Chapter 5

Synthetic and Biological Applications of Benzothiazole Phosphonates

Koteswara Rao Valasani[1, *], Chandra Sekhar Kuruva[2], Veerendra Koppolu[3], Jhansi Rani Vangavaragu[1], Victor W Day[4]

[1]Department of Pharmacology & Toxicology and Higuchi Bioscience Center, School of Pharmacy, University of Kansas, Lawrence, Kansas 66047, USA

[2]Garrison Institute on Aging, Texas Tech University Health Sciences Center, 3601 4th Street, MS 9424, Lubbock, Texas-79430, USA

[3]Biopharmaceutical Development, MedImmune/AstraZeneca, Gaithersburg, MD -20878, USA

[4]Department of Chemistry, University of Kansas, Lawrence, Kansas 66045, USA

*Corresponding author at: 2099 Constant Avenue, University of Kansas, Lawrence, KS 66047, USA. Tel.: +1 (785) 864-5693. E-mail address: kotisvu@gmail.com (V. K. Rao)

Co-Corresponding author: Victor W Day, University of Kansas, Lawrence, KS 66047, USA. Tel.: +1 (785) 864-4347. E-mail address: vwday@ku.edu (V. W. Day)

Abstract

Benzothiazole derivatives have attracted considerable attention over the years as useful biological and pharmacological agents. The benzothiazole scaffold is one of the most frequently encountered heterocyclic moieties in many marine, as well as plant and natural products. Taking Nature's lead, the benzothiazole moiety provides a versatile bicyclic ring system that can be easily modified synthetically in the laboratory. Its synthetic derivatives are known to exhibit a wide range of useful medicinal and therapeutic properties: anticancer, antiviral, antimicrobial, antidiabetic, anti-inflammatory, anticonvulsant and antitubercular. Since the phosphinic acid moiety P(O)OH can mimic carboxylic acids, its incorporation into heterocyclic compounds has stimulated considerable interest in the possibility of producing unique chemical/biological properties for benzothiazole phosphonate derivatives. The pharmacological significance of these compounds in the field of medicinal chemistry could be substantial and this chapter will summarize the development and current status for the synthesis of new benzothiazole phosphonate compounds and report on biological aspects of these compounds that offer the promise of truly useful drugs for treating various maladies.

Keywords

α-Aminophosphonates, Benzothiazole Phosphonates, Biological Applications, Kabachnik-Fields Reaction, Organophosphorus Chemistry

5.1 Introduction

Naturally occurring organophosphorus compounds are not only essential for life but manmade organophosphous species have important applications in medicine, agriculture, industry and technology. Figure 1 illustrates the diversity of organophosphorus compounds. They occur naturally as fundamental building blocks of life itself. And manmade organophosphorus compounds have found use as nerve gases and organic synthetic reactants. [1-6] Phosphorus compounds in general, and phosphonates in particular, are a cornerstone of pharmaceutical drugs. [7-10] Many of these compounds exhibit antifungal [11-13], antiviral [14, 15], antibacterial [16-18], antioxidant [19-21], anticancer [22-25] and significant analgesic/anti-inflammatory properties [26-28]; several examples are shown in Figure 2.

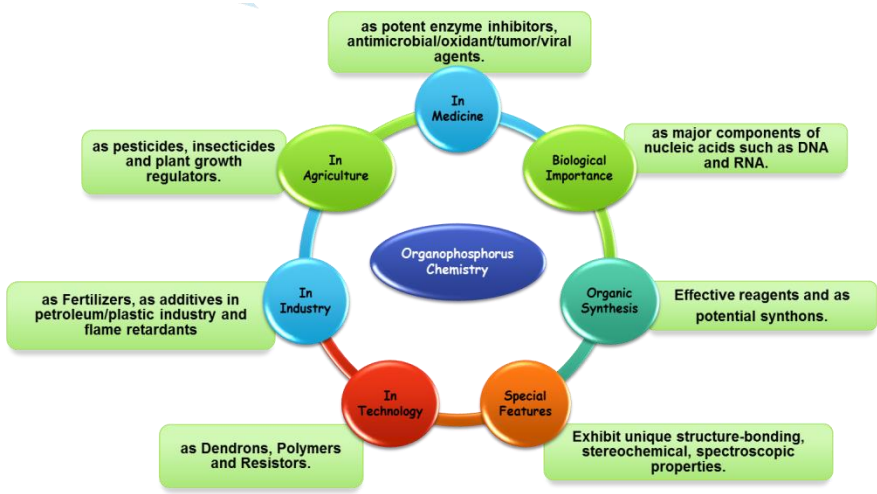


Figure 1. *Applications of Organophosphorus Compounds.*

Heterocyclic chemistry is a complex and fascinating branch of organic chemistry. Naturally occurring compounds containing heterocyclic fragments

are also fundamental to life. They are components of a broad spectrum of biological systems, have diverse applications and can evoke a wide range of chemical and physiological responses. [29-41] Heterocyclic compounds are active components of many drugs, agrochemicals, additives and modifiers used in a variety of industrial applications including cosmetics, reprography, information storage and plastics [42-45].

