Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 43 (2008) 1015–1024
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

Synthesis, properties, and perspectives of *gem*-diphosphono substituted-thiazoles

Wafaa M. Abdou [a,*], Neven A. Ganoub [a], Athina Geronikaki [b], Eman Sabry [a]

[a] *Pesticide Chemistry Department, National Research Centre, Elbohouth Street, D-12622 Dokki, Cairo, Egypt*
[b] *School of Pharmacy, Aristotle, Thessaloniki University, Thessaloniki, Greece*

Received 28 April 2007; received in revised form 6 July 2007; accepted 9 July 2007
Available online 27 July 2007

Abstract

A series of substituted arylidene thiazoles were allowed to react with Wittig–Horner (WH) reagent, tetraethyl methyl-1,1-bisphosphonate, to produce via Michael addition reaction the corresponding heteroarylmethylenebisphosphonates (BPs) in different yields according to the experimental conditions. Acid hydrolysis of the new BPs was undertaken to obtain the corresponding bisphosphonic acids. Prediction and the in vivo activity of the products in the rat adjuvant model are also discussed in terms of structure–activity relationships (SAR).

Keywords: Drug research; Chronic inflammation; Bone resorption; Heteroarylmethylene-1,1-bisphosphonates; α-Phosphonate carbanions

1. Introduction

In our research program on synthesis and antiresorptive potency of a variety of bisphosphonates (BPs) and their related bisphosphonic acids (BP acids) [1–3], it was of interest to introduce another series of these compounds for investigating the structure–activity relationships (SAR). Bisphosphonic acids **I** are synthetic stable analogs of naturally occurring inorganic pyrophosphoric acid **II**, which are resistant to breakdown by enzymatic hydrolysis (Fig. 1) [4,5].

Fig. 1.

This structural analogy and increased stability enabled *gem*-diphosphonates and their related bisphosphonic acids to have high affinity for bone minerals and to accumulate preferentially under the osteoclast so that high concentration can be reached [6,7]. Thus, they can be used in bone scintigraphy [8,9] for the treatment of Paget's disease [10,11] as well as for the preventive treatment of osteoporosis [12] and hypercalcemia of malignant tumors [6,7]. Furthermore, the anti-inflammatory potential of bisphosphonic acids is also tested [13–15]. For example, studies in the rat adjuvant arthritis model with these drugs, especially risedronate [15], demonstrated significant suppression of bone erosion in the joint and consistently revealed significant inhibition of inflammation.

In one of the preceding articles [1–3], we reported a simple and efficient procedure for the synthesis of several examples of *N*-heterocycle substituted-methylene-1,1-bisphosphonic acids **3** derived from the reaction of the parent olefin of different heterocyclic species with tetraethyl methylene-1,1-bisphosphonate (**1**), followed by acid hydrolysis (Scheme 1) [3].

In this communication, our studies focused on thiazole heterocycles with different substituted arylidene species, taking into account that the most active BPs were found in the series in which thiazole (or imidazole) residues were linked via

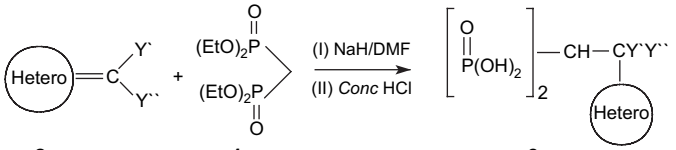
* Corresponding author. Fax: +20 2 7601877.
E-mail address: wabdou@intouch.com (W.M. Abdou).

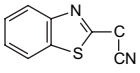
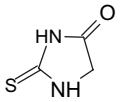
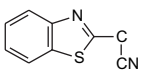
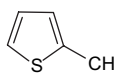
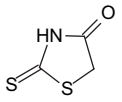
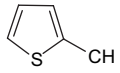
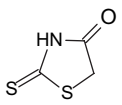
0223-5234/$ - see front matter © 2007 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2007.07.005

a single methylene to C(1)–P_2. Extension of the links causes a marked loss of activity [16]. Furthermore, the prospective potency of our products as antiresorptive agents for treating the inflammatory joint disease as well as other chronic inflammatory diseases was based on the results of the prediction that had been carried out, in the earlier stage. The computer-assisted molecular modeling (CAMM), PASS program, was adopted for designing – in silico – the structures of potentially active molecules for future synthesis. Later on, the in vivo activity of the synthesized BP-acids in the rat adjuvant model from previous [3] and present work was also studied in terms of structure–activity relationships (SAR).

2. Chemistry

In our present systematic study [3], 2-arylidene-cyanomethyl-1,3-benzothiazoles **4** were treated with a little excess of molar amount of tetraethyl methyl-1,1-bisphosphonate (**1**) in dimethylformamide (DMF) containing thrice the amount of NaH at room temperature for the proper time (TLC), poured into ice-water and acidified with conc. HCl. The product mixture was easily separated by solvent extraction and purified by column chromatography to give tetraethyl 2-arylidene-2-(1′, 3′-benzothiazol-2′-yl)ethyl-1,1-bisphosphonates **7** as a major products (71–76%) together with tetraethyl 3-cyano-2-aryl-3(1′,3′-benzothiazol-2′-yl)propanyl-1,1-bisphosphonates **5** (≤7%). Obviously, Michael addition of **1** to **4** at the β-carbon to the cyano group afforded compounds **5** whereas coupling of **4** with **1** with concomitant loss of HCN afforded vinylbisphosphonates **7** [3,17–19].



2&3	Hetero-species	Y`, Y``	2&3	Hetero-species	Y`, Y``
a		H, Ph	e		H, Ph
b		H, furyl	f		CN, CO_2Et
c		H, Ph	g		$(CN)_2$
d		H, p-$C_6H_4NMe_2$			

Scheme 1.

3. Results and discussion

Only one isomer of the respective bisphosphonates **5a–f** was isolated. The configuration of the *exo*-heterocyclic substituents was examined by NMR analysis. The ^{1}H NMR spectrum of **5a**, taken as an example revealed three types of methine protons with different chemical shifts at δ 2.98 (dd, $J_{HH} = 9$ Hz, $^2J_{HP} = 12.8$ Hz, 1H, H^aC), 3.67 (ddd, $J_{HH} = 9$, 11 Hz, $^3J_{P-H} = 4$ Hz, 1H, H^bC), 4.54 (dd, $J_{HH} = 11$ Hz, $^4J_{P-H} = 2.9$ Hz, 1H, CH^c). This large coupling constant (J_{HH}) of H^b with H^a as well as with H^c clearly indicates that H^b is in a *trans*-configuration to H^a and H^c [20]. The unique structure of **5a–f** was also verified by careful inspection of a model in terms of the Newman projection, which confirmed the staggered *anti*-conform for the adducts **5a–f** [21,22].

On the other hand, the vinylbisphosphonates **7a–f** were isolated exclusively in the *Z*-configuration, which was established by NMR analysis. In the ^{1}H NMR spectrum of **7a** the vinyl proton on C3 appeared as an ill-defined doublet of doublet ($^4J_{HH} = 1.1$ Hz, $^4J_{P-H} = 3.2$ Hz, H^b) at 7.31 ppm while the CH^a–P_2 proton (dd, $^4J_{HH} = 1.1$ Hz, $^2J_{HP} = 24$ Hz) was deshielded at 5.04 ppm. According to the small allylic (H–C–C=C–H–) coupling constant ($^4J_{HH} = 0.9$–1.3 Hz) of the allylic moiety and the large P–H coupling constant of H^b ($^4J_{P-H} = 3.2$–3.8 Hz) as well as the result of the inspection of a model in terms of the Newman projection [21,22], adducts **7** should be in the *syn*-configuration of the H-3-proton to H-1-proton.

In the case of **7d** the configuration at the exocyclic double bond was examined by selective NOE experiments, which were also useful for the assignment of the ^{13}C NMR signals. The irradiation of CH^b proton (7.35 ppm) resulted only in the enhancement of the 1-C-triplet (40.03 ppm) and the C-2-doublet (144.6 ppm). Irradiation of the CH^a proton (5.16 ppm) produced an NOE at the 3-C-doublet (139.2 ppm) and at the 2-C-doublet (144.6 ppm), indicating the *syn*-configuration of the H^a proton and the H^b proton.

Next, it was found that when the above reaction (**4** + **1**) was allowed to proceed in absolute ethanol containing sodium ethanolate (*EtONa*), the reaction required less time to complete, yielding **5** and **7** in almost equal yields (≈38%).

Furthermore, the enormous growth in the use of microwave irradiation [23] in synthetic organic chemistry inspired us to perform the same reactions (**4a–f** + **1**) to achieve, under microwave conditions, significantly remarkable rate enhancements and drastic reduction of reaction time. Thus, when the arylidenes **4** and the phosphonyl carbanion **1** were mixed in EtONa/EtOH/DMF solution and heated in a microwave oven, the Michael products **5** were exclusively obtained (≥85%) in 2–5 min see Table 1.

