H), 4.26–3.84 (m, 8H), 3.25–2.82 (m, 2H), 2.57 (ddd, 1H, J = 23.5, 19.3, 6.0 Hz), 1.35–1.14 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.39, 143.45, 141.41, 137.71, 132.771, 131.59, 131.39, 123.36, 121.04, 120.90–120.76 (m, PCHCH$_2$*C*), 119.19, 118.44, 118.07, 110.00, 62.95 (dd, J = 15.1, 6.3 Hz PO*CH*2), 62.79 (dd, J = 17.6, 6.3 Hz PO*CH*2), 37.20 (t, J = 133.4 Hz,

This journal is © The Royal Society of Chemistry 2012

Published on 02 August 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25889G
Downloaded by University of Arizona on 19 December 2012

P*CH*), 20.42 (m, PCH*CH*$_2$), 16.73–16.06 (m, 4C). ^{31}P NMR (243 MHz, $CDCl_3$) δ 39.85, 39.79. IR (KBr) 3163, 2989, 2898, 2227, 1606, 1513, 1444, 1392, 1290, 1225, 1108, 1018, 987, 877, 852, 754, 658, 538, 482 cm^{-1}. *m/z* (EI): 561 (M^+, 13), 424 (100), 272 (14). calcd for $C_{26}H_{33}N_3O_7P_2$, 561.1794; found 561.1795.

Tetraethyl 2-(1-(5-bromopyridin-2-yl)-5-(2-hydroxyphenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4s)

White solid (81%). Mp 104–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, 1H, *J* = 2.3 Hz), 8.14 (s, 1H), 7.80 (dd, 1H, *J* = 9, 3 Hz), 7.77 (s, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.31 (t, *J* = 8.4 Hz, 1H), 7.04–7.00 (m, 2H), 6.93 (t, 1H, *J* = 7.3 Hz), 4.16–3.90 (m, 8H), 3.19–2.86 (m, 2H), 2.49 (tt, 1H, *J* = 23.1, 7.5 Hz), 1.31–1.17 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.40, 150.82, 148.64, 142.08, 141.1, 137.7, 131.45, 130.98, 121.23, 120.85, 119.40, 119.19, 118.53, 118.24, 62.71 (m, PO*CH*$_2$), 37.24 (t, *J* = 133.1 Hz, P*CH*), 20.46, 16.28 (m, PCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 39.91, 39.66. IR (KBr) 3140, 2987, 1614, 1593, 1577, 1506, 1475, 1400, 1290, 1255, 1203, 1157, 1026, 964, 845, 752, 532 cm^{-1}. *m/z* (EI): 617 (M^+, (Br^{81}), 13), 615 (M^+, (Br^{79}), 13), 480 (100), 478 (100). calcd for $C_{24}H_{32}BrN_3O_7P_2$, 615.0899; found 615.0903.

Tetraethyl 2-(5-(2-hydroxy-5-methylphenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4t)

White solid (87%). Mp 90–91 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.69 (s, 1H), 7.34 (d, 2H, *J* = 9.0 Hz), 7.10–7.08 (d, 3H, *J* = 3.8 Hz), 6.87 (d, 1H, *J* = 8.3 Hz), 6.76 (s, 1H), 4.22–3.91 (m, 8H), 3.28–2.79 (m, 2H), 2.71–2.44 (m, 1H), 2.21 (s, 3H), 1.27 (tt, 12H, *J* = 20.2, 7.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.10, 147.55, 140.34, 138.61, 137.58, 131.95, 131.59, 130.07, 124.84, 121.06, 120.35 (q, *J* = 257.9 Hz, *OCF*$_3$), 119.78 (dd, *J* = 10.9, 7.0 Hz, PCHCH$_2$*C*), 118.95, 118.12, 63.03–62.55 (m, PO*CH*$_2$), 37.27 (t, *J* = 133.1 Hz, P*CH*), 20.56 (t, *J* = 4.1 Hz, PCH*CH*$_2$), 20.36, 16.44–16.09 (m, POCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 40.07 (d, *J* = 4.3 Hz,), 39.92 (d, *J* = 4.1 Hz). IR (KBr) 3141, 2987, 1617, 1513, 1475, 1392, 1263, 1223, 1165, 1165, 1016, 968, 837, 796, 522 cm^{-1}. *m/z* (EI): 634 (M^+, 14), 497 (100), 345 (16). calcd for $C_{27}H_{35}F_3N_2O_8P_2$, 634.1821; found 634.1827.