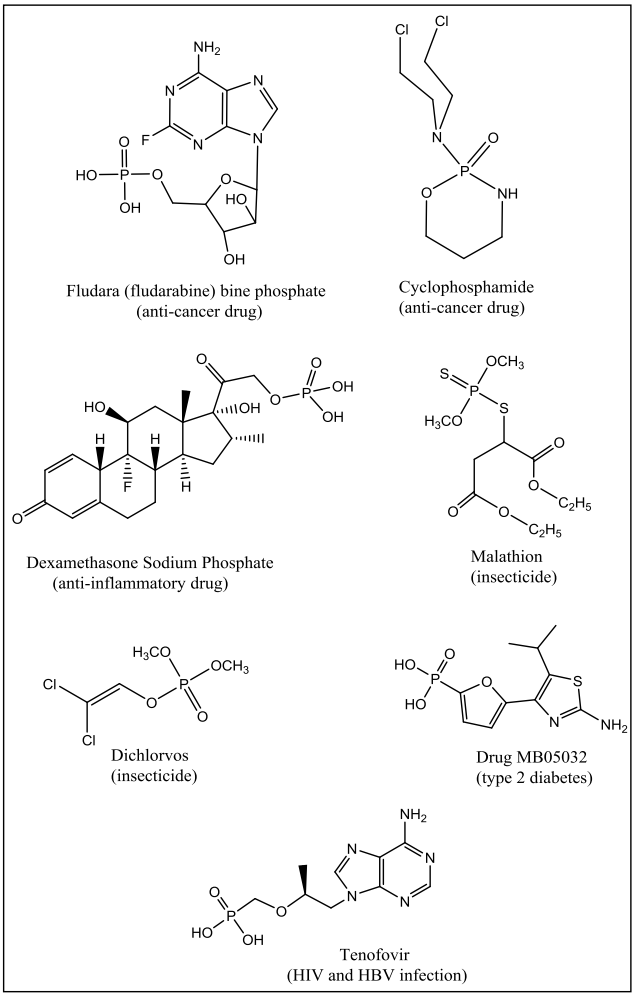


Figure 2. *Examples of Organophosphorus Compounds and Their Applications.*

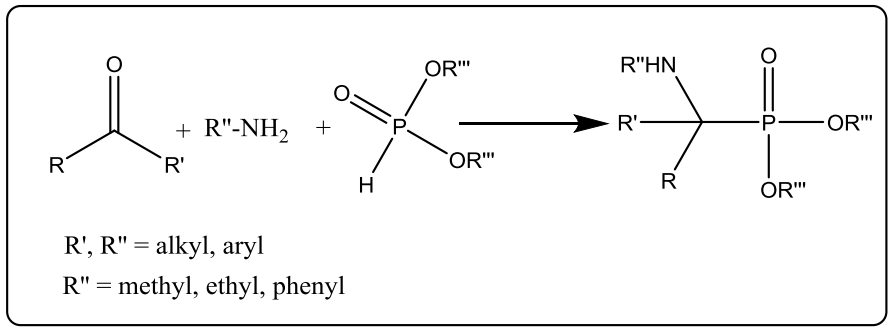
One particularly useful group of heterocyclic compounds, those based on the benzothiazole scaffold, have proved to have special significance in synthetic and pharmaceutical chemistry as drugs because of the broad spectrum of medicinal applications they seem to target. [46-50] Recently, there has been increased interest in the biological activities of benzothiazole phosphonate derivatives because the phosphinic acid moiety $P(O)(OH)_2H$ can mimic carboxylic acids and impart useful solubility (and other) properties to benzothiazole-based drugs. [51, 52] This chapter will focus on recent research involving this new class of potentially useful compounds - benzothiazole phosphonates.

Interest in developing benzothiaole-based drugs has recently heightened due to FDA approval of the benzothiazoyl urea drug, Frentizole, for treating rheumatoid arthritis and systemic lupus erythematosus. Valasani et al. performed structure-activity relationship studies of frentizole derivatives and identified a benzothiazole urea compound with a 30-fold improved potency in inhibiting the enzyme amyloid beta binding alcohol dehydrogenase (ABAD) that is associated with Alzheimer's disease. [53-55] Phosphonates of benzothiazole were synthesized in order to enhance the ability of benzothiazoyl urea compounds to cross the blood brain barrier and reach target organs. Phosphonate derivatization improves the solubility of the benzothiazole moiety, decreases the adverse effects of the drug and enhances the sustained delivery to the target organs. [21, 25, 53-56]. Given the drug like properties of the benzothiazole phosphonates, many researchers have attempted to synthesize these compounds and test their therapeutic potential. Herein, we have attempted to summarize the novel synthetic pathways for benzothiazole phosphonates and their biological applications.

5.2 Synthetic Pathways of Benzothiazole Phosphonates

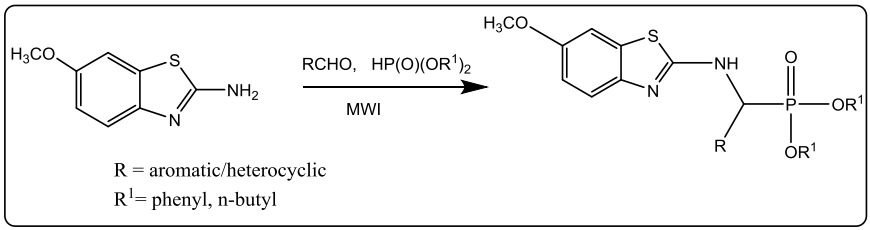
5.2.1 Kabachnik-Fields Reaction

Although numerous synthetic methodologies of benzothiazole α-aminophosphonates exist, the most noteworthy and remarkable one is probably the Kabachnik-Fields reaction that generally uses amines, dialkyl phosphites and carbonyl compounds as the reactants [57, 58] in an organic solvent system under high temperature (Scheme 1). The previous protocols for the synthesis of benzothiazole α-aminophosphonates mainly used simple starting reactants, but the recent approaches favor the use of even sterically-demanding starting materials.



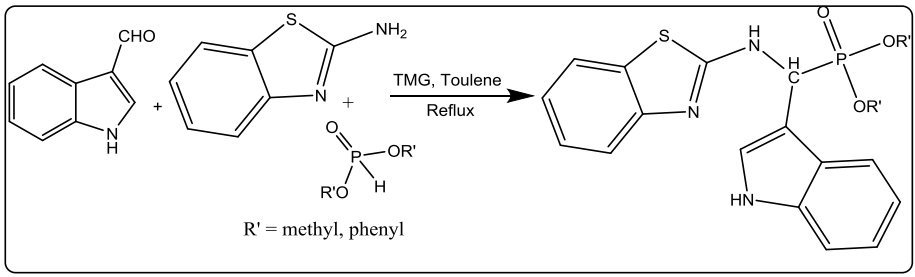
Scheme 1. *General scheme for the synthesis benzothiazoleα-aminophosphonates.*

Rao and coworkers [18] have reported the synthesis of various substituted benzothiazole aminophosphonates by the reaction of substituted aromatic/heterocyclic aldehydes, 2-amino-6-methoxy benzothiazole and dibutyl/diphenyl phosphites *via* the Kabachnik-Fields reaction under microwave irradiation (MWI) conditions (Scheme 2). The synthesized benzothiazole aminophosphonate derivatives were found to possess antimicrobial and antioxidant properties.



