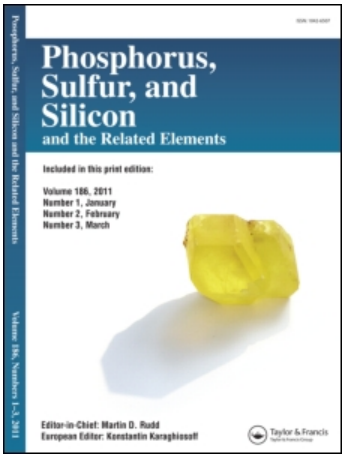

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The Discovery of the Bone-Active Agent Risedronate, and Bisphosphonate Structure-Activity Considerations Including the Aminophenylethane Phosphonate Series

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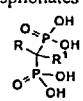
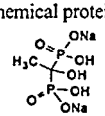
Risedronate was selected for clinical development from a library of more than 200 bisphosphonate analogs for the treatment of a variety of bone diseases. It is a pyridinyl bisphosphonate and is therefore characterized by a nitrogen residue in its structure. Our studies have increased the understanding of the optimal spatial arrangement of the nitrogen and phosphonate moieties required to give the bisphosphonate molecules the geometry necessary for potent antiresorptive activity on bone. A series of aminophenylethane phosphonates have been studied to further demonstrate these geometric requirements.

Keywords: bisphosphonates; risedronate; antiresorptive activity; bone disease; structure-activity relationships; aminophenylethane phosphonates

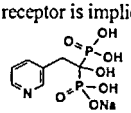
In the late 1960s Fleisch et al found that the bisphosphonates have in-vivo effects on bone metabolism[1]. At the time, it seemed that these simple phosphonate-carbon-phosphonate-hydroxyalkyl analogs of pyrophosphate inhibited resorption through direct mineral effects on the hydroxyapatite phase of calcium phosphate, the principle constituent of bone. This work led to the use of structurally simple members of the class, such as etidronate, for the treatment of a variety of bone-related diseases. In the past 15–20 years, more complex structures in this series have been the focus of a number of laboratories leading to the discovery of novel agents to expand the use of this class of drugs[2]. Research in our laboratories resulted in the screening of more than 200 bisphosphonate compounds. The pyridinyl bisphosphonate, risedronate, was selected for development, and is representative of an analog containing the optimized drug pharmacophore (Fig. 1). An analysis of several structure-activity relationships has been conducted to evaluate the concept of a specific recognition event being involved in the mechanism of antiresorptive activity of bisphosphonates[3]. Thus, a biochemical protein target or receptor is implicated.



Bisphosphonate general structure



Etidronate



Risedronate **(1)**

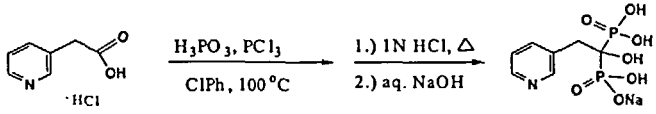
FIGURE 1 Structure of bisphosphonates

Nitrogen-Containing Bisphosphonates

The initial finding that aminoalkyl bisphosphonates, including pamidronate and alendronate, increased antiresorptive potency[4], brought about a significant step forward in the development of novel analogs. Since these compounds exhibited similar mineral effects as the earlier bisphosphonates, this finding not only initiated the study of a variety of new bisphosphonate structures and their nitrogen functionality, but also clearly indicated that the mechanism of antiresorptive activity was not derived solely from direct bone mineral effects. The successful results obtained from the introduction of a nitrogen moiety can be interpreted as an indication that key features of a medicinal chemistry pharmacophore could be elucidated.

The Pyridinyl Analogs and Risedronate

Our studies focused on new basic nitrogen functionalities, taking into account the possibility that the primary amino functionality could have brought about a variety of metabolic issues. After a general survey of ring systems, we focused attention on the pyridinyl variant of nitrogen functionality[5]. We selected risedronate (**1**) for its optimal potency and safety in early screening assays. Risedronate is conveniently synthesized via a condensation of pyridinyl acetic acid, phosphorus acid and PCl_3[6] (Fig. 2). In parallel, we developed an optimized pharmacophore hypothesis to explain the complex structure-activity relationships of the active nitrogen-containing bisphosphonates. This helped to identify conformationally restricted analogs of risedronate and further validated the preference of this drug for an optimal 3-D shape[7]. However, the result was not completely convincing as only one dihedral angle was constrained in the structure.