In our earlier study, we reported that treatment of 5-arylidene-2-thioxo-4-thiazolidinones **9a**,**b** with the carbanion **1** afforded the bisphosphonates **11a**,**b** as the major products (≈47%) along with the monophosphonates **10a**,**b** in ≅25% yield (Scheme 3) [3]. In this context, the reaction of **9a**,**b** with **1** was repeated, under the microwave conditions, to achieve BPs in better yields. However, when **9a**,**b** and **1** were mixed in 1:1.5 ratio in DMF containing EtONa solution

Table 1
Reactions of the substrates **4a–f** and **9a–f** with Wittig–Horner reagent **1** under different conditions

Entry	Ar (Ph–R)	Conditions/temp.	Time (h)	Products	Yield (%)	MP (°C)
1 + 4a	NMe_2-*p*	NaH/DMF/r.t.	2 days	**5a**	≤5	205–207[b]
				7a	71	193–195[c]
1 + 4a	NMe_2-*p*	EtONa/EtOH/r.t.	30 h	**5a**	33	–
				7a	42	
1 + 4a	NMe_2-*p*	EtONa/EtOH/DMF/microwave oven	3 min	**5a**	88	–
1 + 4b	Me-*p*	NaH/DMF/r.t.	2 days	**5b**	7	162–164[c]
				7b	75	147–149[d]
1 + 4b	Me-*p*	EtONa/EtOH/r.t.	30 h	**5b**	32	–
				7b	36	
1 + 4b	Me-*p*	EtONa/EtOH/DMF/microwave oven	3 min	**5b**	86	–
1 + 4c	NO_2-*o*	NaH/DMF/r.t.	3 days	**5c**	≤5	217–218[b]
				7c	74	171–173[d]
1 + 4c	NO_2-*o*	EtONa/EtOH/r.t.	2 days	**5c**	35	–
				7c	38	
1 + 4c	NO_2-*o*	EtONa/EtOH/DMF/microwave oven	5 min	**5c**	92	–
1 + 4d	NO_2-*p*	NaH/DMF/r.t.	3 days	**5d**	8	247–249[d]
				7d	74	213–215[b]
1 + 4d	NO_2-*p*	EtONa/EtOH/r.t.	2 days	**5d**	35	–
				7d	40	
1 + 4d	NO_2-*p*	EtONa/EtOH/DMF/microwave oven	5 min	**5d**	92	–
1 + 4e	Cl-*o*	NaH/DMF/r.t.	2 days	**5e**	8	156–158[e]
				7e	74	133–135[f]
1 + 4e	Cl-*o*	EtONa/EtOH/r.t.	30 h	**5e**	34	–
				7e	36	
1 + 4e	Cl-*o*	EtONa/EtOH/DMF/microwave oven	2 min	**5e**	90	–
1 + 4f	Cl-*p*	NaH/DMF/r.t.	2 days	**5f**	7	209–211[d]
				7f	76	188–190[b]
1 + 4f	Cl-*p*	EtONa/EtOH/r.t.	30 h	**5f**	34	–
				7f	48	
1 + 4f	Cl-*p*	EtONa/EtOH/DMF/microwave oven	5 min	**5f**	90	–
1 + 9a	H	EtONa/EtOH/DMF/microwave oven	10 min	**11a**	85	112–114[f]
1 + 9b	NMe_2-*p*	EtONa/EtOH/DMF/microwave oven	8 min	**11b**	87	155–157[e]
1 + 9c	NO_2-*o*	EtONa/EtOH/DMF/microwave oven	12 min	**11c**	84	163–165[e]
1 + 9d	NO_2-*p*	EtONa/EtOH/DMF/microwave oven	12 min	**11d**	84	212–214[d]
1 + 9e	Cl-*o*	EtONa/EtOH/DMF/microwave oven	9 min	**11e**	90	141–143[f]
1 + 9f	OH-*o*	EtONa/EtOH/DMF/microwave oven	12 min	**11f**	82	135–137[e]

[a] See Section 7 for further details.
[b] Solvent of crystallization: acetonitrile.
[c] Solvent of crystallization: $CHCl_3$.
[d] Solvent of crystallization: EtOH.
[e] Solvent of crystallization: CH_2Cl_2.
[f] Solvent of crystallization: cyclohexane.

(5 mL) and heated in a microwave oven, the bisphosphonates **11a**,**b** were exclusively obtained (≥85% yield) in 8–12 min (see Table 1) after the usual working up. Efforts for detecting and/or separating the, previously obtained, monophosphonates **10** from the reaction mixtures of **9** and **1** were unsuccessful.

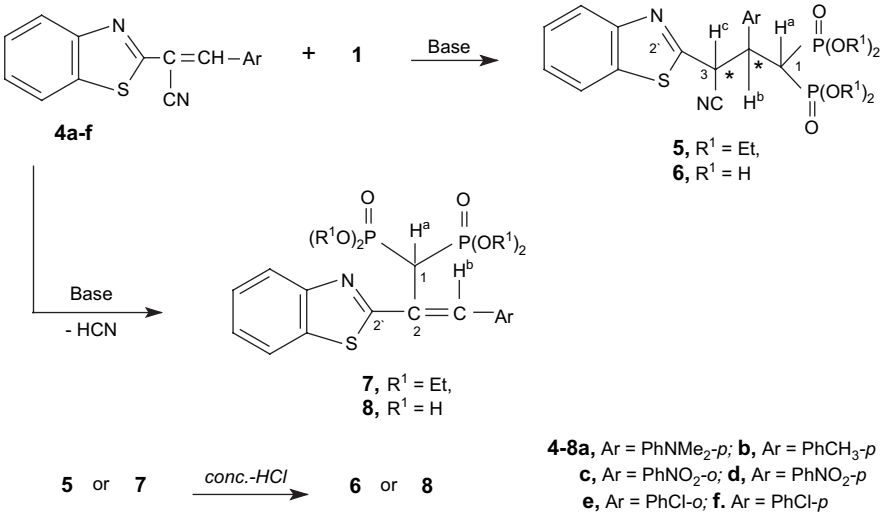
Similar sequence was applied to other arylidenes for the synthesis of more derivatives of bisphosphonate analogs **11c–f** via applying the Wittig–Horner reagent **1** on the parent arylidenes **9c–f** under microwave conditions (Table 1). Elemental analyses and spectral data substantiated the chemical structure **11**. The configuration of the *exo*-hetrocyclic substituents was examined by careful NMR analysis of the three exocyclic methine protons H^a, H^b and H^c (Table 5) as well as by the inspection of a model in terms of the Newman projection [21,22] and by analogy with structure **5** that confirmed the staggered *anti*-conform for the adducts **11a–f**.

As structure–activity studies in several pharma laboratories have identified impressively distinct therapeutic characteristics from 1,1-bisphosphonic acid to 1,1-bisphosphonate ester counterparts [4,5], hydrolysis of the synthesized BPs **5a–f**, **7a–f** and **11a–f** was undertaken to give the corresponding BP acids (*E*)-**6a–f**, (*Z*)-**8a–f** and (*E*)-**12a–f** (Schemes 2 and 3).

The structures suggested for all new compounds are in good agreement with their analytical and spectral data (Tables 4–6).

4. Prediction

Prediction of antiresorptive activity as well as anti-inflammatory was made at the earlier stage of the designed series **6a–f**, **8a–f** and **12a–f** using PASS software [24,25]. The prediction result is presented as a list of activities (Tables 2



Scheme 2.

and 3) with appropriate P_a and P_i, which are the estimates of probability to be active and inactive, respectively.

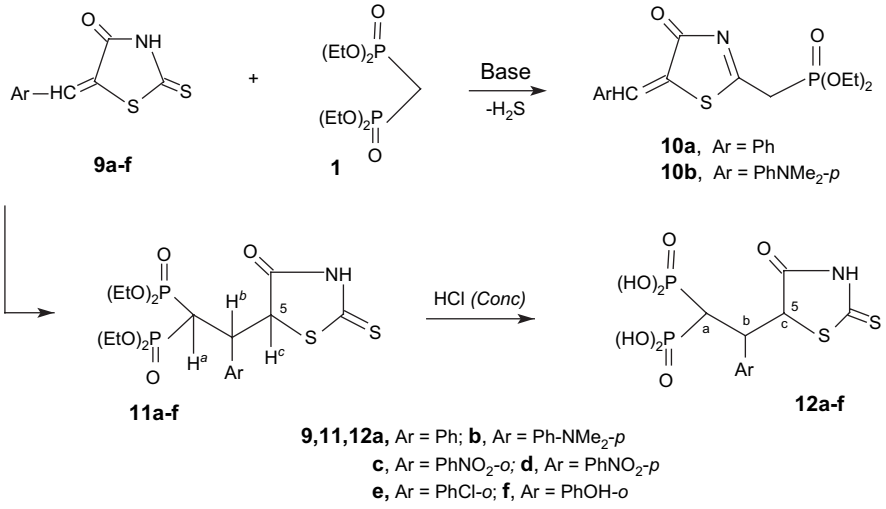
An important criterion for selecting the more prospective compounds is their novelty. If the P_a value is high, e.g. $P_a > 0.7$, one may often find close analogy of known pharmaceutical agents. For instance, in the case of standard antiresorptive agent pamidronate $P_a = 0.96$. If $P_a < 0.7$ the chance to find the activity in experiment is less, but for a compound that is not so similar to known pharmaceutical agents, the less of the P_a value the more chance for this compound to be a new chemical entity (NCE) [26].