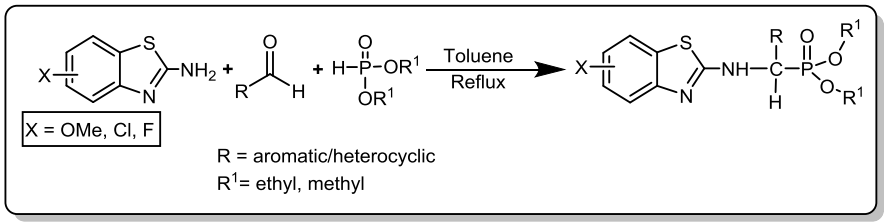
Scheme 2. *Kabachnik-Fields reaction with microwave irradiation.*

Reddy and coworkers [59] havesynthesized α-aminophosphonates by the Kabachnik-Fields reaction of dialkyl-or diphenyl-phosphite, indole-3-carb oxaldehyde and various heterocyclic-, cyclic-or other primary amines in the presence of tetramethylguanidine (TMG) as catalyst in toluene at reflux temperature (Scheme 3). The compounds possessed antimicrobial activity.



Scheme 3. *TMG catalyzed one-pot synthesis of α-aminophosphonates.*

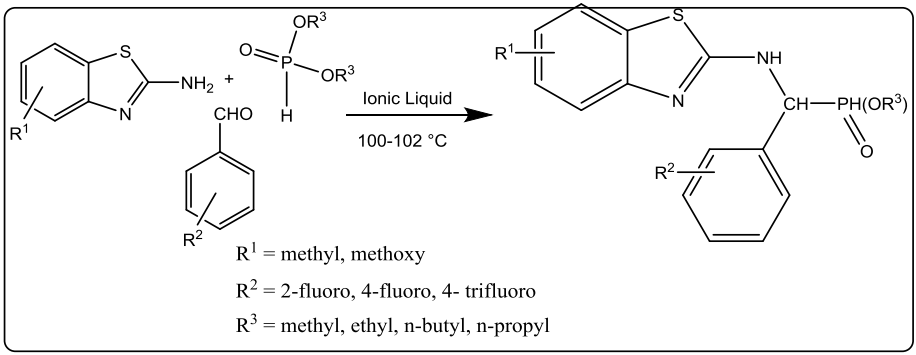
Valasani *et al*. [60] reported the Kabachnik-Fields synthesis of benzothiazole aminophosphonate derivatives using a three-component reaction of equimolar quantities of various 6-methoxybenzo[d]thiazol-2-amines, aromatic/heterocyclic aldehydes and dimethyl-or diethyl- phosphate in the presence of $Mg(ClO_4)_2$ in anhydrous toluene under reflux conditions (Scheme 4). Some of the resulting N-C-P benzothiazole phosphonate derivatives showed potent amyloid beta (Aβ) binding alcohol dehydrogenase enzyme inhibition.



Scheme 4. *Benzothiazole phosphonate derivatives containing the N-C-P scaffold.*

5.2.2 Mannich-Type Addition

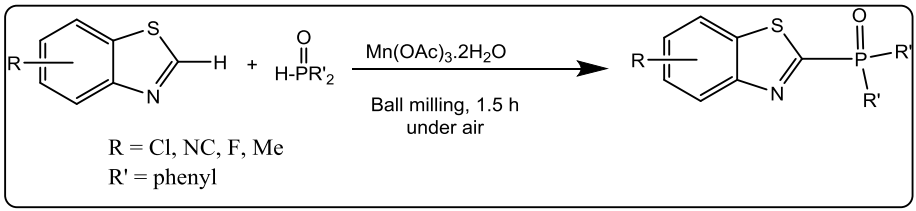
Jinand coworkers [61] have synthesized α-aminophosphonates containing benzothiazole and a fluorine-containing moiety by Mannich-type addition in ionic liquid media with short reaction times and high yields (Scheme 5). The synthesized N-C-P compounds were found to have antitumor activities.



Scheme 5. *Synthesis of N-(benzothiazole-2-yl)-1-(fluorophenyl)-O, O-dialkyl- α -aminophosphonates.*

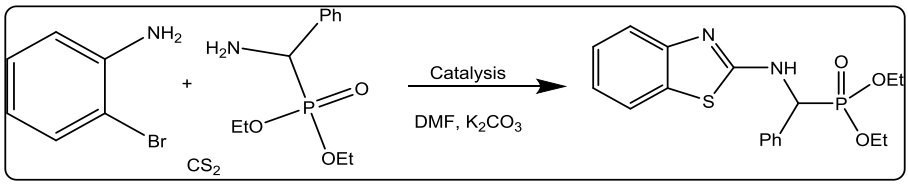
5.2.3 Direct Phosphonylation of Benzothiazole

Liang and coworkers [62] have synthesized structurally diverse C2-phosphonylated benzothiazole/thiazole derivatives with remarkable functional group tolerance and excellent yields by using organophosphorus compounds including phosphinate ester, phosphine oxides, and phosphonate diester promoted by $Mn(OAc)_3$ $2H_2O$ using a ball-milling technique (Scheme 6).



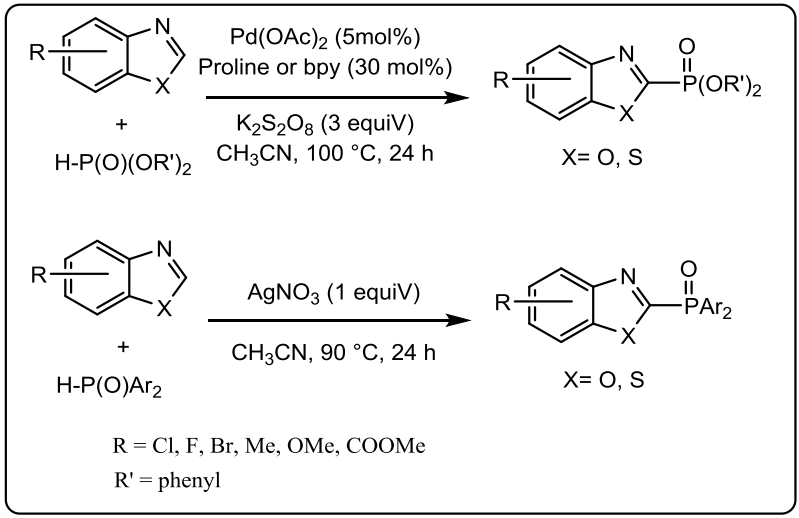
Scheme 6. *Ball-milling conditioned manganese (III) acetate-promoted cross-coupling reaction of benzothiazole/thiazole derivatives with organophosphorus compounds.*

Guand coworkers [63] have synthesizedN-C-Pα-aminophosphonates containing the benzothiazole moiety via a cascade three-component reaction (Scheme 7). The antitumor activities of the target compounds were evaluated against HL-60. One compound showed good cancer inhibitory activity against the tested cell line.



