Methylidynetrisphosphonates: Promising C₁ building block for the design of phosphate mimetics

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Abstract

Methylidynetrisphosphonates are representatives of geminal polyphosphonates bearing three phosphonate (PO₃H₂) groups at the bridged carbon atom. Like well-known methylenebisphosphonates (BPs), they are characterized by a P–C–P backbone structure and are chemically stable mimetics of the endogenous metabolites, i.e., inorganic pyrophosphates (PPᵢ). Because of its analogy to PPᵢ and an ability to chelate metal ions, the 1,1,1-trisphosphonate structure is of great potential as a C₁ building block for the design of phosphate mimetics. The purpose of this review is to present a concise summary of the state of the art in trisphosphonate chemistry with particular emphasis on the synthesis, structure, reactions, and potential medicinal applications of these compounds.

Introduction

Methylidynetrisphosphonic acid, HC(PO₃H₂)₃, or more commonly methylidynetrisphosphonates, XC(PO₃R₂)₃, also called methanetrisphosphonates, are representatives of geminal polyphosphonates among which methylenebisphosphonates, H₂C(PO₃R₂)₂, are well-known as metabolically stable analogues of the naturally occurring inorganic pyrophosphate (PPᵢ) [1-3]. Bisphosphonates are widely used drugs for the treatment and prevention of excessive osteoclast-mediated bone resorption associated with osteoporosis, Paget's disease, and tumour-induced osteolysis [4-6]. In the wide area of polyphosphonate chemistry, gem-trisphosphonates represent a new area of study and many of the important developments in their chemistry are based on their specific properties. The presence of three phosphate (PO₃R₂) substituents at the bridged carbon atom causes pronounced physical and chemical effects and imparts unique electronic characteristics to 1,1,1-trisphosphonated compounds. Most importantly, the replacement of the hydrogen atom attached to the bridge carbon in methylenebisphosphonates by a third ionisable phosphate moiety results in supercharged isosteric systems relative to pyrophosphoric acid [7]. It was also demonstrated that steric effects play a significant role in trisphosphate chemistry and allow efficient control of regio- and stereoisomer chemistry for addition reactions. Moreover, examples of the reactivity of functionalized methylid...
dyenetrishphosphonates \( \text{XC(O)}_3 \text{R}_2 \text{R}_3 \) shown in this review indicate that the nature of the substituent \( \text{X} \) at the central carbon atom is the key to the optimization of their acidic and coordination properties thus providing excellent possibilities for the design of effective phosphate mimetics. Especially successful so far seem to be approaches for the synthesis of trisphosphate-modified nucleotides and nucleosides, which represent a promising class of potential drugs [8].

**Review**

**Preparation of methylidynetrishphosphonates**

**Synthesis via a Michaelis–Arbuzov reaction**

Phosphonate esters are often prepared through Michaelis–Arbuzov reaction of a trialkyl phosphite with an alkyl halide [9]. However, contrary to the early patent claims, trisphosphonate esters cannot be derived from simple trihalomethyl derivatives [10-12]. Indeed, chloroform and bromoform do not react with triethyl phosphite even under harsh conditions [11]. In addition, no reaction occurred between benzotrichloride (PhCCl\(_3\)) and triethyl phosphate at a temperature below 150 °C. The CuCl-catalyzed reaction of PhCCl\(_3\) and (EtO)_\(_3\)P at 120–140 °C produced 1,2-diphenyl-1,1,2,2-tetrachloroethane [13].

The early work reported that the trisphosphate PhC(PO\(_3\)Et\(_2\))\(_3\) was formed from triethyl phosphite and dibenzoyl peroxide when reagents were boiled under reflux in chloroform, but proof of the trisphosphate structure was not given [14]. It was later suggested that the product of this reaction is most likely a phosphate-phosphonate, PhC(PO\(_3\)Et\(_2\))\(_2\)OPO\(_3\)Et\(_2\) [15]. Birum postulated the preparation of the trisphosphate \((\text{Et}_2\text{O}_3\text{P})_3\text{CSPO}_3\text{Et}_2\) from \(\text{Cl}_3\text{CSCl}\) and \(\text{P(OEt)}_3\), but once again, no definitive proof of trisphosphate structure was provided [16,17].