The data in Table 2 demonstrate that PASS program [25] has proved 100% accuracy in its predictions of antiresorptive activity of tested compounds. Nevertheless there is no correlation between predicted values of probability and experimental values (i.e., the calculated P_a value is not proportional to the potency of the compound).

Regarding anti-inflammatory activity, the prediction results in Table 3 show that the most active compounds are **6a**,**f** and **12b** as their P_a values are from 47.7% to 53.8%. This suggests that these compounds differ significantly from the classic anti-inflammatory compounds and that they may be new chemical entities (NCEs).

5. Pharmacological evaluation

The effects on bone resorption, the inflammatory joint disease and chronic inflammatory diseases of the newly synthesized bisphosphonic acids (BP acids) are studied. Evaluation of the antiresorptive activity of the new series **6a–b**, **8a–f**, and **12a–f** relied on assessing the potency in an in vivo bone resorption model. Thus, compounds were tested in thyroparathyroidectomized (TPTX) rats with hypercalcemia induced by 1,25-dihydroxy vitamin D3 [27] to stimulate bone resorption in vivo. All tested compounds (Table 2) showed good to moderate antiresorptive properties compared to available BP-drug pamidronate (**13**). In general, this data indicated only marginal differences for the potency of the tested BP



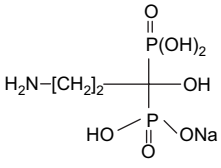
Scheme 3.

Table 2
Antiresorptive activity (ARA), effective dose (ED_{50}) of the new BP acids and predicted activity by PASS program

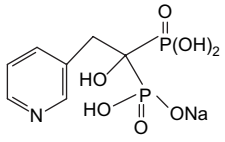
BP acid	*ortho*	*para*	TPTX*-VitD3 ED_{50}[μg/kg]	Prediction P_a	Coincidence *P/E*
13	–	–	85	0.964	+/+
6a	–	$-N(Me)_2$	80	0.688	+/+
6b	–	–Me	110	0.748	+/+
6c	$-NO_2$	–	105	0.672	+/+
6d	–	$-NO_2$	95	0.689	+/+
6e	–Cl	–	90	0.735	+/+
6f	–	–Cl	90	0.731	+/+
8a	–	$-NMe_2$	110	0.580	+/+
8b	–	–Me	125	0.690	+/+
8c	$-NO_2$	–	135	0.682	+/+
8d	–	$-NO_2$	115	0.698	+/+
8e	–Cl	–	105	0.685	+/+
8f		–Cl	118	0.679	+/+
12a	–H	–H	77	0.794	+/+
12b	–	$-(Me)_2$	70	0.746	+/+
12c	$-NO_2$	–	88	0.741	+/+
12d	–	$-NO_2$	85	0.741	+/+
12e	–Cl	–	80	0.778	+/+
12f	–OH	–	78	0.767	+/+

* – All data are generated in thyroparathyroidectomized (APTX) acute in vivo rat model, *P* – prediction; *E* – experiment; *P/E* – accuracy of prediction, +/+ means that both prediction and experiment gives positive results.

acids, due to different arylidene substituents. However, screening results showed that the most active BP acids were found in the series **12a–f**.



13 (Pamidronate)



14 (Risedronate)

Next, BP acids were evaluated in a mouse model of chronic inflammation by adopting the delayed type hypersensitivity granuloma assay as a model of chronic inflammation since bisphosphonates have demonstrated an activity in this model [28–30]. Respectively, mice were previously sensitized to methylated bovine serum albumin (mBSA) and surgically implanted with hydroxyapatite disks (two per mouse), soaked in mBSA, in order to generate granulomas. This model is unaffected by traditional nonsteroidal anti-inflammatory drugs, such as aspirin or ibuprofen [28,29]. Following the delayed type hypersensitivity granuloma reaction (DTH-GRA) technique, previously reported by Nugent et al. [30], BP acids **6a–f**, **8a–f** and **12a–f** were administered subcutaneously in a delayed type hypersensitivity granuloma model, on analogy to the behavior of risedronate and the results are shown in Table 3. BP-risedronate (**14**) was selected for its optimal potency and safety in early screening assays [4–11].

The data in Table 3 show that **14** reproducibly inhibited granuloma wet and dry weights and served as a positive control in other experiments. Compounds **6a**, **12b** [R = $N(Me_2)$], **6f** (R = Cl-*p*) and **12f** (R = OH-*o*) significantly inhibited the granuloma in a dose-dependent manner, while **6c**,**d**, and

Table 3
Delayed type hypersensitivity granuloma,[a] and prediction results of new BP acids

Compound no.	Dose (mg/kg) sc[b]	% Inhibition of granuloma		Prediction (AIA) P_a	Coincidence *P/E*
		Wet wt.	Dry wt.		
14	100	48***	44***	–	–/+
6a	100	53***	58***	0.477	+/+
	60	46***	35*	–	–
6b	100	36*	38*	0.540	+/+
6c	100	48***	51***	0.385	+/+
6d	100	50***	38*	0.438	+/+
6e	100	50***	41**	0.479	+/+
6f	100	52***	53***	0.538	+/+
	60	44**	40**	–	–
8a	100	14	19	0.349	+/+
8b	100	6	13	0.401	+/+
8c	100	8	11	0.670	+/–
8d	100	8	10	–	–/–
8e	150	18	21	0.358	+/–
8f	150	20	20	0.406	+/+
12a	100	46***	39**	–	–/+
12b	100	52***	55***	–	–/+
	60	48***	38**	–	–
12c	100	42**	46***	–	–/+
12d	100	43**	46***	–	–/+
12e	100	38*	44**	–	–/+
12f	100	54***	51***	–	–/+
	60	38*	40**	–	–

P – prediction; E – experiment; *P/E* – accuracy of prediction; +/+ means that both prediction and experiment give positive results; –/– means that both prediction and experiment give negative results; +/– means that prediction gives positive results but experiment gives negative results; –/+ means that prediction gives negative results but experiment give positive results.
[a] ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$; *p* is the percentage of inhibition.
[b] sc: subcutaneously.

12a,**c**,**d** all displayed inhibitory effect, which were equivalent to that of risedronate at 100 mg/kg. BP acids **6b** and **12e** showed moderate activity against the dry weight granuloma. In contrast, vinylbisphosphonic acids **8a–f** showed only marginal activity at higher dose. These results also indicate that the activity of BP acids on arthritic and chronic inflammation is highly dependent on small modifications to the structure, which is not the case for the inhibition of bone resorption.

In summary, the inhibition of bone resorption of the newly synthesized BP acids is significantly high when compared to available BP-drug, pamidronate (**13**, standard). However, we developed an optimized pharmacophore hypothesis to explain the complex structure–activity relationships of the active nitrogen containing bisphosphonate. Nevertheless, investigation of the structure–activity relationship of BP acids, so far, has come to no clear-cut conclusion. Thus, the results obtained are encouraging for further optimization of the antiresorptive properties of these compounds. Furthermore, some of the produced BP acids, e.g., **6a** and **12b**,**f** showed a significant anti-inflammatory activity and were capable of treating the inflammatory joint disease and chronic inflammatory diseases in animals, and could be used to treat Man in the future.

Finally, to summarize the correlation between the prediction results and the pharmacological evaluation, it can be deduced from the data in Tables 2 and 3 that the average

accuracy of prediction (AAP) for antiresorptive activity is ~100% while the average accuracy of prediction (AAP) for anti-inflammatory activity is 55.5%.

6. Conclusion

The studied reactions in the previous [3] and the present investigations are offered as an easy way for the transformation of easily available starting materials to the title BPs and the related BP acids in satisfactory yields. In addition, our protocol demonstrates an efficient site selective method for making addition products in high yields from arylidenes and methyl-1,1-bisphosphonate under microwave conditions.

In parallel, screening results are in agreement with the previously reported [13–15] of the affection of the substituent. Small changes in the structure **A** or **B** moiety in the bisphosphonic acid **I** (see Fig. 1, structure **I**) can lead to extensive alterations in their physicochemical, biological and therapeutic characteristics.

7. Experimental section

All melting points are uncorrected. IR spectra were recorded on a Perkin–Elmer spectrophotometer model 297 using KBr disc. The ^{1}H and ^{13}C NMR spectra were recorded on a JNM-GX-400 Fa Joel spectrometer using TMS as an internal reference. ^{31}P NMR spectra were taken with a Varian CFT-20 (vs. external 85% H_3PO_4). The mass spectra were performed at 70 eV on an MS-50 Kratos (A.E.I.) spectrometer provided with a data system. Elemental analyses were carried out at the Microanalysis Laboratory, Cairo University, Cairo, Egypt. The appropriate precautions in handing moisture-sensitive compounds were observed. Materials and reagents were purchased from Aldrich Company.

