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REVIEW ARTICLE

Recent synthesis of aminophosphonic acids as potential biological importance

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Abstract Aminophosphonic acids are an important group of medicinal compounds, and their synthesis has been a focus of considerable attention in synthetic organic chemistry as well as medicinal chemistry. Although the phosphonic and carboxylic acid groups differ considerably with respect to shape, size, and acidity, α-aminophosphonic acids are considered to be structural analogues of the corresponding amino acids and the transition state mimics peptide hydrolysis. This review summarizes recent developments in the synthesis, characterization and biological activity of α-aminophosphonic acid and *N*-analogues. An account of both uses will be presented, emphasizing one of the potential future developments, and some implications in medicinal chemistry are also disclosed. In addition, a brief account on the characterization of *N*-(phosphonomethyl) glycine derivatives will be presented.

Keywords α-Aminophosphonic acids · *N*-(phosphonomethyl) glycine · Phosphorus trichloride · Dimethyl-H-phosphonate · Biological activity

Introduction

Organophosphorus chemistry is exploring the properties and reactivity of organophosphorus in particular aminophosphonic compounds. Aminophosphonates were almost unknown in the 1950s but now they are the subject of many publications and reviews. The discovery of aminophosphonic acids in living systems stimulated the interest in this group of compounds and the intensive research directed towards synthesis of α-aminophosphonic acid analogues of protein and non-protein amino acids resulted in a new class of drugs and other bioactive compounds with a great variety of commercial applications ranging from agriculture to medicine. Their utilities as enzyme inhibitors, anticancer agents, antibiotics, neuromodulators, plant growth regulators and herbicides, antibacterial, and many other applications have attracted the interests of chemists for a long time (Troev 2006; Kafarski and Lejczak 2000, 2001; Goding 1986; Bigge et al. 1992).

α-Aminophosphonic acids occupy an important place among the various compounds containing a P–C bond and an amino group (Fig. 1), because they are analogues of natural α-amino acids, the 'building blocks' of peptides and proteins. Phosphonates or phosphonic acids are organic compounds containing one or more C–P(O)$(OH)_2$ or C–P(O)$(OR)_2$ (with R = alkyl, aryl) groups. Since the work of Schwarzenbach in 1949, phosphonic acids are known as effective chelating agents. The introduction of an amine group into the molecule to obtain –NH_2–C–P(O)$(OH)_2$ increases the metal binding abilities of the phosphonate. Phosphonates are highly water-soluble while the phosphonic acids are only sparingly soluble. Phosphonates are not volatile and poorly soluble in organic solvents (Franz 1974; Huber and Gilmore 1975; Stemerick 1997; Camden 1997a, b, 1998, 1999, 2000; Oleksyszyn et al. 1994).

Organophosphorus compounds have been extensively used in organic synthesis. Several reviews have been devoted to the synthesis of aminoalkanephosphonic acids (Troev 2006; Kafarski and Lejczak 2000, 2001; Goding

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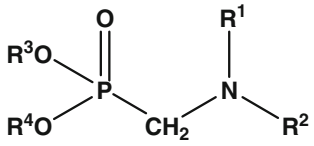


Fig. 1 Aminophosphonic acids and *N*-derivatives

1986). However, most of the described methods for the synthesis of α-aminophosphonic acids use carbonyl compounds such as aldehydes, ketones, or carboxylic acids as starting compounds. The impressive array of applications has recently stimulated considerable effort towards the synthesis of aminophosphonic acids and many methods are now available (Kabachnik and Medved 1952, 1953, Medved and Kabachnik 1954; Fields 1952; Petrov et al. 1974; Galkin et al. 1993; Gancarz and Gancarz 1993; Gancarz 1995, 1993; Maury et al., 1992; Sardarian and Kaboudin, 1997). α-Aminophosphonic acids are obtained reacting amides, or 2-oxazolidinone derivatives with formaldehyde and phosphorus trichloride. α-Aminophosphonic acids bearing heterocyclic, aromatic rings such as furane, anthracene, thiophene, pyrazole, imidazole and pyridine are described (Tyka 1970; Redmore 1978; Engelmann and Pikl 1942; Pikl 1943; Wong and Bunker 1985; Fields et al. 1989; Kraicheva et al. 2002; Kraicheva 2003; Boduszek 1995, 1996; Boto et al. 2005).