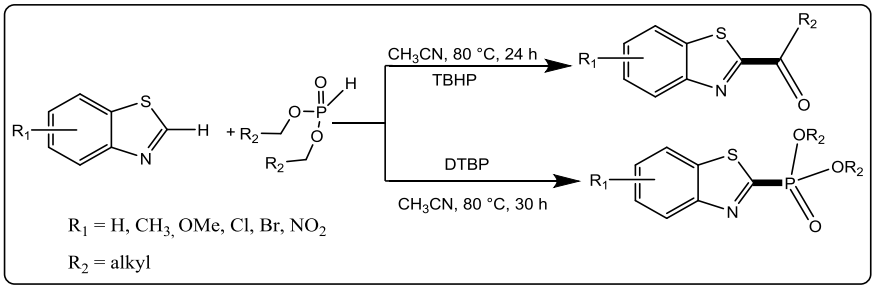
Scheme 7. *CS_2 mediated coupling reaction to synthesize benzothiazole α-aminophosphonates.*

Hui-Jun Zhang [64] and coworkers have synthesized variousbenzo[d] thiazol-2-yldiarylphosphine oxides through silver mediated direct phosphorylation of benzothiazoles and thiazoles. This method is similar to reported Pd-catalyzed reactions which may produce a more convenient synthetic route to a series of novel P, N-ligands (Scheme 8).



Scheme 8. *Direct phosphorylation of benzothiazoles and thiazoles.*

Xiao-Lan Chen and coworkers [65] have developed mild and metal-free methods for the preparation of two kinds of important benzothiazole derivatives, 2-acylbenzothiazoles and dialkyl benzothiazol-2-ylphosphonates. The dialkyl H-phosphonate $(RO)_2P(O)H$ exists in equilibrium with its tautomer dialkylphosphite $(RO)_2POH$. The final product depends on which tautomer reacts: tert-butyl hydroperoxide (TBHP) triggered α-carbon-centered phosphite radical formation, whereas di-tert-butyl peroxide (DTBP) triggered phosphorus-centered phosphonate radical formation. The two types of radicals led respectively to two different reaction processes, the direct C2-acylation of benzothiazoles and C2-phosphonation of benzothiazoles (Scheme 9).



Scheme 9. *Metal-free methods for preparation of 2-acylbenzothiazoles and dialkylbenzothiazol-2-ylphosphonates.*

5.3 Biological Applications of Benzothiazole Phosphonates

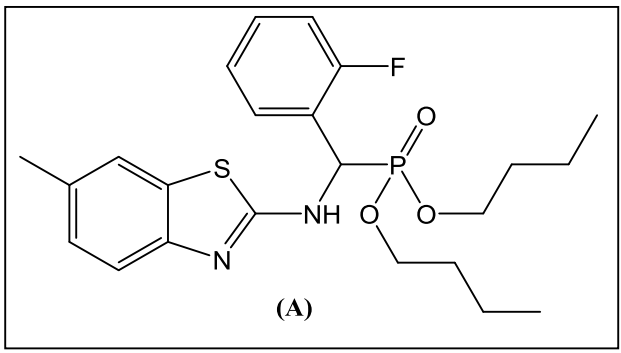
Benzothiazole phosphonates are found to possess a number of useful biological activities such as antitumor activity, antimicrobial activity, antioxidant activity and anti-Alzheimer activity.

5.3.1 Antitumor Activity

Cancer is a serious global health problem impacting millions of people and severely challenging the scientific community to develop new treatment strategies. The current major treatment strategies can be categorized into targeted therapies which attack the cancer cells and their signaling pathways directly and immunotherapies which try to harness the potential of the immune system to battle cancer. [66] The use of benzothiazole phosphonates and their derivatives are considered to betargeted therapy andsome of these compounds have been found to possess antitumor activity.

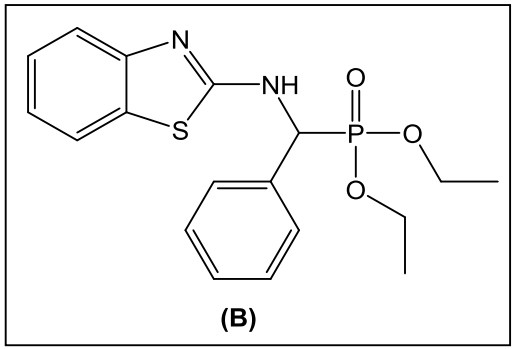
Jin et al. [61] first discovered the antitumor potential of these compounds in *in vitro* studies against a wide range of cancer cell lines such as PC3 (prostate cancer), A431 (human melanoma), A375 (uterus cancer), and Bcap-37(breast cancer) cells. They synthesized several derivatives of α-aminophosphonates

containing a benzothiazole moiety (Scheme 5) by a Mannich-type addition in ionic liquid media and tested their potential in inhibiting proliferation of cancer cell lines in MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. MTT assay measures the cellular cleavage of tetrazolium salt (MTT) into formazan which has an absorbance at 550 nm that increases proportionately with increased formazan concentration in living cells. Compound A showed highest tumor inhibitory activity with 89% inhibition of prostate cancer cells (PC3) and 72% inhibition of human melanoma cells (A431) at 10 μM concentration. The nature of fluorine and alkyl at R^2 and R^3 positions are found to influence the antitumor potential of benzothiozole aminophosphonates as only 2-F at R^2 and n-Bu at R^3 showed great antitumor activity while many other groups showed less antitumor activity. While good antitumor potential was observed in PC3 and A431 cell lines, a poor-to-moderate tumor inhibition was noticed in A375 and Bcap-37 cell lines.