The first authentic synthesis of 1,1,1-trisphosphate derivatives \(\text{1a,b}\) was described by Kukhar, Pasternak and Kirsanov by allowing the addition of triethyl phosphite to dichloromethylene dialkylammonium chloride to proceed in dichloromethane at \(-40^\circ\text{C}\) (Scheme 1) [18].

Other researchers have confirmed this finding [19,20]. Trichloromethylisocyanate [21] and tribromomethylisocyanate [22] react similarly with 3 equivalents of triethyl phosphate forming isocyanate \(\text{2}\), which was characterized by its IR and NMR spectra and also by its reaction products \(\text{3}\) and \(\text{4}\) (Scheme 2). Trisphosphate \(\text{2}\) is also formed by the reaction of \((\text{EtO})_2\text{P(O)}_2\text{C(Cl)}\text{NCO}\) as well as \((\text{EtO})_2\text{P(O)}\text{Cl}_2\text{NCO}\) with 1 or 2 equiv of \((\text{EtO})_3\text{P}\), correspondingly [21].

An unsuccessful attempt to synthesize trisphosphonates from isocyanide dichlorides was made by the combination of Arbuzov reaction and dialkyl phosphate addition. The reaction sequence leads to \(\text{N}\)-phosphorylated bisphosphonates \(\text{5}\) instead of the desired trisphosphonates (Scheme 3) [23,24].

**Scheme 1**: Synthesis of hexaethyl dialkylaminomethylidynetrishphosphonates \(\text{1}\) from dichloromethylene dialkylammonium chlorides.

**Scheme 2**: Synthesis and some transformations of trisphosphonate \(\text{2}\).

**Scheme 3**: Attempt to synthesize trisphosphonates by the combination of Arbuzov reaction and dialkyl phosphate addition.
Synthesis via anionic methylenebisphosphonates

The anionic bisphosphonate \([\text{CH(PO}_3\text{Et)}_2]^-\) proved unreactive with diethyl chlorophosphate, \(\text{ClP(O)(OEt)}_2\), but phosphinylation of the bisphosphonate anion with diethyl chlorophosphite, \(\text{ClP(OEt)}_2\), followed by in situ oxidation with atmospheric oxygen of the presumed phosphinate intermediate to the trisphosphonate 6 was successful (Scheme 4) [25]. An improved version of this method includes oxidation of the phosphinate intermediate with hydrogen peroxide in tetrahydrofuran [26]. Mixed ethyl/isopropyl trisphosphonate ester 9 has been prepared by treatment of the bisphosphonate 7 with diethyl chlorophosphite and sodium hexamethyldisilazane, and subsequent oxidation of the phosphinate intermediate 8 with iodine in pyridine–THF–H\(_2\)O (Scheme 5) [7,27]. It was noted that the intermediate 8 was unstable during either acidic or basic workup and readily decomposed to the starting bisphosphonate 7. However, oxidation of 8 gave stable trisphosphonate ester 9 in 72% yield.

For the synthesis of alkylidene-1,1,1-trisphosphonate esters 12a–f a three-step protocol including synthesis of alkylidene-1,1-bisphosphonates 11 from tetraethyl methylenebisphosphonate (10), phosphinylation and oxidation has been developed (Scheme 6) [26]. Propargyl-substituted trisphosphonate 15 was prepared by conjugate addition of sodium acetylide to ethenylidenebisphosphonate 13 and the subsequent phosphinylation and oxidation (Scheme 7). This compound has been used in an elegant construction (“click” chemistry) of triazole derivatives (see Scheme 17) [26,28].

Synthesis via 7,7-bisphosphonoquinone methides

A unique route to trisphosphonate 18 via addition of diethyl phosphate to 7,7-bisphosphonyl-3,5-di-tert-butylquinone...
methide 17 derived by oxidation of bisphosphonate 16 was developed by Gross and co-workers (Scheme 8) [29]. More recent reports of this type of reaction are from laboratories of Russian researchers [30,31]. They showed that bisphosphonate 16 can be prepared in good yield by the Arbuzov reaction of trimethylsilyl esters of trivalent phosphorus acids with the easily accessible 2,6-di-tert-butyl-4-(dichloromethyl)phenol. In the next step, the bisphosphonate 16 was oxidized with K$_3$Fe(CN)$_6$ into quinone methide 17 in 91% yield. Further addition of diethyl phosphite in the presence of sodium hydride gives the triphosphonate 18 (Scheme 9). Note that bisphosphonate 16 is also available by the reaction 4-hydroxy-3,5-di-tert-butylbenzaldehyde with triethyl phosphite in the presence of malonic ester (yield 53%) [32].