7.1. Reactions of arylidenes *4a–f* with tetraethyl methyl-1,1-bisphosphonate (*1*)

7.1.1. In the presence of NaH as a base

General procedure: to a slurry of 4.8 mmol of sodium hydride dispersion (80% in mineral oil) in 15 mL of anhydrous DMF was added dropwise 1.6 mmol of **1** in 5 mL of dry DMF at 0 °C. The reaction mixture was further stirred at room temperature for 1 h, and a solution of 1.1 mmol of the appropriate substrates **4a–f** in DMF (10 mL) was introduced all at once. After stirring for the appropriate time (TLC, see Table 1), the reaction mixture was poured into 200 mL of distilled water and HCl (1 N) was added (at −5 °C) until the pH of the reaction mixture became acidic, and extracted with AcOEt (3 × 50 mL). The combined organic phase was dried over anhydrous sodium sulfate, followed by removal of the solvent, under reduced pressure. The resulting residue was chromatographed on silica gel (*n*-hexane/ethyl acetate) to give BP-products **5a–f** and **7a–f**. Percentage yields, physical and spectral data of the products are listed in Tables 1, 4 and 5.

Table 4
Physical properties, mass spectra and elemental analyses for BPs **5a–f**, **7a–f** and **11c–f**

Product[a]/color	Mol. form. (M. wt.)	MS: *m/z* (%) = [M^+]	Anal. Found (Calcd.) %					
			C	H	Cl	N	P	S
5a/yellow	$C_{27}H_{37}N_3O_6P_2S$ (593.62)	567 (15) [M^+ − 26], 523 (100)	54.78 (54.63)	6.42 (6.28)	–	6.91 (7.08)	10.56 (10.43)	5.54 (5.40)
5b/yellow	$C_{26}H_{34}N_2O_6P_2S$ (564.58)	538 (17) [M^+ − 26], 523 (100)	55.49 (55.31)	6.17 (6.07)	–	5.11 (4.96)	11.31 (10.97)	5.86 (5.68)
5c/yellow	$C_{25}H_{31}N_3O_8P_2S$ (595.55)	569 (21) [M^+ − 26], 483 (100)	50.32 (50.42)	5.32 (5.25)	–	7.15 (7.06)	10.42 (10.40)	5.50 (5.38)
5d/yellow	$C_{25}H_{31}N_3O_8P_2S$ (595.55)	569 (18) [M^+ − 26], 483 (100)	50.47 (50.42)	5.41 (5.25)	–	7.13 (7.06)	10.32 (10.40)	5.45 (5.38)
5e/yellow	$C_{25}H_{31}ClN_2O_6P_2S$ (585.05)	559 (33) [M^+ − 26], 523 (100)	51.41 (51.33)	5.24 (5.34)	6.17 (6.07)	4.86 (4.79)	10.74 (10.59)	5.34 (5.48)
5f/yellow	$C_{25}H_{31}ClN_2O_6P_2S$ (585.05)	559 (31) [M^+ − 26], 523 (100)	51.47 (51.33)	5.29 (5.34)	6.13 (6.07)	4.67 (4.79)	10.75 (10.59)	5.54 (5.48)
7a/yellow	$C_{26}H_{36}N_2O_6P_2S$ (566.60)	566 (9) [M^+], 522 (100)	55.06 (55.12)	6.44 (6.40)	–	5.06 (4.94)	10.99 (10.93)	5.54 (5.66)
7b/pale yellow	$C_{25}H_{33}NO_6P_2S$ (537.55)	537 (<5) [M^+], 522 (100)	55.96 (55.86)	6.12 (6.19)	–	2.64 (2.61)	11.39 (11.52)	6.05 (5.96)
7c/strew yellow	$C_{24}H_{30}N_2O_8P_2S$ (568.53)	568 (11) [M^+], 522 (100)	50.87 (50.70)	5.21 (5.32)	–	4.98 (4.93)	10.98 (10.89)	5.55 (5.64)
7d/pale yellow	$C_{24}H_{30}N_2O_8P_2S$ (568.53)	568 (12) [M^+], 522 (100)	50.84 (50.70)	5.41 (5.32)	–	4.99 (4.93)	10.97 (10.89)	5.68 (5.64)
7e/pale yellow	$C_{24}H_{30}ClNO_6P_2S$ (558.02)	558 (9) [M^+], 522 (100)	51.76 (51.66)	5.34 (5.42)	6.41 (6.36)	2.57 (2.51)	11.04 (11.10)	5.64 (5.75)
7f/pale yellow	$C_{24}H_{30}ClNO_6P_2S$ (558.02)	558 (10) [M^+], 522 (100)	51.78 (51.66)	5.50 (5.42)	6.47 (6.36)	2.56 (2.51)	11.17 (11.10)	5.86 (5.75)
11c/pale yellow	$C_{19}H_{28}N_2O_9P_2S_2$ (554.52)	553 (13) [M^+ − 1], 507 (100)	41.25 (41.15)	5.02 (5.09)	–	5.14 (5.05)	11.26 (11.17)	11.61 (11.57)
11d/yellow	$C_{19}H_{28}N_2O_9P_2S_2$ (554.52)	553 (10) [M^+ − 1], 507 (100)	41.11 (41.15)	5.02 (5.09)	–	5.17 (5.05)	11.21 (11.17)	11.63 (11.57)
11e/pale yellow	$C_{19}H_{28}ClNO_7P_2S_2$ (544.01)	543 (8) [M^+ − 1], 507 (100)	42.03 (41.95)	5.11 (5.19)	6.47 (6.53)	2.61 (2.57)	11.21 (11.38)	11.66 (11.79)
11f/orange	$C_{19}H_{29}NO_8P_2S_2$ (525.52)	525 (14) [M^+ − 1], 507 (100)	43.55 (43.43)	5.42 (5.56)	–	2.61 (2.67)	11.68 (11.79)	12.31 (12.20)

[a] Data of **11a** and **11b** were previously reported [3].

Table 5
IR, ^{1}H, ^{31}P and ^{13}C NMR spectral data for **5a**−**f**, **7a**−**f** and **11c**−**f**