Chemistry: synthesis of α-aminophosphonates

The diesters of H-phosphonic acid occupy a major position in organophosphorus chemistry since they are frequently intermediates in the synthesis of a variety of bioactive products including aminophosphonates, aminophosphonic acids, P–C phosphonates, hydroxyalkyl phosphonates, etc. The strongly polar character of the phosphoryl group of the H-phosphonates is responsible to a great extent for the reactivity of this class of compounds (Troev 1997, Troev and Tsevi 1998, Troev et al. 1999a, b, Troev 2000; Troev et al. 2008; Rabasso et al. 2006).

Kabachnik and Fields (Kabachnik and Medved 1952, 1953; Medved and Kabachnik 1954; Fields, 1952) have discovered the first method for the preparation of α-aminophosphonic acids. According to Scheme 1 α-aminophosphonates (4) are prepared using one-pot synthesis: a carbonyl compound (aldehyde and ketone) (1), an amine (2) and a dialkyl H-phosphonate (3). The Kabachnik–Fields reaction is very important in drug discovery research for generating peptidomimetic compounds.

The mechanism of the Kabachnik–Fields reaction is shown in the Scheme 2 and depends on the nature of the substrates. The amine (**2**) and dialkyl H-phosphonate (**3**) form a complex in which either one of the partners may react with the carbonyl (**1**) compound. Usually, the basicity of the amine determines the reaction pathway. In the Kabachnik–Fields reaction mixture, two nucleophiles: dialkyl phosphite and the amine compete for the electrophilic carbonyl compound. Experimental results revealed that the first stage of the Kabachnik–Fields reaction, namely, the formation of a dialkyl phosphite–amine (***I***) complex is of critical importance for further reaction pathway. Depending on the acidity–basicity relationship between the dialkyl phosphite and the amine, the readily polarizable complex can have a structure like (***I***).

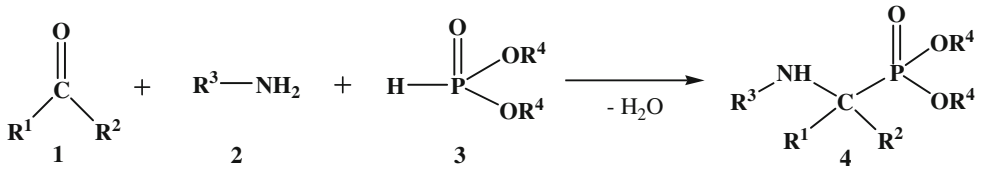
If additional catalysts are used, both acids and bases can have a positive influence on the reaction rate. Sometimes, the chemical yield and the diastereoselectivity of the formation of α-aminophosphonates are higher in two-component systems using preformed imines. In this case, due to the phosphonate–phosphite tautomerism, the addition to the imine could occur by either a four- or five-membered transition state (Cherkasov 1998).

The lanthanide triflates, catalyzing the Kabachnik–Fields reaction gave excellent yields in ionic liquids under MW irradiation (see Scheme 3) (Mu et al. 2006). All of the examined catalysts showed higher activity in [bmin][BF_4] and [bmin][PF_6] than in other ionic liquids. (Lee et al. 2002; Bhattacharya and Rana 2008).