Tetraethyl 2-(5-(5-chloro-2-hydroxyphenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4u)

White solid (84%). Mp 124–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 7.69 (s, 1H), 7.37–7.27 (m, 2H), 7.25 (dd, 1H, *J* = 8.8 2.7 Hz), 7.10 (d, 2H, *J* = 8.2 Hz), 6.96 (d, 1H, *J* = 2.6 Hz), 6.92 (d, 1H, *J* = 8.8 Hz), 4.08 (dtd, 8H, *J* = 14.2, 7.1, 2.1 Hz), 3.27–3.01 (m, 1H), 3.00–2.79 (m, 1H), 2.58 (tdd, 1H, *J* = 23.5, 9.2, 5.9 Hz), 1.40–1.18 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.46, 147.83, 140.37, 138.28, 136.21, 131.24, 130.94, 125.35, 125.07, 121.19, 120.63, 120.34 (q, *J* = 258.3 Hz, O*CF*$_3$), 120.12 (dd, *J* = 11.0, 6.7 Hz, PCHCH$_2$*C*), 119.97, 63.21–62.64 (m, PO*CH*$_2$), 37.40 (t, *J* = 133.4 Hz, P*CH*), 20.49 (t, *J* = 4.4 Hz, PCH*CH*$_2$), 16.27 (dd, *J* = 13.6, 6.0 Hz, POCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 39.81, 39.78. IR (KBr) 3073, 2985, 1608, 1516, 1467, 1444, 1408, 1394, 1263, 1223, 1162, 1022, 968, 837, 651 cm^{-1}. *m/z* (EI): 656 (M^+, (Cl^{37}), 4), 654 (M^+, (Cl^{35}), 12), 519 (37), 517 (100), 463 (35). calcd for $C_{26}H_{32}ClF_3N_2O_8P_2$, 654.1275 found 654.1269.

Tetraethyl 2-(5-(5-chloro-2,4-dihydroxyphenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-pyrazol-4-yl)ethane-1,1-diyldiphosphonate (4v)

White solid (60%). Mp 156–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (br s, 1H), 8.21 (br s, 1H), 7.64 (s, 1H), 7.40–7.32 (m, 2H), 7.13 (s, 1H), 7.10 (d, 2H, *J* = 8.2 Hz), 6.87 (s, 1H), 4.18–3.80 (m, 8H), 3.13–2.92 (m, 2H), 2.68 (tt, 1H, *J* = 24.0, 7.1 Hz), 1.30 (td, 6H, *J* = 7.1, 4.4 Hz), 1.22 (td, 6H, *J* = 7.0, 4.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.31, 154.85, 147.52, 140.78, 138.49, 136.82, 131.27, 124.82, 121.14, 119.80–119.54 (m, PCHCH$_2$*C*), 111.61, 109.06, 105.33, 63.09–62.88 (m, PO*CH*$_2$), 37.10 (t, *J* = 133.6 Hz, P*CH*), 20.67, 16.37–15.92 (m, POCH$_2$*CH*$_3$). ^{31}P NMR (243 MHz, $CDCl_3$) δ 39.69 (s), 39.54 (s). IR (KBr) 3219, 2989, 1621, 1603, 1514, 1423, 1392, 1261, 1225, 1166, 1024, 979, 850, 810, 531 cm^{-1}. *m/z* (EI): 672 (M^+, (Cl^{37}), 4), 670 (M^+, (Cl^{35}), 12), 535 (33), 533 (100), 345 (16). calcd for $C_{26}H_{32}ClF_3N_2O_9P_2$, 670.1224; found 670.1217.

Tetraethyl 2-(5-(2-hydroxyphenyl)-1-(4-(trifluoromethyl) phenyl)-1*H*-pyrazol-4-yl)ethene-1,1-diyldiphosphonate (3p)

Yellow solid. Mp 91–92 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.72 (s, 1H), 7.75 (d, 2H, *J* = 8.5 Hz), 7.53 (dd, 1H, *J* = 46.2, 29.1 Hz), 7.47 (d, 2H, *J* = 8.5 Hz,), 7.35 (t, 1H, *J* = 7.8 Hz), 7.15 (d, 1H, *J* = 7.5 Hz,), 6.98–6.83 (m, 2H), 4.20–3.80 (m, 8H), 1.30–1.17 (m, 6H), 1.13 (t, 6H, *J* = 7.0 Hz). IR (KBr) 3427, 2916, 1610, 1628, 1576, 1513, 1486, 1442, 1385, 1336, 1246, 1178, 935, 798, 756, 677 cm^{-1}.