Compound no.	IR (KBr) ν_{max} (cm^{-1})	^{1}H and ^{31}P NMR δ (ppm)	^{13}C NMR δ (ppm)
5a[a]	2212 (CN), 1455 (N═C−S), 1281 (P═O), 1052, 1023 (P−O−C).	1.31 (dt, $J_{HH} = 6.8$ Hz, $^{4}J_{PH} = 3.8$ Hz, 12H, 4CH_3), 2.98 (dd, $J_{HH} = 9$ Hz, $^{2}J_{PH} = 12.8$ Hz, 1H, H^{a}C), 3.13 [s, 6H, N(CH_3)$_2$], 3.67 (ddd, $J_{HH} = 9$, 11 Hz, $^{3}J_{PH} = 4$ Hz, 1H, H^{b}C), 3.99 (qt, $J_{PH} = 11.5$ Hz, 8H, 4H_2CO), 4.54 (dd, $J_{HH} = 11$ Hz, $^{4}J_{PH} = 2.9$ Hz, 1H, CH^{c}), 7.46−8.13 (m, 8H, *H*-Ph); δ_P: (2s) 19.43, 21.82.	16.1 (t, $^{3}J_{PC} = 2.9$ Hz, 4CH_3), 34.9 [N(CH_3)$_2$], 41.9 (t, $^{1}J_{PC} = 133$ Hz, *C*−P$_2$), 44.4 (d, $^{2}J_{PC} = 7$ Hz, *C*H^{b}), 48.8 (d, $^{3}J_{PC} = 4.5$ Hz, *C*H−CN), 62.3 (t, $^{2}J_{CP} = 6.7$ Hz, 4CH_2O), 113.9 (*C*N), 117.6, 118.7, 121.8, 122.6, 124.1, 127.4, 132.8, 151.9, 153.6, 157.1 (Het. and Ph-*C*).
5b[b]	2208 (CN), 1441 (N═C−S), 1254 (P═O), 1128, 1041 (P−O−C).	1.32 (dt, $J_{HH} = 7$ Hz, $^{4}J_{PH} = 4$ Hz, 12H, 4CH_3), 2.32 (s, 3H, H_3C−Ph), 3.26 (dd, $J_{HH} = 9$ Hz, $^{2}J_{PH} = 12$ Hz, 1H, H^{a}C), 3.77 (ddd, $J_{HH} = 9$, 11 Hz, $^{3}J_{PH} = 6$ Hz, 1H, H^{b}C), 4.13 (qt, $J_{PH} = 10.5$ Hz, 8H, 4H_2CO), 4.54 (dd, $J_{HH} = 10.5$ Hz, $^{4}J_{PH} = 2.9$, 1H, CH^{c}), 7.43−8.16 (m, 8H, *H*-Ph); δ_P: (2s) 21.1, 22.6.	16.5 (t, $^{3}J_{PC} = 3.4$ Hz, 4CH_3), 22.6 (s, *C*H_3−Ph), 40.3 (t, $^{1}J_{PC} = 130$ Hz, *C*−P$_2$), 43.6 (d, $^{2}J_{PC} = 7$ Hz, *C*H^{b}), 49.4 (d, $^{3}J_{PC} = 4.5$ Hz, *C*H−CN), 62.2 (t, $^{2}J_{CP} = 7.3$ Hz, 4CH_2O), 112.8 (*C*N), 121.8, 122.6, 124.7, 133.1, 135.3, 136.2, 136.9, 144.3, 152.9, 158.4 (Het. and Ph-*C*).
5c[a]	2227 (CN), 1425 (N═C−S), 1258 (P═O), 1068, 1039 (P−O−C).	1.28 (dt, $J_{HH} = 6.5$ Hz, $J_{PH} = 3.9$ Hz, 12H, 4CH_3), 3.37 (dd, $J_{HH} = 9$ Hz, $^{2}J_{PH} = 13.8$ Hz, 1H, H^{a}C), 3.73 (ddd, $J_{HH} = 9$, 11 Hz, $^{3}J_{PH} = 6$ Hz, 1H, H^{b}C), 3.95 (qt, $J_{PH} = 11.5$ Hz, 8H, 4H_2CO), 4.63 (dd, $J_{HH} = 11$ Hz, $^{4}J_{PH} = 2.7$ Hz, 1H, H^{c}C), 7.49−8.14 (m, 8H, *H*-Ph); δ_P: (2s) 20.19, 21.88.	15.3 (t, $^{3}J_{PC} = 3.4$ Hz, 4CH_3), 40.8 (t, $^{1}J_{PC} = 140$ Hz, *C*−P$_2$), 44.3 (d, $^{2}J_{PC} = 6$ Hz, *C*H^{b}), 49.6 (d, $^{3}J_{PC} = 4$ Hz, *C*H−CN), 62.6 (t, $^{2}J_{PC} = 6.7$ Hz, 4 OCH_2), 112.8 (*C*N), 121.2, 126.3, 129.8, 133.8, 134.7, 148.1, 154.2, 158.7 (Het and Ph-*C*).
5d[a]	2223 (CN), 1443 (N═C−S), 1262 (P═O), 1130, 1063 (P−O−C).	1.29 (dt, $J_{HH} = 7$ Hz, $J_{PH} = 3.8$ Hz, 12H, 4CH_3), 2.98 (dd, $J_{HH} = 9$ Hz, $^{2}J_{PH} = 12.8$ Hz, 1H, H^{a}C), 3.57 (ddd, $J_{HH} = 9$, 11 Hz, $^{3}J_{PH} = 4.6$ Hz, 1H, H^{b}C), 3.88 (qt, $J_{PH} = 10.8$ Hz, 8H, 4H_2CO), 4.39 (dd, $J_{HH} = 10.5$ Hz, $^{4}J_{PH} = 3.1$ Hz, 1H, H^{c}C), 7.42−8.05 (m, 8H, *H*-Ph); δ_P: (2s) 20.25, 21.92.	16.3 (t, $^{3}J_{PC} = 4.5$ Hz, 4CH_3), 40.5 (t, $^{1}J_{CP} = 136$ Hz, *C*−P$_2$), 43.9 (d, $^{2}J_{PC} = 6$ Hz, *C*H^{b}), 49.1 (d, $^{3}J_{PC} = 4.5$ Hz, *C*H−CN), 61.8 (t, $^{2}J_{PC} = 7.6$ Hz, 4 OCH_2), 112.6 (*C*N), 120.5, 122.5, 126.4, 129.3, 130.6, 133.8, 148.3, 152.1, 155.5 (Het. and Ph-*C*).
5e[a]	2208 (CN), 1441 (N═C−S), 1253 (P═O), 1133, 1041 (P−O−C).	1.32 (dt, $J_{HH} = 6.5$ Hz, $J_{PH} = 4$ Hz, 12H, 4CH_3), 2.93 (dd, $J_{HH} = 9$ Hz, $^{2}J_{PH} = 11.5$ Hz, 1H, H^{a}C), 3.57 (ddd, $J_{HH} = 9$, 11 Hz, $^{3}J_{PH} = 3.8$ Hz, 1H, H^{b}C), 4.09 (dd, $J_{HH} = 10.2$ Hz, $^{4}J_{PH} = 2.8$ Hz, 1H, CH^{c}), 4.31 (qt, $J_{PH} = 12$ Hz, 8H, 4H_2CO), 7.4−8.09 (m, 8H, *H*-Ph); δ_P: 23.02, 21.68.	16.2 (t, $^{3}J_{PC} = 4.8$ Hz, 4CH_3), 41.6 (t, $^{1}J_{PC} = 132$ Hz, *C*−P$_2$), 45.9 (d, $^{2}J_{PC} = 7.5$ Hz, *C*H^{b}), 50.8 (d, $^{3}J_{PC} = 4.5$ Hz, *C*H−CN), 61.8 (t, $^{2}J_{PC} = 6.5$ Hz, 4 OCH_2), 113.4 (*C*N), 121.4, 126.2, 129.6, 134.7, 140.1, 152.5, 156.03 (Het. and Ph-*C*).
5f[a]	2227 (CN), 1445 (N═C−S), 1255 (P═O), 1135, 1074 (P−O−C).	1.39 (dt, $J_{HH} = 7$ Hz, $J_{PH} = 4$ Hz, 12H, 4CH_3), 3.20 (dd, $J_{HH} = 10.3$ Hz, $^{2}J_{PH} = 11.5$ Hz, 1H, H^{a}C), 3.35 (ddd, $J_{HH} = 9$, 11 Hz, $^{3}J_{PH} = 6$ Hz, 1H, H^{b}C), 4.07 (dd, $J_{HH} = 11$ Hz, $^{4}J_{PH} = 3.2$ Hz, 1H, H^{c}C), 4.26 (qt, $J_{PH} = 11.3$ Hz, 8H, 4H_2CO), 7.38 (m, 8H, *H*-Ph); δ_P: (2s) 23.2, 21.7.	15.1 (t, $^{3}J_{PC} = 3.7$ Hz, 4CH_3), 40.2 (t, $^{1}J_{PC} = 133$ Hz, *C*−P$_2$), 45.9 (d, $^{2}J_{PC} = 7.5$ Hz, *C*HPh), 49.1 (d, $^{3}J_{PC} = 4.5$ Hz, *C*H^{b}), 62.2 (t, $^{2}J_{PC} = 6.7$ Hz, 4CH_2O), 113.4 (*C*N), 121.4, 126.6, 133.4, 140.1, 135.5, 143.4, 151.6, 157.5 (Het. and Ph-*C*).
7a[b]	1618 (C═CHPh), 1425 (N═C−S), 1268 (P═O), 1110, 1085 (P−O−C).	1.05, 1.23 (2dt, $J_{HH} = 7$ Hz, $J_{PH} = 4.6$ Hz, 12H, 4CH_3), 3.1, 3.17 [2s, 6H, N(CH_3)$_2$], 3.98−4.14 (m, 8H, 4H_2CO), 5.04 (dd, $^{4}J_{HH} = 1.1$ Hz, $^{2}J_{PH} = 24$ Hz, 1H, H^{a}C), 7.31 (dd, $^{4}J_{HH} = 1.1$ Hz, $^{4}J_{PH} = 3.2$ Hz, H^{b}C), 7.71−8.1 (m, 8H, *H*-Ph); δ_P: (2s) 20.78, 22.13.	15.6 (t, $^{3}J_{PC} = 4.2$ Hz, 4CH_3), 31.8, 32.6 [2s, N(CH_3)$_2$], 42.8 (t, $^{1}J_{PC} = 148$ Hz, *C*−P$_2$), 61.5 (t, $^{2}J_{PC} = 6$ Hz, 4CH_2O), 122.7, 124.7, 125.1, 126.4, 135.1, 152.6, 158.3 (Het. and Ph-*C*), 133.4 (d, $^{3}J_{PC} = 4.5$ Hz, *C*3), 142.9 (d, $^{2}J_{PC} = 9.8$ Hz, *C*2).
7b[a]	1616 (C═CHPh), 1459 (N═C−S), 1256 (P═O), 1121, 1072 (P−O−C).	0.99, 1.27 (2dt, $J_{HH} = 6.5$ Hz, $J_{PH} = 3.2$ Hz, 12H, 4CH_3), 2.29 (s, 3H, H_3C−Ph), 3.98−4.19 (m, 8H, 4H_2CO), 5.21 (dd, $^{4}J_{HH} = 0.9$ Hz, $^{2}J_{PH} = 18.6$ Hz, 1H, H^{a}C), 7.37 (dd, $^{4}J_{HH} = 0.9$ Hz, $^{4}J_{PH} = 3.8$ Hz, H^{b}C), 7.72−8.01 (m, 8H, *H*-Ph); δ_P: (2s) 19.58, 21.41.	15.9 (t, $^{3}J_{CP} = 4.5$ Hz, 4CH_3), 21.9 (s, *C*H_3−Ph), 43.2 (t, $^{1}J_{CP} = 145$ Hz, *C*−P$_2$), 61.9 (t, $^{2}J_{CP} = 5.9$ Hz, 4CH_2O), 119.7, 121.4, 122.5, 126.4, 130.1, 132.5, 141.3, 143.0 (Het. and Ph-*C*), 136.6 (d, $^{3}J_{CP} = 5.8$ Hz, *C*3), 144.6 (d, $^{2}J_{CP} = 8.7$ Hz, *C*2).
7c[a]	1626 (C═CHPh), 1449 (N═C−S), 1258 (P═O), 1110, 1082 (P−O−C).	1.16, 1.28 (2dt, $J_{HH} = 7$ Hz, $J_{PH} = 4.2$ Hz, 12H, 4H_3C), 4.01−4.26 (m, 8H, 4H_2CO), 5.08 (dd, $^{4}J_{HH} = 1.3$ Hz, $^{2}J_{PH} = 20.6$ Hz, 1H, H^{a}C), 7.35 (dd, $^{4}J_{HH} = 1.3$ Hz, $^{4}J_{PH} = 3.4$ Hz, H^{b}C), 7.76−8.34 (m, 8H, *H*-Ph); δ_P: (2s) 20.22, 22.91.	15.3 (t, $^{3}J_{PC} = 3.7$ Hz, 4CH_3), 44.98 (t, $^{1}J_{PC} = 144$ Hz, *C*−P$_2$), 62.8 (t, $^{2}J_{PC} = 7.4$ Hz, 4CH_2O), 120.4, 122.6, 124.3, 126.7, 139.1, 139.7, 142.5, 156.1, 156.9 (Het. and Ph-*C*), 137.2 (d, $^{3}J_{PC} = 6.2$ Hz, *C*3), 144.9 (d, $^{2}J_{CP} = 9.4$ Hz, *C*2).