This reaction mode takes place also for the interactions of quinone methide 17 with diphenylphosphinite and quinone methide 19 with diethyl phosphite (Scheme 10) [33]. However, when the same researchers tried to obtain triphosphorus derivatives with one phosphono and two phosphinoxido groups using quinone methides 19 and 21 as starting materials, phosphorylation of the aromatic nucleus via splitting off a tert-butyl group as isobutene and formation of bisphosphonates 22 and 23 was observed. The same happened when quinone methide 21 was treated with diphenylphosphinite (Scheme 11). The primary step of this reaction, which proceeds under mild alkaline conditions, is presumably a direct attack of the diphenylphosphinyl anion in 3-position, followed by the splitting off of isobutene [33,34].

Variations on the Arbuzov reaction have also been tested in the preparation of triphosphonate 18. Thus, a phosphorylation in three steps could be performed on monophosphonylated quinone methide 25. The starting compound was first phosphorylated with triethyl phosphite to give the phosphonium betain 26. This compound was subsequently transformed into the corresponding 7,7-bisphosphonoquinone methide 27 by treatment with bromine. Heating of 27 under reflux in triethyl phosphite resulted in the trisphosphonate 18 in a yield of 40%. The phosphonium betain 26, which was expected from the reaction of 27 and triethyl phosphite was unstable and could not be isolated (Scheme 12) [35]. It should be noted that compound 18 can be easily oxidized to the corresponding stable phenoxyl radical with PbO$_2$ in toluene [36].
Synthesis from diazomethylenebisphosphonates

The feasibility of synthesizing trisphosphonate esters under mild conditions via metal-carbenoid-mediated P–H insertion reactions was demonstrated by Gross et al. [25]. In particular, the reaction between tetraethyl diazomethylenebisphosphonate and diethyl phosphite in the presence of copper(II) bis(acetylacetone) provides trisphosphonate ester 6 (Scheme 13). The yield is poor (20%) but the product can be isolated in the pure state and the method is presumably general (cf. [37]). The starting tetraalkyl diazomethylenebisphosphonates are prepared...
by the reaction of tosyl azide [38,39] or 2-naphthalenesulfonil azide [40] with the corresponding methylenebisphosphonate precursors in the presence of a base.

Various methods
Quite interestingly, at room temperatures diethyl phosphite reacts with tert-butylphosphaethyne in the presence of sodium metal to form 1,1-bis(diethoxyphosphoryl)-2,2-dimethylpropylphosphine (29) (Scheme 14) [41]. The proof of structure 29 was given but no details were provided on the reaction course.

Reactions of methyldynetrisphosphonate esters
The C(PO$_3$R$_2$)$_3$ group is chemically resistant to attack by bases and oxidizing/reducing agents. Upon treatment of hexaethyl methyldynetrisphosphonate (6) with NaH in THF, formation of the sodium salt was suggested by a downfield shift in the $^{31}$P NMR spectrum (from 14 to 32 ppm). However, no further alkylation reaction could be observed with benzyl bromide and allyl bromide, presumably because of high stabilization and strong steric shielding of the carbanionic center [26]. In fact, the importance of steric factors in the reactivity of trisphosphonate esters manifested in many reactions of $\alpha$-alkyl-substituted trisphosphonates. Thus, attempted cross metathesis of allyl derivative 12b with 2-methyl-2-buten and the Grubbs second-generation catalyst afforded the unexpected cis and trans-1,2-disubstituted olefins 30 as the major product and only a small amount of the expected trisubstituted olefin 31. However, under similar conditions stericly less congested analogue 12e smoothly undergoes cross metathesis to give the desired trisubstituted olefin 32 in high yield (Scheme 15) [26].