(A)

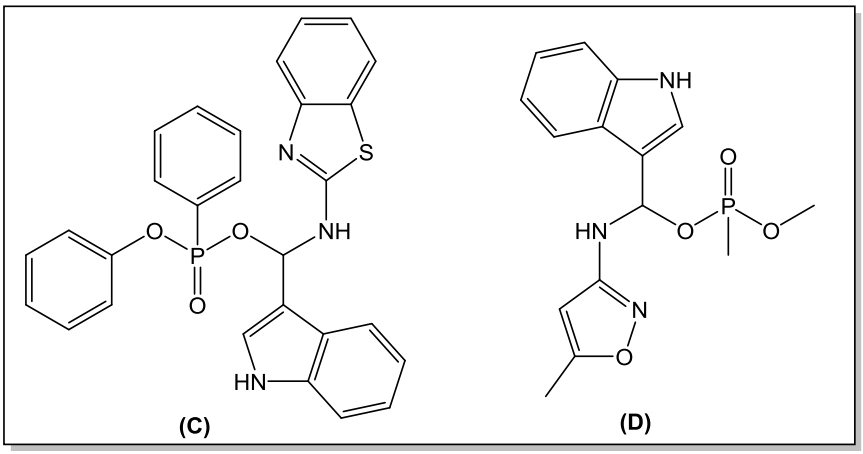
Liju*et al*. [63] synthesized a variety of benzothiazole phosphonate derivatives and screened them for antitumor activities against human acute promyelocytic leukemia cell line (HL-60) in MTT tests. Compound B, O, O'-Diethyl-α-(benzothiazole-2-yl) amino-(4- nitrophenylmethyl)phosphonate, possessed high antitumor activity and inhibited the proliferation of HL-60 with an IC50 value of 8.2 μmol/L.



(B)

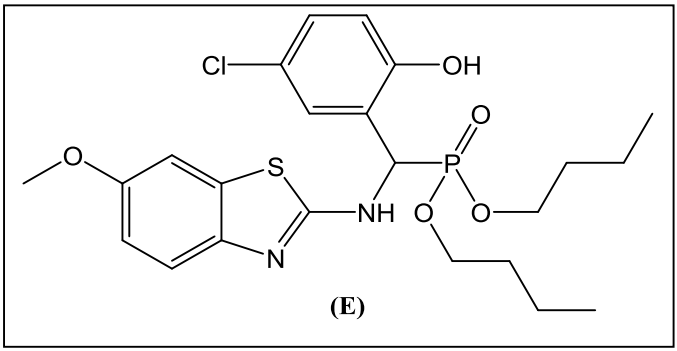
5.3.2 Antimicrobial Activity

Increasing resistance of bacteria and fungi to current antimicrobial compounds has dramatically increasedthe need for developing new compounds to treat bacterial and fungal infections [67-69]. Benzothionate aminophosphonates and their derivatives are one such group of compounds with antimicrobial potential. Two compounds, diphenyl (benzo[d]thiazol-2-ylamino)(1H-indol-3-yl)methyl phosphonate(C) and diphenyl (5-methylisoxazol-3-ylamino) (1H-indol-3-yl)methyl phosphonate (D)were found to be more effective than penicillin in inhibiting the growth of *Staphylococcus aureus* and *Escherichia coli* [59]. Several derivatives of benzothionateaminophosphonates showed antifungal properties against *Aspergillus niger* and *Helminthosporium oryzae* and are found to be more efficient than a standard antifungal Griseofulvin. Compound C is more effective than Griseofulvin for inhibiting *Aspergillus niger* and D is more effective against *Helminthosporium oryzae*.



5.3.3 Antioxidant Activity

Rao *et al.* [18] designed a simple and efficient synthesis of α-aminophosphonates using the reaction between amino-6-methoxy-benzothiazole and dibutyl/diphenyl phosphite with microwave irradiation. The compounds were tested for antioxidant and antimicrobial properties. The antioxidant property was evaluated by estimation of ferric thiocyanate using linoleic acid emulsion. The oxidation of linoleic acid releases peroxidases that oxidize ferrous ions to ferric ions leading to formation of a complex ferric thiocyanate. Compound E, dibutyl (5-chloro-2-hydroxyphenyl) (6-methoxybenzo [d] thiazol-2-ylamino) methylphosphonate, yielded more ferric thiocyanate than the ferric thiocyanate in presence of vitamin C and is therefore considered a promising antioxidant. Some fragments such as 2-amino-6-methoxy benzothiazole and bromo/chloro/nitro salicylaldehyde attached to diphenyl phosphite were found to have both antimicrobial and antioxidant properties.

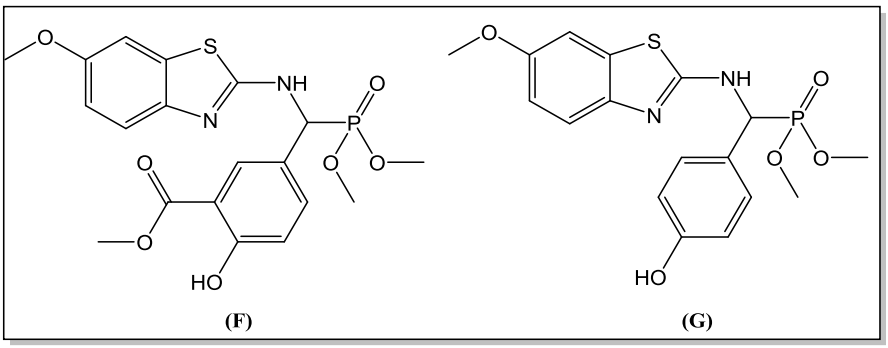


(E)

5.3.4 Benzothiazole α-Aminophosphonate Derivatives for Treating Alzheimer's Disease

Alzheimer's disease is a type of dementia in adults caused by neuronal stress and neuronal cell death that leads to poor cognitive ability and memory. [70-74] Mitochondrial and synaptic dysfunctions are common in patients with Alzheimer's disease and are caused by interaction of amyloid beta (Aβ) protein with amyloid beta binding alcohol dehydrogenase (ABAD). Valasani *et al*. [60] used surface plasmon resonance (SPR) screening to show that several benzothiazole α-aminophosphonate derivatives bind to ABAD and therefore potentially prevent the Aβ-ABAD interactions [75]. The compounds that were shown to bind to ABAD were subsequently examined for improvement in mitochondrial functions. Compounds F and G showed improvements in mitochondrial functions such as increased levels of ATP and Cytochrome C Oxidase, anenzyme associated with the mitochondrial respiratory chain. Besides being shown to inhibit Aβ-ABAD interactions, benzothiazole phosphonate derivatives also possess the ability to cross the blood-brain barrier in *in vivo* mice studies and thus hold great potential for AD therapy [56]. This general procedure also offers great promise for identifying and synthesizing more powerful drugs for treating other neurological diseases like amyotrophic lateral

sclerosis (ALS) that are presently being treated with benzothiazole based drugs like riluzole. [76-79]



5.4 Conclusions

This chapter highlighted synthetic routes and biological applications of benzothiazole phosphonate compounds. These compounds combine the desirable characteristics of the phosphonic acid moiety and the benzothiazole heterocyclic to produce species with enhanced chemical and biological properties that can hopefully be used as improved therapeutic anticancer, antitumor, antioxidant, antimicrobial and anti-Alzheimer's agents. The anti-Alzheimer'scompounds are highly soluble, cross the blood-brain barrier and are found to be less toxic in *in vitro* and *in vivo* mouse studies than their nonphosphorylated analogues. The clinical potential of these compounds as effective and safe drugs for human use is currently being explored. Besides producing more effective species through phosphorylation of known drugs, it is hoped that even more powerful molecules can be developed by comparing structure-activity relationship studies of known benzothiazole phosphonates with those for appropriately modified derivatives.