(*continued on next page*)

Table 5 (*continued*)

Compound no.	IR (KBr) ν_{max} (cm^{-1})	^{1}H and ^{31}P NMR δ (ppm)	^{13}C NMR δ (ppm)
7d[a]	1622 (C═CHPh), 1445 (N═C−S), 1258 (P═O), 1120, 1069 (P−O−C).	1.07, 1.2 (2dt, $J_{HH} = 7$ Hz, $J_{PH} = 4.5$ Hz, 12H, $4H_3C$), 4.01−4.25 (m, 8H, $4H_2CO$), 5.16 (dd, $^{4}J_{HH} = 1.1$ Hz, $^{2}J_{PH} = 23.6$ Hz, 1H, $H^{a}C$), 7.35 (dd, $^{4}J_{HH} = 1.1$ Hz, $^{4}J_{PH} = 3.4$ Hz, $H^{b}C$), 7.76−8.36 (m, 8H, *H*-Ph); δ_P: (2s) 20.19, 22.9.	15.2 (t, $^{3}J_{PC} = 3.7$ Hz, $4CH_3$), 40.03 (t, $^{1}J_{PC} = 148$ Hz, $C-P_2$), 62.4 (t, $^{2}J_{PC} = 5.6$ Hz, $4CH_2O$), 120.5, 124.3, 126.9, 139.1, 142.3, 156.3, 157.1 (Het. and Ph-*C*), 139.2 (d, $^{3}J_{PC} = 8$ Hz, *C*3), 144.6 (d, $^{2}J_{PC} = 8.9$ Hz, *C*2).
7e[a]	1618 (C═CHPh), 1443 (N═C−S), 1281 (P═O), 1133, 1053 (P−O−C).	1.23, 1.36 (2dt, $J_{HH} = 6.8$ Hz, $J_{PH} = 4.2$ Hz, 12H, $4H_3C$), 4.02−4.35 (m, 8H, $4H_2CO$), 5.06 (dd, $^{4}J_{HH} = 1.2$ Hz, $J_{PH} = 24.6$ Hz, 1H, $H^{a}C$), 7.34 (dd, $^{4}J_{HH} = 1.2$ Hz, $^{4}J_{PH} = 3.3$ Hz, $H^{b}C$), 7.74−8.08 (m, 8H, *H*-Ph); δ_P: (2s) 21.19, 23.14.	15.4 (t, $^{3}J_{PC} = 2.8$ Hz, $4CH_3$), 46.1 (t, $J_{PC} = 140$ Hz, $C-P_2$), 61.4 (t, $^{2}J_{PC} = 6.2$ Hz, $4CH_2O$), 119.6, 121.9, 123.4, 126.1, 129.8, 130.8, 134.5, 141.2, 152.2 (Het. and Ph-*C*), 137.1 (d, $^{3}J_{PC} = 3.8$ Hz, *C*3), 145.4 (d, $^{2}J_{PC} = 8.5$ Hz, *C*2).
7f[a]	1618 (C═C−Ph), 1448 (N═C−S), 1268 (P═O), 1118, 1047 (P−O−C).	1.03, 1.41 (2dt, $J_{HH} = 6.8$ Hz, $J_{PH} = 4.6$ Hz, 12H, $4H_3C$), 4.01−4.37 (m, 8H, $4H_2CO$), 5.13 (dd, $^{4}J_{HH} = 1.1$ Hz, $J_{PH} = 26$ Hz, 1H, $H^{a}C$), 7.32 (dd, $^{4}J_{HH} = 1.1$ Hz, $^{4}J_{PH} = 2.2$ Hz, $H^{b}C$), 7.77−8.10 (m, 8H, *H*-Ph); δ_P: (2s) 21.17, 23.19.	15.7 (t, $^{3}J_{PC} = 3.8$ Hz, $4CH_3$), 42.9 (t, $^{1}J_{PC} = 140$ Hz, $C-P_2$), 62.3 (t, $^{2}J_{PC} = 6.5$ Hz, $4CH_2O$), 124.3, 126.3, 129.8, 130.7, 134.5, 141.3, 152.1 (Het. and Ph-*C*), 137.7 (d, $^{3}J_{PC} = 3.8$ Hz, *C*3), 148.6 (d, $^{2}J_{PC} = 9.8$ Hz, *C*2).
11c[a]	3415 (NH), 1686 (C═O), 1436 (C═S), 1252 (P═O), 1128, 1047 (P−O−C).	1.21, 1.36 (2dt, $J_{HH} = 7$ Hz, $^{4}J_{PH} = 4.2$ Hz, $4CH_3$), 2.78 (dd, $J_{HH} = 9.5$ Hz, $^{2}J_{PH} = 10.5$ Hz, 1H, CH^{a}), 3.46 (ddd, $J_{HH} = 9.5$, 10.6 Hz, $^{3}J_{PH} = 6$ Hz, 1H, $H^{b}C$), 3.89−4.02 (2qt, $^{3}J_{PH} = 10.5$ Hz, 8H, $4H_2CO$), 4.34 (dd, $J_{HH} = 10.6$ Hz, $^{3}J_{PH} = 2.3$ Hz, 1H, $H^{c}C$), 7.47−8.07 (m, 4H, *H*-Ph), 9.45 (s, 1H, HN^{c}); δ_P: (2s) 21.34, 23.89.	16.4 (t, $^{3}J_{CP} = 2.8$ Hz, $4CH_3$), 38.2 (t, $^{1}J_{CP} = 133$ Hz, $CH-P_2$), 44.7 (d, $^{2}J_{CP} = 8$ Hz, CH^{b}), 48.1 (d, $^{3}J_{CP} = 4.7$ Hz, 5-*CH*), 62.2 (t, $^{2}J_{CP} = 6.8$ Hz, $4CH_2O$), 124.8, 131.8, 136.2, 147.3, 153.1 (*C*-Ph), 176.5 (*C*═O), 202.5 (*C*═S).
11d[b]	3418 (NH), 1680 (C═O), 1435 (C═S), 1258 (P═O), 1122, 1049 (P−O−C).	1.03, 1.31 (2dt, $J_{HH} = 6.5$ Hz, $^{4}J_{PH} = 4.5$ Hz, $4CH_3$), 2.65 (dd, $J_{HH} = 9.6$ Hz, $^{2}J_{HP} = 11.2$ Hz, 1H, CH^{a}), 3.63 (ddd, $J_{HH} = 9.6$, 11 Hz, $^{3}J_{PH} = 6$ Hz, 1H, CH^{b}), 3.99−4.21 (2qt, $^{3}J_{PH} = 10.8$ Hz, 8H, $4H_2CO$), 4.62 (dd, $J_{HH} = 11.2$ Hz, $^{4}J_{PH} = 3.3$ Hz, 1H, CH^{c}), 7.43−8.11 (m, 4H, *H*-Ph), 9.42 (s, 1H, HN^{c}); δ_P: (2s) 21.26, 23.12.	16.1 (t, $^{3}J_{PC} = 3.5$ Hz, $4CH_3$), 37.6 (t, $^{1}J_{PC} = 133$ Hz, $CH-P_2$), 40.3 (d, $^{2}J_{PC} = 8$ Hz, CH^{b}), 48.2 (d, $^{3}J_{PC} = 4.2$ Hz, 5-*C*), 62.1 (t, $^{2}J_{CP} = 7.3$ Hz, $4CH_2$), 126.4, 132.1, 136.1, 144.3, 152.8 (*C*-Ph), 173.3 (*C*═O), 202.6 (*C*═S).
11e[b]	3410 (NH), 1683 (C═O), 1432 (C═S), 1262 (P═O), 1155, 1083 (P−O−C).	1.06, 1.23 (2dt (br), $J_{HH} = 7.5$ Hz, $^{4}J_{PH} = 4.7$ Hz, $4CH_3$), 3.02 (dd, $J_{HH} = 9$ Hz, $^{2}J_{PH} = 12.8$ Hz, 1H, CH^{a}), 3.81 (ddd, $J_{HH} = 9$, 11 Hz, $^{3}J_{PH} = 6$ Hz, 1H, CH^{b}), 4.13−4.28 (2qt, $^{3}J_{PH} = 11.3$ Hz, 8H, $4H_2CO$), 4.46 (dd, $J_{HH} = 11$ Hz, $^{4}J_{PH} = 3.3$ Hz, 1H, $H^{c}C$), 7.42−8.13 (m, 4H, *H*-Ph), 9.65 (s, 1H, HN^{c}); δ_P: (2s) 22.31, 23.92.	16.4 (t, $^{3}J_{PC} = 3.4$ Hz, $4CH_3$), 38.5 (t, $^{1}J_{PC} = 138$ Hz, $CH-P_2$), 42.8 (d, $^{2}J_{PC} = 8$ Hz, CH^{b}), 48.3 (d, $^{3}J_{PC} = 4.2$ Hz, 5-*C*), 61.8 (t, $^{2}J_{CP} = 7.3$ Hz, $4CH_2O$), 126.2, 127.1, 133.3, 136.2, 144.9, 153.4 (*C*-Ph), 179.8 (*C*═O), 202.9 (*C*═S).
11f[b]	3458−3364 (OH and NH), 1683 (C═O), 1436 (C═S), 1266 (P═O), 1144, 1085 (P−O−C).	0.98, 1.12 (2dt, $J_{HH} = 6.8$ Hz, $^{4}J_{PH} = 3.8$ Hz, $4CH_3$), 2.84 (dd, $J_{HH} = 9$ Hz, $^{2}J_{PH} = 12.4$ Hz, 1H, CH^{a}), 3.35 (ddd, $J_{HH} = 10.2$, 11 Hz, $^{3}J_{PH} = 6$ Hz, 1H, CH^{b}), 3.98−4.18 (2q, $^{3}J_{PH} = 11.2$ Hz, 8H, $4H_2CO$), 4.58 (dd, $J_{HH} = 11$ Hz, $^{4}J_{PH} = 3.3$ Hz, 1H, $H^{c}C$), 7.46−8.01 (m, 4H, *H*-Ph), 9.82 (s, 1H, HN^{c}), 10.47 (s, 1H, HO−Ph); δ_P: (2s) 21.63, 23.1.	16.2 (t, $^{3}J_{P-C} = 4.6$ Hz, $4CH_3$), 39.6 (t, $^{1}J_{P-C} = 137$ Hz, $CH-P_2$), 41.8 (d, $^{2}J_{PC} = 8$ Hz, CH^{b}), 48.9 (d, $^{3}J_{PC} = 4.2$ Hz, 5-*C*), 62.3 (t, $^{2}J_{PC} = 7.4$ Hz, $4CH_2$), 126.4, 127.4, 136.3, 144.9, 153.4 (*C*-Ph), 178.4 (*C*═O), 202.3 (*C*═S).