(2-Hydroxyphenyl)(2-*p*-tolylpyrimidin-5-yl)methanone (3w)

Yellow solid. Mp 154–156 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.81 (s, 1H), 9.09 (s, 2H), 8.44 (d, 2H, *J* = 8.2 Hz), 7.59 (t, 2H, *J* = 8.7 Hz), 7.35 (d, 2H, *J* = 8.3 Hz), 7.12 (d, 1H, *J* = 8.7 Hz), 6.96 (t, 1H, *J* = 7.6 Hz), 2.46 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.02 166.58, 163.26, 157.64, 142.61, 137.34, 133.77, 132.55, 129.65, 128.92, 128.55, 119.33, 118.95, 118.91, 21.65. IR (KBr) 3423, 3131, 2988, 1616, 1589, 1522, 1469, 1448, 1392, 1367, 1325, 1213, 1166, 1128, 1063, 1022, 962, 845, 757, 613, 532 cm^{-1}. *m/z* (EI): 290 (M^+, 100), 272 (32%). calcd for $C_{18}H_{14}N_2O_2$, 290.1055; found 290.1054.

Acknowledgements

This work was financially supported by the "Interdisciplinary Cooperation Team" Program for Science and Technology Innovation of the Chinese Academy of Sciences, the National

Natural Science Foundation of China (No. 20602010), and SIMM1203ZZ-0103.