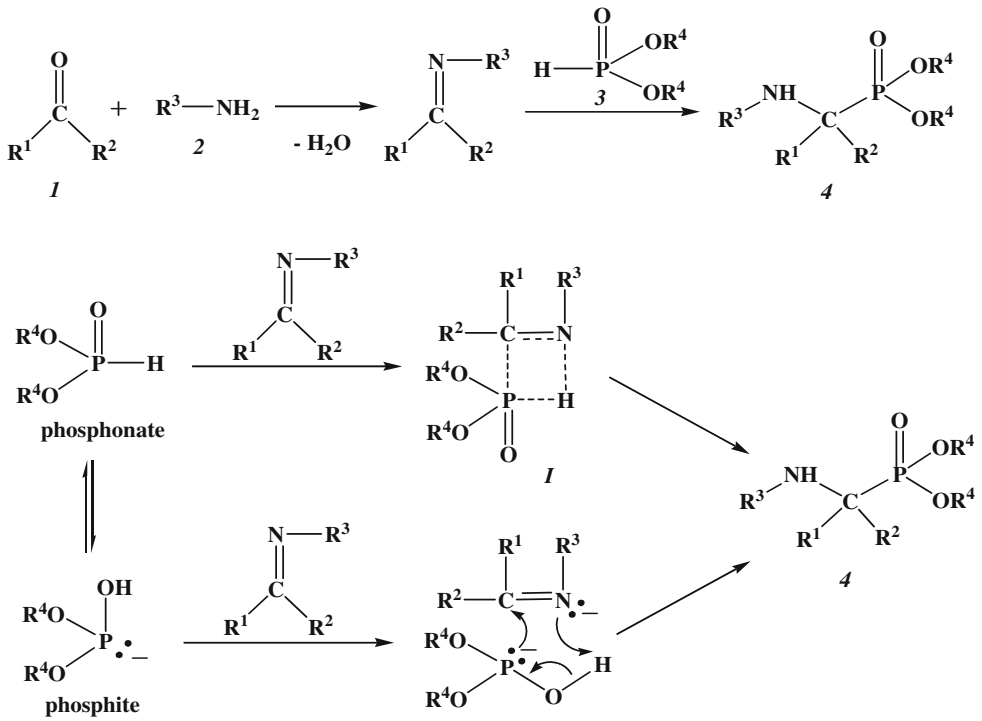
In the early 1940s Pikl and Engelmann (Redmore 1978; Engelmann and Pikl 1942; Pikl 1943) published two patents describing the use of a three-component reaction mixture consisting of amide, formaldehyde and phosphorus trichloride for the preparation of aminomethylphosphonic acids (see Scheme 4). They even proposed a mechanism for the reaction, in which an intermediate *N*-(hydroxymethyl)amide was formed. Reaction with phosphorus trichloride then resulted in conversion of the hydroxyl group into an easily leaving group, which underwent phosphate–phosphonate rearrangement either intermolecular or via nucleophilic substitution by a second molecule of phosphorus trichloride.

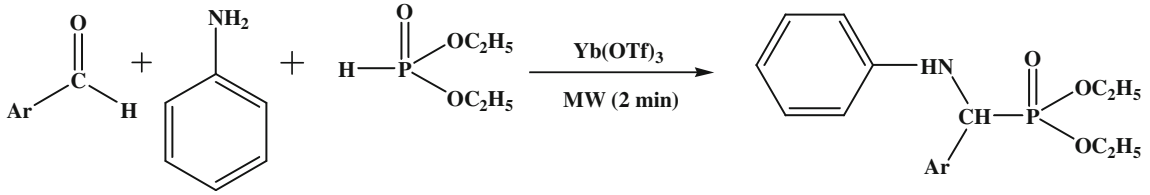
Recently *N*-(phosphonomethyl)glycine derivatives (Fig. 2) were synthesized and characterized by our group (Naydenova et al. 2003, 2006, 2007, 2008a, b; Todorov et al. 2006a, b; 2008; Todorov et al. 2007). The novel aminophosphonic acids were synthesized by two different methods. For the synthesis of ***1–3*** and ***12–19*** compounds we used Engelmann and Pikl's procedure (Engelmann and Pikl 1942 ; Pikl 1943). As a starting compound were used 2-oxazolidinone derivatives or (9H-fluoren-9-yl)urea, phosphorus trichloride and formaldehyde, in the molar ratio −1:2:2. The 1-[(dimethoxyphosphono)methylamino] cycloalkanecarboxylic acids with 5-, 6-, 7-, 8- and 12-membered rings (***7–11***) were prepared via the Kabachik–Fields reaction. The Cα,α-disubstituted amino acids Ac5c, Ac6c, Ac7c, Ac8c and Ac12c were prepared following the