[a] Solvents of NMR:DMSO-d_6.

[b] Solvents of NMR:$CDCl_3$.

[c] Proton exchangeable with D_2O.

Table 6
Analytical data, physical properties, IR and NMR spectra for the products **6a–f**, **8a–f** and **12b–f**

Compound no.[a,b,c]	Yield[d] (%)	Mp (°C)/solvent	Mol. form. (M. wt.)	Anal. Found (Calcd.) %					
				C	H	Cl	N	P	S
6a[e]	82	>300/H_2O/acetone	$C_{19}H_{21}N_3O_6P_2S$ (481.41)	47.49 (47.40)	4.46 (4.40)	–	8.82 (8.73)	12.97 (12.87)	6.73 (6.66)
6b	78	230–232/acetone	$C_{18}H_{18}N_2O_6P_2S$ (452.36)	47.89 (47.79)	4.12 (4.01)	–	6.05 (6.19)	13.72 (13.69)	7.01 (7.09)
6c	87	>300/H_2O/acetone	$C_{17}H_{15}N_3O_8P_2S$ (483.34)	42.28 (42.25)	3.02 (3.13)	–	8.55 (8.69)	12.88 (12.82)	6.67 (6.63)
6d	84	>300/H_2O/acetone	$C_{17}H_{15}N_3O_8P_2S$ (483.34)	42.31 (42.25)	3.04 (3.13)	–	8.53 (8.69)	12.92 (12.82)	6.71 (6.63)
6e	83	218–220/AcOEt	$C_{17}H_{15}ClN_2O_6P_2S$ (472.83)	43.31 (43.18)	3.26 (3.20)	7.56 (7.51)	5.99 (5.93)	13.17 (13.10)	6.89 (6.78)
6f	85	187–188/EtOH	$C_{17}H_{15}ClN_2O_6P_2S$ (472.83)	43.24 (43.18)	3.28 (3.20)	7.43 (7.51)	5.96 (5.93)	13.19 (13.10)	6.86 (6.78)
8a	88	>300/H_2O/acetone	$C_{18}H_{20}N_2O_6P_2S$ (454.38)	47.72 (47.58)	4.53 (4.44)	–	6.11 (6.17)	13.79 (13.63)	7.17 (7.06)
8b[f]	84	198–200/MeCN	$C_{17}H_{17}NO_6P_2S$ (425.34)	48.13 (48.00)	4.10 (4.03)	–	3.35 (3.29)	14.52 (14.56)	7.66 (7.54)
8c	86	262–264/MeOH	$C_{16}H_{14}N_2O_8P_2S$ (456.31)	42.21 (42.12)	3.00 (3.09)	–	6.04 (6.14)	13.51 (13.57)	7.13 (7.03)
8d	92	>300/H_2O/acetone	$C_{16}H_{14}N_2O_8P_2S$ (456.31)	42.01 (42.12)	2.96 (3.09)	–	6.18 (6.14)	13.48 (13.57)	7.13 (7.03)
8e	88	178–180/EtOH	$C_{16}H_{14}ClNO_6P_2S$ (445.8)	43.19 (43.11)	3.07 (3.17)	8.11 (7.96)	3.25 (3.14)	13.84 (13.89)	7.23 (7.19)
8f	81	300–305/H_2O/acetone	$C_{16}H_{14}ClNO_6P_2S$ (445.8)	43.18 (43.11)	3.08 (3.17)	8.01 (7.96)	3.21 (3.14)	14.08 (13.89)	7.16 (7.19)
12b	91	224–225/EtOH	$C_{13}H_{18}N_2O_7P_2S_2$ (440.37)	35.54 (35.46)	4.05 (4.12)	–	6.46 (6.36)	14.16 (14.07)	14.61 (14.56)
12c	92	241–243/MeOH	$C_{11}H_{12}N_2O_9P_2S_2$ (442.30)	29.94 (29.87)	2.69 (2.73)	–	6.30 (6.33)	14.07 (14.00)	14.57 (14.50)
12d	92	>300/H_2O/acetone	$C_{11}H_{12}N_2O_9P_2S_2$ (442.30)	29.96 (29.87)	2.77 (2.73)	–	6.21 (6.33)	14.13 (14.00)	14.42 (14.50)
12e[g]	88	200–202/MeOH	$C_{11}H_{12}ClNO_7P_2S_2$ (431.8)	30.56 (30.60)	2.73 (2.80)	8.27 (8.22)	3.34 (3.24)	14.48 (14.34)	14.99 (14.85)
12f	92	178–180/EtOH	$C_{11}H_{13}NO_8P_2S_2$ (413.31)	32.22 (31.97)	3.25 (3.17)	–	3.47 (3.39)	14.85 (14.99)	15.57 (15.52)

[a] Data of **12a** were previously reported [3].

[b] IR (KBr): ν_{max} cm^{-1} of all products showed stretching bands in the regions 3330–3250 (P–OH) and 1224–1235 (P=O, bonded).

[c] ^{31}P NMR (D_2O) of all products showed signals in the range δp 20–23 ppm.

[d] Yields are based on the consumed corresponding bisphosphonate.

[e] δ_H (D_2O) (ppm): 2.93 (dd, $J_{HH} = 7$ Hz, $J_{PH} = 12.6$ Hz, 1H, *H*C–P_2), 3.1 [s, 6H, N(CH_3)$_2$], 3.68 (ddd, $J_{HH} = 9$, 11 Hz, $J_{PH} = 4$ Hz, 1H, H^bC), 4.31 (dd, $J_{HH} = 11$ Hz, $J_{P-H} = 4.3$ Hz, 1H, H^cC), 7.44–8.09 (m, 8H, *H*-Ph).

