Journal of Biosciences and Medicines, 2024, 12, 239-244
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Aminated Cyclopropylmethylphosphonates as Potent Prostate Cancer Inhibitors

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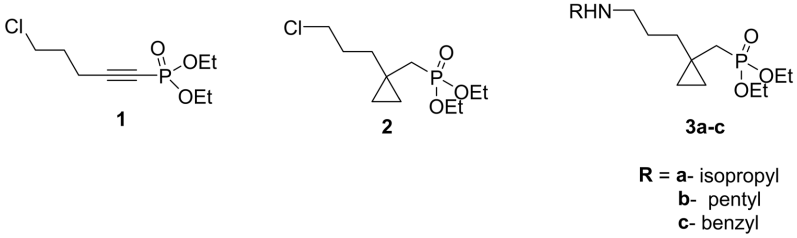
How to cite this paper: Al Quntar, A.A.A. and Abasy, I. (2024) Aminated Cyclopropylmethylphosphonates as Potent Prostate Cancer Inhibitors. *Journal of Biosciences and Medicines*, **12**, 239-244.
https://doi.org/10.4236/jbm.2024.127022

Received: June 17, 2024
Accepted: July 20, 2024
Published: July 23, 2024

Abstract

Inspired by the anti-pancreatic promising results of our novel aminated cyclopropylmethylphosphonate compounds, an in vitro anti-prostate cancer activity exploration of these compounds was carried out on human prostate cancer cell line PC-3, and showed potent inhibiting activity at low micromolar concentrations (with an IC50 of approximately 45 μM).



Keywords

Prostate Cancer, Cancer, Cyclopropylphophonates, Aminophosphonates, Cyclopropanes, Phosphonates, Alkynylphosphonates, Anti-Cancer, Prostate

1. Introduction

Prostate cancer (PCa) is the first most diagnosed cancer in men in 112 countries and is the leading cause of cancer-related death among men in 48 countries [1]. The major risk factors of this disease include family history, ethnic groups and obesity in which family inheritance is considered as one of the most predisposing factors [2].

Prostate cancer is diagnosed routinely based on elevated values of prostate-specific antigen (PSA), or analysis of prostate biopsy materials, and detec-

tion of DNA specific markers. The rectal examination and magnetic resonance imaging also could be used [3] [4].

Treatment strategies of PC are varied and are dependent on the stage of the disease [5] including, androgen deprivation therapy (ADT) [6], radiotherapy [7], surgery [8], chemotherapy [9], and others [10].

Despite the major improvements in diagnosis and treatment approaches, prostate cancer still remains a leading cause of cancer-related mortality among men globally [11]. Among 10 million clinically diagnosed PCa men, approximately 0.7 million are living with metastatic PCa, and more than 0.4 million deaths occur annually. This mortality rate is expected to increase by the coming years [12].

Due to these facts and the resistant of the prostate cancer cells to various treatments, which can affect the course of the disease and survival [13], there is an increasing need for other approaches of treatments with the emphases on the chemotherapy together with complete prostate prostatectomy [14]. Accordingly, this necessitates the search for new chemotherapy agents with higher efficacy and minimum side effects.

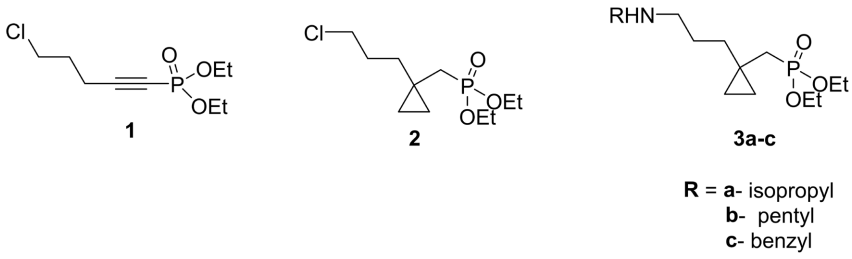
We believe that aminophosphonates compounds might be a candidate to this purpose due to their broad utilities such as anticancer [15], enzyme inhibitors [16], antibiotics [17], fungicides [18], anti-viral agents [19], herbicides [20] and others [21].

This work is an extension of our long ongoing research on organophosphonates compounds [22]-[24], and is devoted to aminated cyclopropylmethylphosphonates, which demonstrated anti-pancreatic cancer activity [25].

2. Results and Discussion

So, in pursue to our recently reported encouraging anti-pancreatic results of the novel cyclopropylmethylphosphonate compounds **3**, we determined to investigate their potential against other types of tumours [25].