Notes and references

1 K. Onizawa and H. Yoshida, *Head Face Med.*, 2006, **2**, 9.
2 R. Amerling, N. B. Harbord, J. Pullman and D. A. Feinfeld, *Blood Purif.*, 2010, **29**, 293–299.
3 (*a*) Y. Zhang, A. Leon, Y. Song, D. Studer, C. Haase, L. A. Koscielski and E. Oldfield, *J. Med. Chem.*, 2006, **49**, 5804–5814; (*b*) J. R. Green, *Oncologist*, 2004, **9**(Suppl. 4), 3–13.
4 A. Obojska, L. Berlicki, P. Kafarski, B. Lejczak, M. Chicca and G. Forlani, *J. Agric. Food Chem.*, 2004, **52**, 3337.
5 (*a*) A. Balakrishna, M. V. Narayana Reddy, P. V. Rao, M. A. Kumar, B. S. Kumar, S. K. Nayak and C. S. Reddy, *Eur. J. Med. Chem.*, 2011, **46**, 1798–1802; (*b*) R. G. Russell, *Pediatrics*, 2007, **119**(Suppl 2), S150–S162; (*c*) R. S. Ehrick, M. Capaccio, D. A. Puleo and L. G. Bachas, *Bioconjugate Chem.*, 2008, **19**, 315–321.
6 (*a*) B. Pan, A. N. Farrugia, L. B. To, D. M. Findlay, J. Green, K. Lynch and A. C. W. Zannettino, *J. Bone Miner. Res.*, 2004, **19**, 147–154; (*b*) B. Pan, L. B. To, A. N. Farrugia, D. M. Findlay, J. Green, S. Gronthos, A. Evdokiou, K. Lynch, G. J. Atkins and A. C. W. Zannettino, *Bone (San Diego, CA, U.S.)*, 2004, **34**, 112–123; (*c*) F. Saad and P. Mulders, *Anti-Cancer Agents Med. Chem.*, 2012, **12**, 129–136.
7 A. A. Reszka and G. A. Rodan, *Mini-Rev. Med. Chem.*, 2004, **4**, 711–719.
8 J. Donath, M. Krasznai, B. Fornet, P. Gergely Jr. and G. Poor, *Rheumatology*, 2004, **43**, 89–94.
9 Y.-S. Lin, J. Park, J. W. De Schutter, X. F. Huang, A. M. Berghuis, M. Sebag and Y. S. Tsantrizos, *J. Med. Chem.*, 2012, **55**, 3201–3215.
10 (*a*) D. Simoni, N. Gebbia, F. P. Invidiata, M. Eleopra, P. Marchetti, R. Rondanin, R. Baruchello, S. Provera, C. Marchioro, M. Tolomeo, L. Marinelli, V. Limongelli, E. Novellino, A. Kwaasi, J. Dunford, S. Buccheri, N. Caccamo and F. Dieli, *J. Med. Chem.*, 2008, **51**, 6800–6807; (*b*) P. Clézardin, F. H. Ebetino and P. G. J. Fournier, *Cancer Res.*, 2005, **65**, 4971–4974.
11 Y. Zhang, R. Cao, F. Yin, F. Y. Lin, H. Wang, K. Krysiak, J. H. No, D. Mukkamala, K. Houlihan, J. Li, C. T. Morita and E. Oldfield, *Angew. Chem., Int. Ed.*, 2010, **49**, 1136–1138.
12 J. H. No, F. de Macedo Dossin, Y. Zhang, Y.-L. Liu, W. Zhu, X. Feng, J. A. Yoo, E. Lee, K. Wang, R. Hui, L. H. Freitas-Junior and E. Oldfield, *Proc. Natl. Acad. Sci. U. S. A.*, 2012, **109**, 4058–4063.
13 A. P. Singh, Y. Zhang, J. H. No, R. Docampo, V. Nussenzweig and E. Oldfield, *Antimicrob. Agents Chemother.*, 2010, **54**, 2987–2993.
14 Y. Zhang, R. Cao, F. Yin, M. P. Hudock, R.-T. Guo, K. Krysiak, S. Mukherjee, Y.-G. Gao, H. Robinson, Y. Song, J. H. No, K. Bergan, A. Leon, L. Cass, A. Goddard, T.-K. Chang, F.-Y. Lin, E. V. Beek, S. Papapoulos, A. H. J. Wang, T. Kubo, M. Ochi, D. Mukkamala and E. Oldfield, *J. Am. Chem. Soc.*, 2009, **131**, 5153–5162.
15 S. K. Singh, P. G. Reddy, K. S. Rao, B. B. Lohray, P. Misra, S. A. Rajjak, Y. K. Rao and A. Venkateswarlu, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 499–504.
16 V. Krystof, P. Cankar, I. Frysova, J. Slouka, G. Kontopidis, P. Dzubak, M. Hajduch, J. Srovnal, W. F. de Azevedo, M. Orsag, M. Paprskarova, J. Rolcik, A. Latr, P. M. Fischer and M. Strnad, *J. Med. Chem.*, 2006, **49**, 6500–6509.
17 (*a*) B. W. Dymock, X. Barril, P. A. Brough, J. E. Cansfield, A. Massey, E. McDonald, R. E. Hubbard, A. Surgenor, S. D. Roughley, P. Webb, P. Workman, L. Wright and M. J. Drysdale, *J. Med. Chem.*, 2005, **48**, 4212–4215; (*b*) P. A. Brough, W. Aherne, X. Barril, J. Borgognoni, K. Boxall, J. E. Cansfield, K.-M. J. Cheung, I. Collins, N. G. M. Davies, M. J. Drysdale, B. Dymock, S. A. Eccles, H. Finch, A. Fink, A. Hayes, R. Howes, R. E. Hubbard, K. James, A. M. Jordan, A. Lockie, V. Martins, A. Massey, T. P. Matthews, E. McDonald, C. J. Northfield, L. H. Pearl, C. Prodromou, S. Ray, F. I. Raynaud, S. D. Roughley, S. Y. Sharp, A. Surgenor, D. L. Walmsley, P. Webb, M. Wood, P. Workman and L. Wright, *J. Med. Chem.*, 2007, **51**, 196–218; (*c*) R. Baruchello, D. Simoni, G. Grisolia, G. Barbato, P. Marchetti, R. Rondanin, S. Mangiola, G. Giannini, T. Brunetti, D. Alloatti, G. Gallo, A. Ciacci, L. Vesci, M. Castorina, F. M. Milazzo, M. L. Cervoni, M. B. Guglielmi, M. Barbarino, R. Foderà, C. Pisano and W. Cabri, *J. Med. Chem.*, 2011, **54**, 8592–8604.
18 (*a*) J. Gao, X. Chu, Y. Qiu, L. Wu, Y. Qiao, J. Wu and D. Li, *Chem. Commun.*, 2010, **46**, 5340–5342; (*b*) W. M. Abdou, N. A. Ganoub, A. F. Fahmy and A. A. Shaddy, *Monatsh. Chem.*, 2006, **137**, 105–116; (*c*) H. Skarpos, S. N. Osipov, D. V. Vorob'eva, I. L. Odinets, E. Lork and G. V. Roschenthaler, *Org. Biomol. Chem.*, 2007, **5**, 2361–2367.
19 V. Y. Sosnovskikh, V. S. Moshkin and M. I. Kodess, *Tetrahedron*, 2008, **64**, 7877–7889.
20 (*a*) D. Pinto, A. Silva and J. J. Cavaleiro, *Tetrahedron*, 1999, **55**, 10187–10200; (*b*) F. Xie, G. Cheng and Y. Hu, *J. Comb. Chem.*, 2006, **8**, 286–288.
21 H. Ding, G. Xu, J. Wang, Y. Zhang, X. Wu and Y. Xie, *Heteroat. Chem.*, 2004, **15**, 549–555.
22 R. G. Nandgaonkar and V. N. Ingle, *Asian J. Chem.*, 2005, **17**, 2016–2018.

Published on 02 August 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25889G
Downloaded by University of Arizona on 19 December 2012

 This journal is © The Royal Society of Chemistry 2012