Scheme 1 Kabachnik–Fields reaction

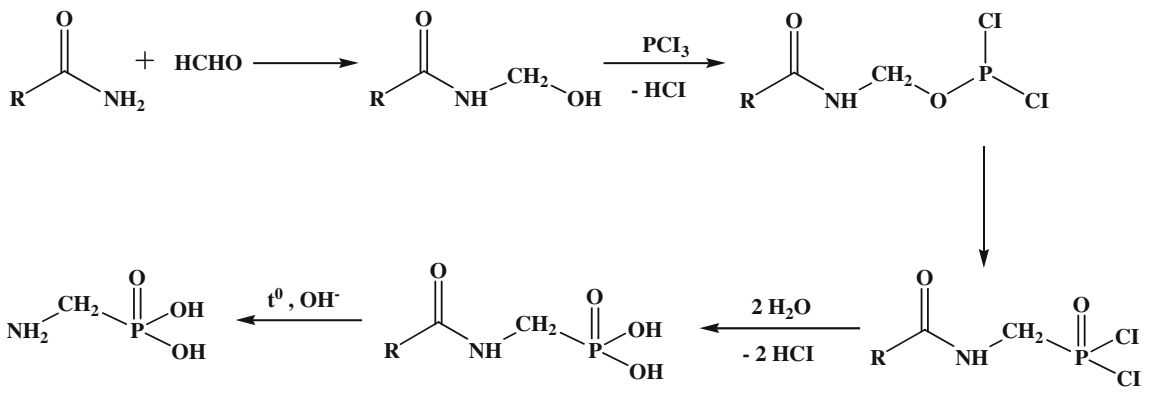


Scheme 2 Mechanism of the Kabachnik–Fields reaction





Scheme 3 Synthesis of aminophosphonates under MW irradiation



Scheme 4 Engelmann and Pikl's procedure

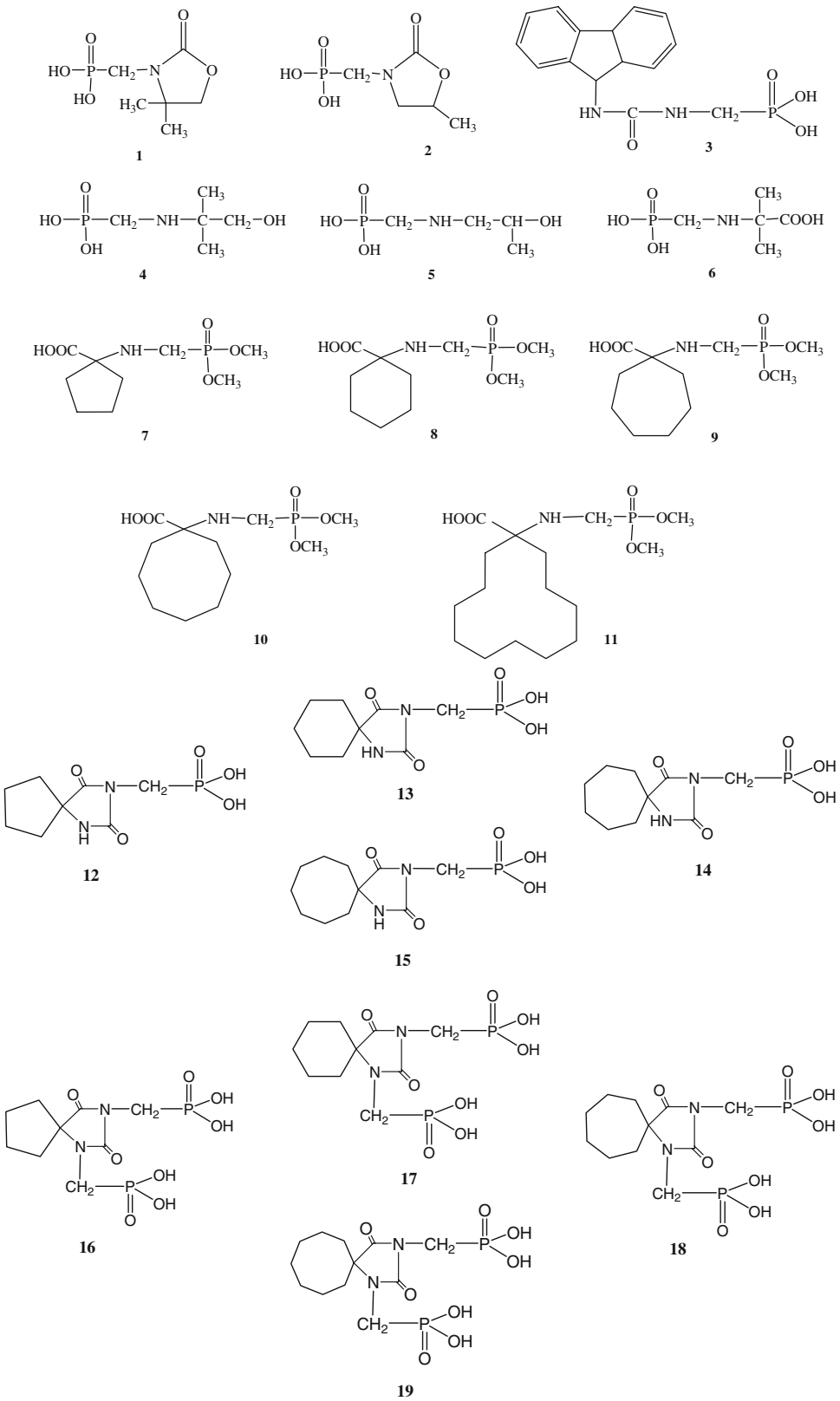


Fig. 2 Structures of the newly synthesized α-aminophosphonic acids (**1–19**)

procedure, which involves the formation of cycloalkane-spiro-5-hydantoin from a cyclic ketone, followed by alkaline hydrolysis to the cyclo-aminoacid. All of the newly compounds (see Fig. 2) were proved by means of IR, ^{1}H, $^{13}C\{^{1}H\}$ and ^{31}P NMR spectroscopy (Naydenova et al. 2003, 2006, 2007, 2008a, b; Todorov et al. 2006a, b, 2008).

The ^{31}P-NMR spectroscopy is the most precise method for determining the structure of the phosphorus-containing compounds. Chemical shifts for ^{31}P depend on imbalance of σ-bonds caused by the difference in electronegativity of the atoms and by the effect of the free electron pairs, degree of occupation of phosphorus *d*-orbitals, and deviation from geometric symmetry.

In addition, the following factors influence the phosphorus chemical shifts:

- degree of ionization of the bonds,
- formation of complexes with cations,
- valence angle O–P–O and torsion angle,
- and temperature and solvent.