In a similar sense, reduction of the trisphosphonate 12e with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by standard oxidative workup afforded the primary alcohol 33 in reasonable yield, but the 1-allyl-substituted trisphosphonate 12b did not undergo hydroboration with 9-BBN. However, treatment of 12b with borane in THF resulted in conversion to the primary alcohol 34 in good yield (Scheme 16) [26]. A further example of the reactivity of trisphosphonates is provided by a click reaction of 3-butyln-1-ylidynetrisphosphonate 15 with benzyl azide, which results in novel triazole compound 35 bearing the trisphosphonate function (Scheme 17) [26].
In contrast to methylenebisphosphonate esters, methyldi- nitrophosphonate esters have a tendency to undergo dephosphonylation when subjected to acid hydrolysis. Thus, although the bisphosphonate $\text{PhCH}_2\text{CH(PO}_3\text{Et}_2\text{)}_2$ smoothly undergoes hydrolysis to the corresponding bisphosphonic acid by treatment with HCl under reflux, benzyltrisphosphonate $\text{PhCH}_2\text{C(PO}_3\text{Et}_2\text{)}_3$ undergoes dephosphonylation under similar conditions [25,26]. Synthesis of free trisphosphonic acids could be carried out by transsilylation of the corresponding hexaalkyl trisphosphonates with $\text{Me}_3\text{SiBr}$ in the presence of a base followed by hydrolysis or alcoholysis [42]. This methodology has been particularly successful for preparing the parent methyldi- nitrophosphonic acid and its salts. Thus, heating 9 with $\text{Me}_3\text{SiBr}$ in dichloromethane followed by solvolysis in the presence tri-$\text{n}$-butylamine gave methyldi-nitrophosphonic acid as its tris(tributylammonium) salt. This product was converted into its trisodium salt by precipitation from a methanol solution using a NaI solution in acetone [7]. The method has been also applied to the preparation of the trisphosphonate salts 37. Treatment of trisphosphonic acid ester 12b with $\text{Me}_3\text{SiBr}$ and collidine resulted in the formation of the silyl ester 36, which was converted into a mixed sodium and collidinium salt 37 by the addition of 1 N aqueous NaOH (Scheme 20) [26].

Similarly, a sodium salt of an acid-labile trisphosphonic acid 38 could be prepared with minimal P–C scission by carbonate-buffered hydrolysis of in situ formed silyl ester (Scheme 19) [43].

Amino-substituted trisphosphonate esters $\text{Alk}_2\text{N–C(PO}_3\text{Et}_2\text{)}_3$ are even less resistant to acid dephosphonylation than the parent trisphosphonate esters, HC(PO$_3R_2$)$_3$, or their α-carbo-substituted derivatives. In particular, in the case of aminotrisphosphonate ester 1a all standard synthetic routes to phosphonic acids (A–C) via acidic hydrolysis of phosphonate esters lead to the elimination of one phosphoryl group and the formation of bisphosphonic acid 39. Even with $\text{Me}_3\text{SiBr/H}_2\text{O}$, transsilylation and solvolysis under mild conditions afforded only the dephosphorylated product (Scheme 20) [43].
The result of the methylation of trisphosphonate 1a depends on the reagent: treatment of 1a with methyl p-toluenesulfonate or dimethyl sulfate leads to the expected quaternary ammonium salts 40, while with iodomethane one phosphoryl group is split off, and a mixture of bisphosphonates 41 and 42 is formed (Scheme 21) [20].

In a fascinating series of publications, Blackburn and co-workers have realized the synthesis of “supercharged” mimics of pyrophosphoric acid capable of introducing additional anionic charge relative to simple methylenebisphosphonates when built into ATP and ApnA analogues [7,8,27,44]. They demonstrated that methylidynetriphosphonic acid and especially its halogenated derivatives are key structure blocks in the synthesis of the nucleotide analogues with enhanced affinity for receptors and better charge correlation with transition states for selected kinases. Two synthetically useful approaches to the parent trisphosphononic acid HC(PO₃H₂)₃ have been developed. One of the procedures is based on the treatment of trisphosphonate salt 38 with a mixture of hydrogen peroxide in trifluoroacetic acid (Scheme 22). An alternative and more efficient synthesis of methylidynetriphosphonic acid uses a transsilylation of hexaalkyl trisphosphonate 9 followed by hydrolysis [27].