References

[1] Bentrude, W. G. and T. B. Min, *Free-Radical Chemistry of Organophosphorus Derivatives - Nonequivalence of Alkoxy Groups in (Ro)4p.* Journal of the American Chemical Society, 1972. 94(3): p. 1025-&.

[2] Thakore, A. N., P. Pope, and Oehlschl. Ac, *Studies in Organophosphorus Chemistry - Reaction of Epoxides with Tertiary Phosphine Dihalides.* Tetrahedron, 1971. 27(13): p. 2617-&.

[3] Kosfeld, R., G. Hagele, and W. Kuchen, *Use of Indor Technique in Solution of Structural Problems in Organophosphorus Chemistry.* Angewandte Chemie-International Edition, 1968. 7(10): p. 814-&.

[4] Borowitz, I. J., M. Anschel, and Firstenb. S, *Organophosphorus Chemistry. 4. Reactions of Trialkyl Phosphites with Alpha-Halo Ketones.* Journal of Organic Chemistry, 1967. 32(6): p. 1723-&.

[5] Nordheider, A., J. D. Woollins, and T. Chivers, *Organophosphorus-Tellurium Chemistry: From Fundamentals to Applications.* Chemical Reviews, 2015. 115(18): p. 10378-10406.

[6] Hagele, G., M. Murray, and C. Papadopoulos, *Applications of Modern Nmr Methods to Organophosphorus Chemistry.* Phosphorus Sulfur and Silicon and the Related Elements, 1993. 77(1-4): p. 641-644.

[7] Demkowicz, S., et al., *Selected organophosphorus compounds with biological activity. Applications in medicine.* Rsc Advances, 2016. 6(9): p. 7101-7112.

[8] Ahmadibeni, Y., et al., *Applications of polymer-bound phosphitylating reagents in the synthesis of organophosphorus compounds.* Abstracts of Papers of the American Chemical Society, 2007. 233.

[9] Ghisalba, O., et al., *Microbial-Degradation and Utilization of Selected Organophosphorus Compounds - Strategies and Applications.* Chimia, 1987. 41(6): p. 206-215.

[10] Kilpatrick, J. W. and H. F. Schoof, *Effectiveness of 7 Organophosphorus Compounds as Space Applications against Musca Domestica.* Journal of Economic Entomology, 1963. 56(5): p. 560-&.

[11] Soni, K., et al., *Antifungal activity and some novel organo-phosphorus compounds: Preparation and spectral characterization.* Phosphorus Sulfur and Silicon and the Related Elements, 2008. 183(10): p. 2457-2463.

[12] Sasaki, M., et al., *Studies on Organo-Phosphorus Fungicides. 2. Synthesis and Antifungal Activity of O, O-Dialkyl O-Aryl Phosphorothioates and Related-Compounds.* Journal of Pesticide Science, 1984. 9(4): p. 737-744.

[13] Sasaki, M., et al., *Studies on Organo-Phosphorus Fungicides. 1. Antifungal Activity of [Hydroxy(Pyridin-3-Yl)Methyl]-Phenylphosphinates and Related-Compounds.* Journal of Pesticide Science, 1984. 9(4): p. 717-723.

[14] De Clercq, E., *Antivirals for the treatment of herpesvirus infections.* J Antimicrob Chemother, 1993. 32 Suppl A: p. 121-32.

[15] Smee, D. F., R. W. Sidwell, and B. B. Barnett, *Combination of antiviral immunotoxin and ganciclovir or cidofovir for the treatment of murine cytomegalovirus infections.* Antiviral Res, 1996. 32(3): p. 165-71.

[16] Bauer, H. and S. M. Rosenthal, *STUDIES IN CHEMOTHERAPY XI. Antibacterial Action of Phosphorus Compounds. Preliminary Report.* Public Health Reports, 1939. 54(47): p. 2093-2095.

[17] Rao, V. K., et al., *Synthesis and Antimicrobial Activity of Novel Iminophosphocin Derivatives.* Chinese Journal of Chemistry, 2009. 27(12): p. 2379-2384.

[18] Rao, A. J., et al., *Microwave Assisted One-pot Synthesis of Novel alpha-Aminophosphonates and Their Biological Activity.* Bulletin of the Korean Chemical Society, 2010. 31(7): p. 1863-1868.

[19] Holcik, J., J. L. Koenig, and J. R. Shelton, *The Antioxidant Activity of Phosphorus-Compounds. 1. Decomposition of Hydroperoxides by Pentaerythritol Diphosphites.* Polymer Degradation and Stability, 1983. 5(5): p. 373-397.

[20] Schwetlick, K., *Mechanisms of Antioxidant Action of Organic Phosphorus-Compounds.* Pure and Applied Chemistry, 1983. 55(10): p. 1629-1636.

[21] Rao, V. K., et al., *Synthesis, spectral characterization and biological evaluation of phosphorylated derivatives of galanthamine.* European Journal of Medicinal Chemistry, 2010. 45(1): p. 203-209.

[22] Konieczny, M., G. Sosnovsky, and P. Gutierrez, *In the Search for New Anti-Cancer Drugs. 1. Anti-Tumor Activity of Various Nitroxyl-Containing and Aziridine-Containing Phosphorus-Compounds.* Zeitschrift Fur Naturforschung Section B-a Journal of Chemical Sciences, 1981. 36(7): p. 888-891.

[23] Congiatu, C., et al., *Novel potential anticancer naphthyl phosphoramidates of BVdU: Separation of diastereoisomers and assignment of the absolute configuration of the phosphorus center.* Journal of Medicinal Chemistry, 2006. 49(2): p. 452-455.