The typical range for the ^{31}P chemical shifts in the diesters of H-phosphonic acid is 0–15 ppm referenced to 85% H_3PO_4. The phosphorus atom of α-aminophosphonic acids in the ^{31}P NMR spectrum appears at 15–25 ppm.

Aminophosphonic acids: biological activity

The first natural phosphonate, 2-aminoethylphosphonic acid (Fig. 3), was identified in 1959 and occurs in plants and many animals, mostly in membranes. Phosphonates are quite common among different organisms, from prokaryotes to eubacteria and fungi, molluscs, insects and others. The biological role of the natural phosphonates is still poorly understood. Until now no bis- or poly-phosphonates have been found to occur naturally (Horiguchi and Kandatsu 1959; Kafarski and Lejczak 2000; Troev 2006).

The main class of compounds employed in the control of pests are organophosphorus, aminophosphonic acids in particular. These compounds have a common target, which is the arthropod nervous system. Organophosphorus acts as classical acetylcholinesterase (AChE) inhibitors. These compounds remain as one of the most interesting classes of insecticides from both the commercial and toxicological points of view. The relative low risk aminophosphonate insecticides offer to mammals is due to their selectivity, which is attributable to structural differences in the molecular targets associated with amino acid changes, different metabolic activation and detoxication, and/or with their biodegradability (Troev 2006).