The tris(tributylammonium) salt of methylidynetriphosphonic acid was transformed into an ADP analogue 45 and into an analogue of ATP 46 using the method of Poulter and the phosphomorpholidate procedure of Khorana and Moffatt, respectively. Diadenosine tetraphosphate analogue 47 was obtained upon treatment of chloromethylidynetriphosphonic acid 44 with excess AMP morpholidate. The incorporation of the third adenylate moiety was found to be extremely slow; however, the use of tetrazole as catalyst allowed the preparation of P₁,P₂,P₃-tris(5'-adenylyl)methylidynetriphosphonate 48 and the tripodal P₁⁻,5'-adenosyl P₂,P₃-bis(5'-adenylyl)methylidynetriphosphonate 49 in good yields. Compounds 48 and 49 provide the first examples of species in which three adenylate moieties are linked together by a methylidynetriphosphonic core (Scheme 24) [8].

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**Scheme 21:** Methylation of trisphosphonate 1a.

**Scheme 22:** Synthesis of the free methylidynetriphosphonic acid via trisphosphonate salt 38.

**Scheme 23:** Synthesis of halomethylidynetriphosphonate salts 43 and 44 by modified Gross’s procedure.
Table 1: Ionisation constants for polyphosphonic acids determined in the range 3.5 < pH < 10.5 at 37 °C and 0.152 M NaCl [7].

| Polyphosphonic acid | pK$_{a3}$ | pK$_{a4}$ | pK$_{a5}$ | Net charge at pH 7.0 |
|---------------------|-----------|-----------|-----------|---------------------|
| O(P$_2$O$_5$H)$_2$  | 6.6       | 9.4       | –         | 2.72                |
| HO$_2$C(HPO$_2$)$_2$| 7.24      | 10.11     | 3.35      |
| HO$_2$S(HPO$_2$)$_2$| 6.61      | 10.57     | 3.71      |
| HC(P$_2$O$_5$H)$_2$ | 6.46      | 9.90      | 3.77      |
| ClC(P$_2$O$_5$H)$_2$| 5.92      | 9.08      | 3.92      |
| FC(P$_2$O$_5$H)$_2$| 5.77      | 8.86      | 3.95      |

*aThe strongly acidic dissociation constants were off-scale for measurements by titration.*

Under the conception of Blackburn, methyldiennetratisphosphonic acid, HC(P$_2$O$_5$H)$_3$, can be viewed as a “supercharged” mimic of pyrophosphoric acid (PP$_3$) since the introduction of a third ionizable phosphate (PO$_3$H$_2$) group into methylenebisphosphonic acid delivers additional charge at physiological pH. Thus, the parent methyldiennetratisphosphonic acid and its fluoro-and chloro-substituted derivatives have at least one more negative charge than pyrophosphate at pH 7 (Table 1) [7,27].

X-ray structure analysis of trisphosphonic salt [FC(P$_2$O$_5$H)$_3$]$^{3-}$3Na$^+$ supported its isosteric character relative to pyrophosphate. In particular, the P–C–P geometry (both the P–C bond distance and the P–C–P angle) is close to the geometry in the methylenebisphosphonate salts while the phosphorus–phosphorus distance is close to that observed for methylenebisphosphonates and pyrophosphate salts (Figure 1) [7].

Structure features, spectroscopic and acid properties

Methyldiennetratisphosphonic acid as tris(cyclohexylamine) salt, HC(P$_2$O$_5$H)$_3$·3C$_6$H$_11$NH$_2$, is a stable, easy to handle colorless solid (mp 210–211 °C; $^{31}$P NMR (H$_2$O) $\delta$ 12.8 ppm; $^1$H NMR (D$_2$O) $\delta$ 2.73 (CH), $J_{PC}$ = 22.3 Hz; $^{13}$C NMR (D$_2$O) $\delta$ 45.16 (CH), $J_{PC}$ = 102.2 Hz) [25]. Methyldiennetratisphosphonic acid hexaethyl ester, HC(P$_2$O$_5$Et)$_3$, is a light yellow oil (bp 135–138 °C/0.01 mmHg; $^{31}$P NMR (CHCl$_3$) $\delta$ 14.4 ppm; $^1$H NMR (CDCl$_3$) $\delta$ 3.23 (CH), $J_{PC}$ = 24.2 Hz; $^{13}$C NMR (CDCl$_3$) $\delta$ 40.34 (CH), $J_{PC}$ = 40.3 Hz) [26]. As expected, trisphosphonate ester HC(P$_2$O$_5$Et)$_3$ is a strong carbon acid (titration with NaOH gave a pK$_{a}$ of ~6.5) [26].