[f] δ_H (D_2O): 2.34 (s, 3H, H_3C–Ph), 5.17 (dd, $J_{HH} = 1.2$ Hz, $J_{PH} = 13.6$ Hz, 1H, *H*C–P_2), 7.31 (dd, $^4J_{HH} = 1.1$ Hz, $^4J_{PH} = 3.2$ Hz, H^bC), 7.39–8.12 (m, 8H, *H*-Ph).

[g] δ_H (D_2O): 3.08 (dd, $J_{HH} = 10.6$ Hz, $^2J_{PH} = 11.8$ Hz, 1H, H^aC), 3.53 (ddd, $J_{HH} = 9$, 11 Hz, $^3J_{P-H} = 3.5$ Hz, 1H, H^bC), 4.08 (d of d, $J_{HH} = 10.5$ Hz, $^3J_{PH} = 3.3$ Hz, 1H, H^cC), 7.42–8.11 (m, 4H, *H*-C_6H_4).

7.1.2. In the presence of EtONa as a base

General procedure: to a stirred solution of 1.6 mmol of tetraethyl methyl-1,1-bisphosphonate (**1**) and 3 mmol of Na in 10 mL dry EtOH was added dropwise a solution of 1.1 mmol of the appropriate substituted arylidenes **4a–f** in 15 mL EtOH at 0 °C. The resulting mixture was allowed to warm to r.t., and stirred for the proper time (TLC, Table 1). HCl (1 N) was added (at −5 °C) until the pH of the reaction mixture became acidic. The mixture was extracted with AcOEt (3 × 50 mL) and the combined organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent, under vacuum, the resulting residue was chromatographed on silica gel (*n*-hexane/ethyl acetate) to give BP-products **5a–f** and **7a–f**. Percentage yields, physical and spectral data of the products are listed in Tables 1, 4 and 5.

*7.1.3. Reactions of **4a–f** and **9a–f** with **1** under microwave conditions*

General procedure: 1.2 mmol of **4a–f** or **9a–f** was added to a mixture of 5 mL EtONa in 10 mL dry DMF and 1.5 mmol Wittig–Horner **1** in a Pyrex glass beaker. Microwave irradiation (MW domestic type oven 1000 W with a frequency 2450 MHz, National Jp) was applied for 2–12 min (each pulse of 1 min). After the completion of the reaction (TLC analysis), the mixture was poured onto ice-cold water, acidified (HCl, 1 N), extracted (AcOEt), dried, and evaporated till dryness. The precipitate was washed with CH_2Cl_2 and filtered to give the BPs **5a–f** or **11a–f**. Percentage yields, physical and spectral data of the products are listed in Tables 1, 4 and 5.

7.1.4. Acid hydrolysis of synthesized BPs

General procedure: 0.3 g of bisphosphonates **5a–f**, **7a–f**, or **11b–f** was dissolved in 20 mL conc HCl, and the mixture was heated under reflux for ≈20 h (TLC), followed by evaporation to dryness under reduced pressure. After triturating with CH_2Cl_2, the precipitate that formed was filtered off and washed twice with ethanol/water (1:2, v/v) to give the required bisphosphonic acids **6a–f**, **8a–f**, or **12b–f**. Percentage yields, physical and spectral data are listed in Table 6.

7.2. Biological evaluation

7.2.1. Bone absorption

ED_{50} values for bone resorption biosynthesis inhibition in rats ('the rat model') were determined as described by Green et al. [27].

7.2.2. Chronic inflammation

Delayed type hypersensitivity granuloma of BP-acids was determined as described by Nugent et al. [30].

Acknowledgement

This research has been supported by the Egyptian Government (National Research Centre).

References

[1] W.M. Abdou, M.D. Khidre, A.A. Sediek, Lett. Org. Chem. (LOC) 3 (2006) 634–639.
[2] W.M. Abdou, N.A. Ganoub, A.F. Fahmy, A.A. Shaddy, Monatsh. Chem. 137 (2006) 105–116.
[3] W.M. Abdou, N.A. Ganoub, Y.O. Elkhoshnieh, Synlett (2003) 785–790.
[4] H. Fleisch, Bisphosphonates: A New Class of Drugs in Diseases of Bone and Calcium Metabolism, in: P.F. Baker (Ed.), Handbook of Experimental Pharmacology, vol. 83, Springer, Berlin/Heidelberg, 1988, pp. 441–465.
[5] F.H.M. Ebetino, D. Francis, M.J. Rogers, R.G.G. Russell, Rev. Contemp. Pharmacother. 9 (1998) 233–243.
[6] H. Shinoda, G. Admek, R. Felix, H. Fleisch, R. Schenk, P. Hagan, Calcif. Tissue Int. 35 (1983) 87–99.
[7] R. Schenk, W.A. Merz, R. Muhlbauer, R.G.G. Russell, H. Fleisch, Calcif. Tissue Res. 11 (1973) 196–214.
[8] I. Fogelman, R.G. Bessent, J.F. Turner, D.L. Citrin, I.T. Boyce, W.R. Greig, J. Nucl. Med. 19 (1978) 270–275.
[9] M.D. Francis, I. Fogelman, 99m Tc-Diphosphonate uptake Mechanisms on Bone, in: I. Fogelman (Ed.), Bone Scanning in Clinical Practice, Springer Verlag, London, 1987, pp. 1–6.
[10] D.L. Douglas, R.G.G. Russell, C.G. Preston, M.A. Prenton, T. Duckworth, J.A. Kanis, F.E. Preston, J.S. Woodhead, Lancet 1 (1980) 1043–1047.
[11] E.S. Siris, A.A. Chines, R.D. Altman, J.P. Brown, C.C. Johnston, R. Lang, M.R. McClung, L.E. Mallette, P.D. Miller, W.G. Ryan, F.R. Singer, J.R. Tucci, R.A. Eusebio, P.J. Bekker, J. Bone Miner. Res. 13 (1998) 1032–1038.
[12] R.G.G. Russell, Phosphorus Sulfur Silicon Relat. Elem. 144–146 (1999) 793–820.
[13] N.G. Almstead, S.M. Dansereau, M.D. Francis, C.M. Snider, F.H. Ebetino, Phosphorus Sulfur Silicon Relat. Elem. 144–146 (1999) 325–328.
[14] L. Flora, Arthritis Rheum. 22 (1979) 340–346.
[15] M.D. Francis, K. Hovancik, R.W. Boyce, Int. J. Tissue React. 11 (1989) 239–352.
[16] L.]Widler, K.A. Jaeggi, J.R. Green, Phosphorus Sulfur Silicon Relat. Elem. 144–146 (1999) 5–8.
[17] S. Trippet, J. Chem. Soc. (1962) 4733–4734.
[18] W.M. Abdou, N.A. Ganoub, Heterocycl. Commun. 1 (1995) 387–393.
[19] W.M. Abdou, N.A. Ganoub, A.A. Shaddy, Tetrahedron 54 (1998) 9079–9088.
[20] R.M. Silverstein, G.C. Bassler, T.C. Morril (Eds.), Spectrometric Identification of Organic Compounds, fourth ed. John Wiley and Sons, Inc., New York, 1981.
[21] IBM Editorial Staff, Alchemy III, 3D-Molecular Modeling Software Users Guide, Tripos Associates, Inc., Subdivision of Evans and Sutherland, 1992.
[22] I.L. Finar, Organic Chemistry, vol. 1, The English Language Book Society and Longman Group Limited, England, 1962, pp 77–82.
[23] C.O. Kappe, A. Stadler, Microwaves in Organic and Medicinal Chemistry in, in: A. Loupy, C.O. Kappe (Eds.), Microwaves in Organic Synthesis, second ed. Wiley-VCH, 2005.
[24] Visit: Website: http://www.ibmc.msk.ru/PASS
[25] V.V. Poroikov, D.A. Filimonov, W.D. Ihlenfeld, T.A. Gloriozova, A.A. Lagunin, Yu.V. Borodina, A.V. Stepanchikova, M.C. Nicklaus, J. Chem. Inf. Comput. Sci. 43 (2003) 228–236.
[26] V. Poroikov, D. Filimonov, in: C. Helma (Ed.), Predictive Toxicology, Taylor and Francis, 2005, pp. 459–480.
[27] J.R. Green, K. Müller, K.A. Jaeggi, J. Bone Miner. Res. 9 (1994) 745–751.
[28] C.J. Dunn, A.J. Gibbons, S.K. Miller, Agents Actions 27 (1989) 365–368.
[29] D.R. White, E.L. Fritzen, Jr. US 5,635,496, 1997, June 3.
[30] R.A. Nugent, M. Murphy, S.T. Schlachter, C.J. Dunn, R.J. Smith, N.D. Staite, L.A. Galinet, S.K. Shields, D.G. Aspar, K.A. Richard, N.A. Rohloff, J. Med. Chem. 36 (1993) 134–139.