α-Aminophosphonic acids are considered to be structural analogues of the corresponding amino acids, thus acting as competitive inhibitors and they can act as false substrates during the course of amino acid metabolism. Amino acids and peptides pass through cancer cells four or five times more easily than through normal cells. Aminophosphonic acids are effective in suppressing the tumor growth and are investigated as potential lead compounds with anticancer activity. A pharmaceutical composition for treatment of mammals, warm blooded animals and humans, comprising a pharmaceutical carrier and an effective amount of a chemotherapeutic agent and anticancer compound was selected from the group consisting of *N*-(phosphonomethyl) glycine derivatives (Camden 1997a, b, 1998, 1999, 2000).

Aminophosphonic acids are mainly used as insecticides, herbicides, bactericides, plant-growth regulators, enzyme inhibitors, anticancer agents, etc. The most significant discoveries of the past 25 years have been those which led to the development of aminophosphonates as agrochemicals, especially the commercial development of the glyphosate. It was shown that the compound behaved in a similar way to glycine, suppressing the growth of tobacco rootlets. The mechanism of the action of glyphosate is thought to be associated with the metabolism of aromatic amino acids. *N*-(phosphonomethyl) glycine (see Fig. 4) is a highly effective herbicide because of its potent and specific inhibition of 5-enolpyruvoylshikimate 3-phosphate synthase (EPSPS). These discoveries were a tremendous stimulus to the synthesis and biological screening of structural analogues (Naylor 2002; Chykaliuk et al. 1980; Sprankle et al. 1975; Sandberg et al. 1980; Lolas and Coble 2006; Richard et al. 2005; Baird et al. 1971).

N-(Phosphonomethyl) glycine is effective in inhibiting test-tube growth of *Plasmodium falciparum*, the parasite that causes malaria. Moreover, it has been found that the *N*-(phosphonomethyl) glycines are especially effective in suppressing the growth of cancer, tumor, virus or bacteria. A pharmaceutical composition for treatment of mammals, warm blooded animals and humans, comprising a pharmaceutical carrier and an effective amount of a chemotherapeutic agent and anticancer compound was selected from the group consisting of *N*-(phosphonomethyl) glycine derivatives (Rueppel et al. 1977; Grossbard and Atkinson 1985; Tomlin 1997; Amrhein et al. 1980; Haslam 1974; Franz et al. 1997; Preston et al. 1987; Meek and Villafranca 1980).

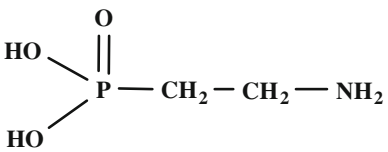


Fig. 3 2-Aminoethylphosphonic acid

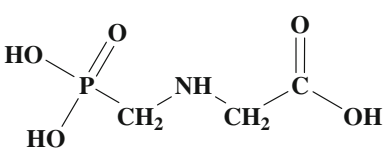


Fig. 4 *N*-(phosphonomethyl) glycine

Aminophosphonates have three main properties: they are effective chelating agents for di- and tri-valent metal ions; they inhibit crystal growth and scale formation, and they are quite stable under harsh chemical conditions. Phosphonates are also used more and more in medicine to treat various bone and calcium metabolism diseases and as carriers for radionuclides in bone cancer treatments (Kafarski and Lejczak 2000; Goding 1986; Finlay et al. 2005; Djokic et al. 2008; Hackenberg and Bartling 1959).

For the total characterization of these newly synthesized aminophosphonic acids it is very important and appropriate to investigate their genotoxic, antiproliferative and cytotoxic effects. These effects of the newly synthesized aminophosphonic acids (***1–11***) were investigated for the first time by our group. Chromosome aberration test was applied to solve the main task. This test allows detection of the possible genotoxic effect and the type of the chromosome aberrations. The carried out cytogenetical investigations, structural chromosome aberrations (breaks and fragments) and intrachromosome exchanges (centromer/centromeric and telomere/telomeric fusions), showed that the newly synthesized aminophosphonic acids possess moderate clastogenic effect. The proliferative activity of bone marrow cell populations was determined by evaluation of their mitotic index. Most of the investigated compounds demonstrated low genotoxic effect.