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Structural features of the trisphosphonate 18 were studied by NMR spectroscopy and by single-crystal X-ray diffraction. Only one $^{31}$P NMR signal is observable for three equivalent phosphonate moieties in CHCl$_3$. In contrast, the $^{31}$P solid-state NMR spectrum of 18 revealed three separable signals. The nonequivalence of the signals was attributed to hydrogen bonds and supported by crystallographic analysis. The molecules 18 bonded via hydrogen bonds form chains [45].
Short overview of biomedical application

Methylidynetrismiphonate, H[(PO3H2)3]3−3BuNH2+, and its fluoro (43) and chloro (44) derivatives do not detectably inhibit human-tumor-suppressor protein Fhit, but are strong inhibitors of the lupine enzyme. By contrast, the adenylated polyphosphonates AdoPPCCl(P)PAdo (47) and (AdoPP)3CH (48) strongly and competitively inhibit Fhit while they are less effective as inhibitors of the lupine enzyme. Since the detection of levels of Fhit protein is an important problem relating to cancers, Fhit-selective inhibitors such as 47 and 48 can be valuable as Fhit diagnostics [8].

\[ \beta,\gamma\text{-Chlorophosphonomethylene–ATP, AdoPPCCl(P)P, is a} \]
weak antagonist at P2X2/3 receptors (IC50 about 10 μM) [46].

The antioxidant activity of the compound ArC(PO3Et)3 (Ar = 2,6-t-Bu2-4-MeC6H2) was studied in a model oxidation of oleic acid and with biological objects (liver homogenates of Wistar rats) [36].

Among polyphosphonic acids with a geminal arrangement of phosphonic groups efficient complexones and regulators of calcium exchange in humans were found [47-49]. Some data on the use of the methylidynetrismiphosphonic acid and its derivatives as complexones were also published. The trisphosphonic acids HC(PO3H2)3 and CIC(PO3H2)3 are better chelating agents in the detergent compositions than methylenebisphosphonic acid and its alkali-metal salts and also sequester more calcium and magnesium ions, for example, than does H2C(PO3H2)2 [50,51]. The complexion behavior of the polydentate ligand Me2NC(PO3Et)3 toward CrO3+ ion has shown that the trisphosphonate molecule is coordinated in solution by its three donor (P=O, Me2N) functions [52]. Evidently, further detailed structure studies of the individual complexes and the complex-forming driving factors are desired in order to understand trisphosphonate coordination abilities.

Conclusion

There has been a considerable interest in the preparation and use of the geminal phosphonates, XC(PO3R2)3, because of the widespread biomedical application of methylenebisphosphonates as mimetics of biologically important pyrophosphate. Much of the trisphosphonate reactivity profile follows intuition based on the bisphosphate analogy. However, despite the structural similarity to bisphosphonates, methylidylnetrismiphosphonic acid and its derivatives differ in their geometry, coordination properties and reactivity pathways. A particularly interesting characteristic of trisphosphonates is the possibility of constructing systems based on Blackburn’s conception of supercharged nucleotide analogues in which an additional negative charge is provided without elongation of the polyphosphate chain. But there are still a lot of other aspects of their chemistry that remain to be investigated. From a synthetic point of view, since the introduction of a heteroatom substitut at the bridged carbon atom permits both modulation of pKa values and hydrogen bonding, there is a need for profound study of α-functionalized trisphosphate systems. Such compounds can be promising building blocks for the synthesis of false substrates or enzyme inhibitors involved in phosphate-based processes. In particular, some heterocyclic compounds functionalized by trisphosphate substituents merit in-depth biological study. A further practical potential for trisphosphate compounds is the development of new phosphorus-containing dendrimers and related species. Considerable interest is also associated with the use of trisphosphonic acids as ligands for calcium ligation and as potential bone affinity agents. Finally, there is no doubt that organometallic and coordination chemistry will benefit from future innovative application of these compounds.

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