1

FIGURE 2 Synthesis of risedronate

Aminophenyl Alkyl Bisphosphonates

The design of conformationally rigid analogs is one way to test the hypothesis of a rationale for the active bisphosphonates. To further extend the concept that a preferred orientation is required for antiresorptive activity, a series of aminophenyl analogs were also designed. It was hypothesized that within this series we could design not only new antiresorptive active agents, but also analogs that were conformationally inhibited from fitting the hypothesized active pharmacophore. Thus, a series of bisphosphonate analogs were synthesized (**2-6**) within the aminophenyl R^2 substituent series. This exercise was conducted over several bone affinity classes to demonstrate the generality of the concept in respect to the biochemical pharmacophore of these agents[8]. All R^1-hydroxy-substituted compounds were synthesized via the keto phosphonate intermediate (Fig. 3)[9]. In example 2,

R^2 is OEt in the intermediate $H(O)PR^2OEt$. Where R^1 is hydrogen, standard alkylation chemistry was used[10] to prepare 4.

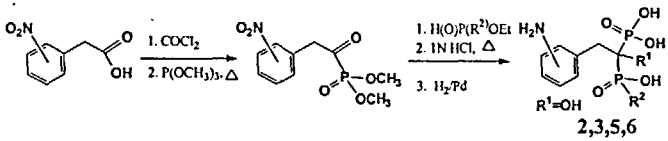


FIGURE 3 Synthesis of a series of phosphonate analogs within the aminophenyl substituent series. In the prep. of **2**, R^2 is OEt in $H(O)PR^2OEt$.

TABLE I Lowest effective dose (LED) in a series of bisphosphonate analogs (NA = no significant activity). General Structure in Figure 3. Where R^1 is hydrogen, standard alkylation chemistry was used[10] to prepare compound 4.

	ortho	meta	para	LED (mg P/kg)*
2.	$R^1=R^2=OH$			0.01 T
3.	$R^1=OH$, $R^2=CH_3$			0.1 T
4.		$R^1=H$, $R^2=OH$		NA(10) S
5.		$R^1=OH$, $R^2=CH_3$		NA(10) S
6.			$R^1=OH$, $R^2=CH_3$	NA(10) T

*All data are generated in either TPTX (T) or Schenk (S) acute in-vivo rat models[11].

This series of bisphosphonate analogs provided additional evidence of the need for a specific orientation of the nitrogen functionality in the pharmacophore for potent antiresorptive activity of bisphosphonates. *Ortho* aminophenyl substitution was shown to have the optimal orientation for the amine functionality, while the *meta* and *para* substituents appeared to be restrained from orienting this functionality properly. This concept is evident not only from biological results, but also from MM2-based molecular modeling calculations. In these studies, it was seen that the nitrogen functionality of the *para* aminophenyl analog in particular could not approach the region of space that other active analogs appeared to fill with their nitrogen moiety. This region of space continues to be best shown by the nitrogen moiety in the conformationally restrained, antiresorptive active octahydropyridine-bisphosphonate NE-58025[2,12]. It should be noted that although differences exist in the bone-targeting component of these varied examples[13], the pattern is collectively and completely consistent within the hydroxyphosphonomethylphosphinate series (3,5,6)[2].

CONCLUSION

The pyridinyl bisphosphonate risedronate was selected as a drug for development and has been approved in the US for the treatment of Paget's disease under the name Actonel™. It is in late-stage clinical trials for the treatment of osteoporosis. Analysis of a number of structure-activity relationships, including the aminophenylethane phosphonate class fully, support the concept that a specific recognition event is involved as a biochemical component of the mechanism of antiresorptive activity of bisphosphonates, independent of direct physical chemical mineral effects.

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