The cytotoxic activity of the tested compounds was evaluated using the MTT-dye reduction assay in a panel of human tumor cell lines, namely the acute myeloid leukemia HL-60, the chronic myeloid leukemias LAMA-84 and K-562, the non-Hodgkin lymphoma DOHH-2, the Hodgkin lymphoma HD-MY-Z and the urinary bladder carcinoma Ej (see Fig. 5).

The encountered cytotoxic potential of the tested aminophosphonates in a panel of in vitro tumor test systems, together with their previously established moderate clastogenic potential warrants further detailed exploitation of this structural scaffold, in order to define more precisely the structure activity rules and the mechanistic peculiarities for this novel class of cytotoxic agents.

All of the tested compounds induced 50% inhibition of the malignant cell proliferation at relatively high micromolar concentrations. In order to elucidate mechanistically the encountered cytotoxic effects, we carried out quantitative determination of the ability of these compounds to induce oligonucleosomal DNA fragmentation, which is a key hallmark feature of apoptosis, by means of 'cell death detection' ELISA (Naydenova et al. 2003, 2006, 2007, 2008a, b; Todorov et al. 2006a, b, 2008; Momekov et al. 2007).

They exhibited moderate clastogenicity, low antiproliferative activity on mice bone marrow cells and well expressed cytotoxicity against human tumor cell lines. The *1-[(dimethoxyphosphoryl)methylamino]cyclooctanecarboxylic acid* (***10***) and *1-[(dimethoxyphosphoryl)methylamino]cyclododecanecarboxylic acid* (***11***) proved superior to the remaining compounds and were found to trigger apoptotic cell death in DOHH-2 cells (Naydenova et al. 2003, 2006, 2007, 2008a, b; Todorov et al. 2006a, b, 2008; Momekov et al. 2007). These results unambiguously indicate that the newly synthesized aminophosphonates exert antineoplastic potential, combined with low clastogenicity. These discrepancies between the cytotoxic/antiproliferative potential of ***10*** and ***11*** against tumor cells, on one hand, and embryonal kidney cells, on the other hand, could be largely attributed to their ability to trigger apoptotic cell death at low micromolar concentrations as evidenced by the established DNA-fragmentation in DOHH-2 cells. Moreover, aminophosphonic acids have been found to accumulate more intensively in malignant cells than in normal cells, which could contribute to the established selective cytotoxicity.

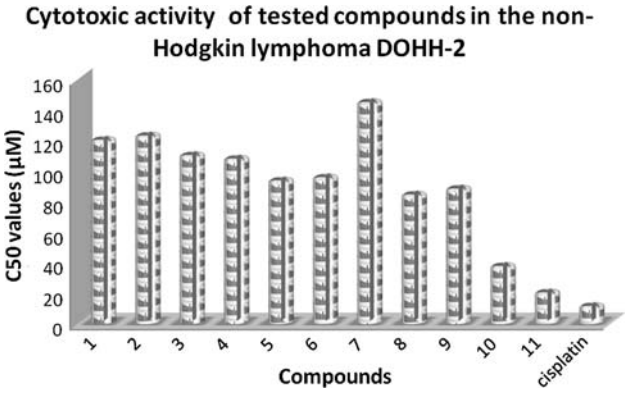


Fig. 5 Cytotoxic activity of tested compounds in the non-Hodgkin lymphoma DOHH-2

Conclusions

Although aminophosphonic acids have been known for more than 60 years they still represent a somewhat undiscovered group of potential biologically active substances. The representative newly synthesized compounds and their biological activity shown in this review indicate at least their usefulness as the lead compounds for the design and preparation of new drugs. Especially successful seem to be the approaches for the design of anticancer agents.

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