[24] Yolles, S., T. D. Leafe, and F. J. Meyer, *Timed-Release Depot for Anticancer Agents.* Journal of Pharmaceutical Sciences, 1975. 64(1): p. 115-116.

[25] Rao, V. K., et al., *Design, Synthesis and Anti Colon Cancer Activity Evaluation of Phosphorylated Derivatives of Lamivudine (3TC).* Letters in Drug Design & Discovery, 2011. 8(1): p. 59-64.

[26] Chitra, M., et al., *Antitumor, anti-inflammatory and analgesic property of embelin, a plant product.* Chemotherapy, 1994. 40(2): p. 109-13.

[27] Orsini, F., G. Sello, and M. Sisti, *Aminophosphonic acids and derivatives. Synthesis and biological applications.* Curr Med Chem, 2010. 17(3): p. 264-89.

[28] Naydenova, E. D., P. T. Todorov, and K. D. Troev, *Recent synthesis of aminophosphonic acids as potential biological importance.* Amino Acids, 2010. 38(1): p. 23-30.

[29] Barham, P., et al., *Molecular Gastronomy: A New Emerging Scientific Discipline.* Chemical Reviews, 2010. 110(4): p. 2313-2365.

[30] Pineschi, M., *Advances in the Ring Opening of Small-Ring Heterocycles with Organoboron Derivatives.* Synlett, 2014. 25(13): p. 1817-1826.

[31] Zwanenburg, B., et al., *Sulfur substituted small-ring heterocycles.* Phosphorus Sulfur and Silicon and the Related Elements, 1997. 120: p. 453-454.

[32] Smith, P. A. S., *Small Ring Heterocycles, Pt 2, Azetidines, Beta-Lactams, Diazetidines, and Diaziridines - Hassner, A.* Journal of the American Chemical Society, 1984. 106(6): p. 1893-1893.

[33] Small *Ring Heterocycles, Part 1, Aziridines, Azirines, Thiiranes, Thiirenes – Hassner, A.* Journal of the American Chemical Society, 1983. 105(20): p. 6369-6369.

[34] Hahn, L. T. and B. Weinstein, *Chemistry of Some Small Ring Nitrogen-Sulfur Heterocycles.* Abstracts of Papers of the American Chemical Society, 1979(Sep): p. 45-45.

[35] Padwa, A., P. H. J. Carlsen, and A. Ku, *Photo-Chemical Transformations of Small Ring Heterocycles. 97. Role of Substituents in Controlling Mode of Intra-Molecular Cycloaddition of Nitrile Ylides.* Journal of the American Chemical Society, 1978. 100(11): p. 3494-3505.

[36] Padwa, A. and P. H. J. Carlsen, *Photochemical-Transformations of Small Ring Heterocycles. 81. Carbenic Reactions of Nitrile Ylides - Example of a Stepwise 1,3-Dipolar Cycloaddition.* Journal of the American Chemical Society, 1977. 99(5): p. 1514-1523.

[37] Imbach, J. L., et al., *Mass Spectra of Small-Ring Heterocycles. I. Some 1-Alkyl-2-Phenyl-3-Aroylazetidines.* Journal of Organic Chemistry, 1967. 32(10): p. 3123-&.

[38] Willemse. Lc and Vanderke.Gj, *Investigations on Organolead Compounds. 2. Reaction of Triphenylplumbyllithium with Small-Ring Heterocycles - Functionally Substituted Organolead Compounds.* Journal of Organometallic Chemistry, 1965. 4(1): p. 34-&.

[39] Valasani, K. R., et al., *Acetylcholinesterase Inhibitors: Structure Based Design, Synthesis, Pharmacophore Modeling, and Virtual Screening.* Journal of Chemical Information and Modeling, 2013. 53(8): p. 2033-2046.

[40] Vangavaragu, J. R., et al., *Identification of human presequence protease (hPreP) agonists for the treatment of Alzheimer's disease.* European Journal of Medicinal Chemistry, 2014. 76: p. 506-516.

[41] Valasani, K. R., et al., *Structure based design, synthesis, pharmacophore modeling, virtual screening, and molecular docking studies for identification of novel cyclophilin D inhibitors.* J Chem Inf Model, 2014. 54(3): p. 902-12.

[42] Yadav, J. S., A. Antony, and B. V. S. Reddy, *Recent Advances in the Applications of Ionic Liquids for the Synthesis of Bioactive Six-Membered N-Heterocycles.* Current Organic Synthesis, 2011. 8(6): p. 787-809.

[43] Dabholkar, V. V. and N. V. Bhusari, *Synthesis and Biological Applications of Some Novel Spiro Heterocycles Containing 1,3,4-Thiadiazine, Thiazole, and Oxazole Derivatives.* Journal of Heterocyclic Chemistry, 2013. 50(1): p. 155-158.

[44] Kumar, V., et al., *Pyrazole containing natural products: synthetic preview and biological significance.* Eur J Med Chem, 2013. 69: p. 735-53.

[45] Seth, S., *A Comprehensive Review on Recent advances in Synthesis & Pharmacotherapeutic potential of Benzothiazoles.* Antiinflamm Antiallergy Agents Med Chem, 2015. 14(2): p. 98-112.

[46] Gill, R. K., R. K. Rawal, and J. Bariwal, *Recent Advances in the Chemistry and Biology of Benzothiazoles.* Archiv Der Pharmazie, 2015. 348(3): p. 155-178.

[47] Singh, M. and S. K. Singh, *Benzothiazoles: how relevant in cancer drug design strategy?* Anticancer Agents Med Chem, 2014. 14(1): p. 127-46.

[48] Tripathi, R. C., M. M. Singh, and J. D. Kohli, *Anthelmintic screening of substituted bis-benzothiazoles.* Indian J Psychol, 1958. 2(3): p. 446-51.

[49] Sharma, P. C., et al., *Medicinal significance of benzothiazole scaffold: an insight view.* J Enzyme Inhib Med Chem, 2013. 28(2): p. 240-66.

[50] Taylor, A. P., et al., *Modern advances in heterocyclic chemistry in drug discovery.* Org Biomol Chem, 2016. 14(28): p. 6611-37.

[51] Montchamp, J. L., *Phosphinate chemistry in the 21st century: a viable alternative to the use of phosphorus trichloride in organophosphorus synthesis.* Acc Chem Res, 2014. 47(1): p. 77-87.

[52] Berger, O. and J. L. Montchamp, *Phosphinate-containing heterocycles: A mini-review.* Beilstein J Org Chem, 2014. 10: p. 732-40.

[53] Somogyi, G., et al., *Targeted drug delivery to the brain via phosphonate derivatives - I. Design, synthesis and evaluation of an anionic chemical delivery system for testosterone.* International Journal of Pharmaceutics, 1998. 166(1): p. 15-26.

[54] Somogyi, G., et al., *Targeted drug delivery to the brain via phosphonate derivatives - II. Anionic chemical delivery system for zidovudine (AZT).* International Journal of Pharmaceutics, 1998. 166(1): p. 27-35.

[55] Somogyi, G., P. Buchwald, and N. Bodor, *Targeted drug delivery to the central nervous system via phosphonate derivatives (Anionic delivery system for testosterone).* Pharmazie, 2002. 57(2): p. 135-137.

[56] Vangavaragu, J. R., et al., *Determination of small molecule ABAD inhibitors crossing blood-brain barrier and pharmacokinetics.* J Alzheimers Dis, 2014. 42(1): p. 333-44.

[57] Cherkasov, R. A. and V. I. Galkin, *The Kabachnik-Fields reaction: Synthetic potential and the problem of the mechanism.* Uspekhi Khimii, 1998. 67(10): p. 940-968.

[58] Pettersen, D., et al., *Direct access to enantiomerically enriched alpha-amino phosphonic acid derivatives by organocatalytic asymmetric hydrophosphonylation of imines.* Journal of Organic Chemistry, 2006. 71(16): p. 6269-6272.

[59] Reddy, M. V. N., et al., *One-pot synthesis of novel alpha-amino phosphonates using tetramethylguanidine as a catalyst.* Arkivoc, 2007: p. 246-254.

[60] Valasani, K. R., et al., *Structure-Based Design and Synthesis of Benzothiazole Phosphonate Analogues with Inhibitors of Human ABAD-A beta for Treatment of Alzheimer's Disease.* Chemical Biology & Drug Design, 2013. 81(2): p. 238-249.

[61] Jin, L. H., et al., *Synthesis, X-ray crystallographic analysis, and antitumor activity of N-(benzothiazole-2-yl)-1-(fluorophenyl)-O, O-dialkyl-alpha-aminophosphonates.* Bioorganic & Medicinal Chemistry Letters, 2006. 16(6): p. 1537-1543.

[62] Li, L., J. J. Wang, and G. W. Wang, *Manganese(III) Acetate-Promoted Cross-Coupling Reaction of Benzothiazole/Thiazole Derivatives with Organophosphorus Compounds under Ball-Milling Conditions.* J Org Chem, 2016. 81(13): p. 5433-9.

[63] Gu, L. J., et al., *Novel Synthetic Route to a-Aminophosphonates Containing Benzothiazole Moiety.* Chinese Journal of Chemistry, 2012. 30(10): p. 2483-2487.

[64] Zhang, H. J., et al., *Silver-mediated direct phosphorylation of benzothiazoles and thiazoles with diarylphosphine oxides (vol 51, pg 3450, 2015).* Chemical Communications, 2015. 51(94): p. 16871-16871.

[65] Chen, X. L., et al., *Peroxides as "Switches" of Dialkyl H-Phosphonate: Two Mild and Metal-Free Methods for Preparation of 2-Acylbenzothiazoles and Dialkyl Benzothiazol-2-ylphosphonates.* Journal of Organic Chemistry, 2014. 79(17): p. 8407-8416.

[66] VKR, K. V. a. V., *CTLA-4 Antibodies in Cancer Immunotherapy.* MOJ Immunol, 2016. 3(3): p. 00092.

[67] Koppolu, V., et al., *Small-Molecule Inhibitor of the Shigella flexneri Master Virulence Regulator VirF.* Infection and Immunity, 2013. 81(11): p. 4220-4231.

[68] Skredenske, J. M., et al., *Identification of a Small-Molecule Inhibitor of Bacterial AraC Family Activators.* Journal of Biomolecular Screening, 2013. 18(5): p. 588-598.

[69] Clomburg, J. M. and R. Gonzalez, *Biofuel production in Escherichia coli: the role of metabolic engineering and synthetic biology.* Applied Microbiology and Biotechnology, 2010. 86(2): p. 419-434.

[70] Rao, V. K., E. A. Carlson, and S. S. Yan, *Mitochondrial permeability transition pore is a potential drug target for neurodegeneration.* Biochim Biophys Acta, 2014. 1842(8): p. 1267-72.

[71] Du, H., et al., *Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memory in Alzheimer's disease.* Nat Med, 2008. 14(10): p. 1097-105.

[72] Valasani, K. R., et al., *Acetylcholinesterase inhibitors: structure based design, synthesis, pharmacophore modeling, and virtual screening.* J Chem Inf Model, 2013. 53(8): p. 2033-46.

[73] Vangavaragu, J. R., et al., *Identification of human presequence protease (hPreP) agonists for the treatment of Alzheimer's disease.* Eur J Med Chem, 2014. 76: p. 506-16.

[74] Valasani, K. R., et al., *Identification of a Small Molecule Cyclophilin D Inhibitor for Rescuing Abeta-Mediated Mitochondrial Dysfunction.* ACS Med Chem Lett, 2016. 7(3): p. 294-9.

[75] Valaasani, K. R., et al., *Identification of human ABAD inhibitors for rescuing Abeta-mediated mitochondrial dysfunction.* Curr Alzheimer Res, 2014. 11(2): p. 128-36.

[76] Lee, C. T., et al., *Riluzole and prognostic factors in amyotrophic lateral sclerosis long-term and short-term survival: a population-based study of 1149 cases in Taiwan.* J Epidemiol, 2013. 23(1): p. 35-40.

[77] Kakuta, T., et al., *Riluzole-induced lung injury in two patients with amyotrophic lateral sclerosis.* Intern Med, 2012. 51(14): p. 1903-7.

[78] Dupuis, L., et al., *A randomized, double blind, placebo-controlled trial of pioglitazone in combination with riluzole in amyotrophic lateral sclerosis.* PLoS One, 2012. 7(6): p. e37885.

[79] Coleman, N., et al., *The Riluzole Derivative 2-Amino-6-trifluoromethylthio-benzothiazole (SKA-19), a Mixed K(Ca)2 Activator and Na-V Blocker, is a Potent Novel Anticonvulsant.* Neurotherapeutics, 2015. 12(1): p. 234-249.