Accordingly, the emphasis was on the prostate cancer due to the fact that it is considered to be one of the most aggressive and lethal cancers for men as mentioned above. The compounds in **Scheme 1** were in vitro tested on human prostate cancer cell line PC-3 (The American Type Culture Collection, Manassas, VA, USA) and interestingly they showed impressive activity in suppression of the prostate cancer in the cell line as shown in **Figure 1**.



Scheme 1. Phosphonate compounds tested against prostate cancer.

Diethyl ((1-propylcyclopropyl)methyl)phosphonate **2** and the chlorinated substrate **1** were also tested beside compounds **3**(a-c) as references in order to investigate the contribution of the amine group to the activity.

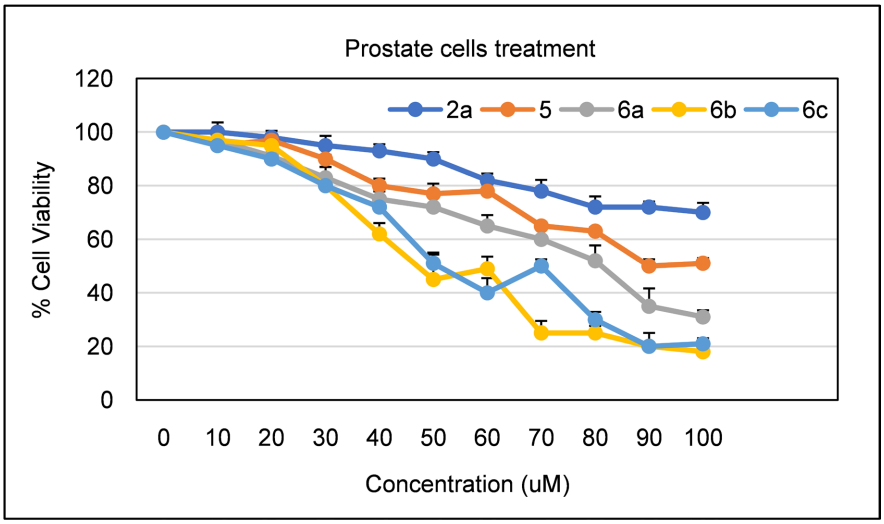


Figure 1. In vivo anti-prostate cancer activity of compounds (**1**, **2**, **3**a-c).

From one side the results showed that, the incorporation of the amine group significantly boosted the activity against pancreatic cancer cells as depicted in **Figure 1**. From the other side, while the aminated derivative diethyl ((1-(3-(isopropylamino)propyl)cyclopropyl)methyl)phosphonate **3**a displayed mild potency in inhibiting pancreatic cell proliferation, compounds diethyl ((1-(3-(pentylamino)propyl)cyclopropyl)methyl)phosphonate **3**b and diethyl (1-(4-(benzylamino)butyl)cyclopropyl)methyl)phosphonate **3**c showed a high potential as anti-prostatic cancer by exhibiting a potent cell suppression at low micromolar concentrations with an IC50 of approximately 45 µM.

In summary, in addition to their anti-pancreatic efficacy, aminated cyclopropylmethylphosphonates compounds possessed notable anti-prostate cancer activity, precisely when an alkyl chain or benzylamine group was incorporated into the cyclopropylmethylphosphonate framework. These results will be an instigation for an in vivo futural experimental exploration.

3. Experimental

Cell Culture and Cell Proliferation Assay

The human prostate cancer cell line PC-3 (The American Type Culture Collection, Manassas, VA, USA) was used in this experiment, cells were maintained in RPMI 1640 media supplemented with 10% (v/v) FBS and 100 units/mL penicillin and 100 g/mL streptomycin. Cells were grown at 37˚C with 5% CO. The proliferation assay was done in 96-well plates and started with seeding the PC-3 cells into 96-well plates at a density of 4×10^3 cells per well in a volume of 100 µl, cells were incubated at 37˚C for 24 hours. This was followed by treating the PC-3 cells

with different concentration of tested compounds (starting from 0 up to 100 mM), three replicated samples were assayed for each treatment and concentration. Cells were left for another 48 hours and cell viability was determined using the 3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2-h-tetrazolium bromide; MTT assay. This was done by the addition of 20 µL (prepared as 5 mg/ml) of the (MTT) reagent to each well and incubated for another 4 hours. Subsequently, supernatant was discarded and 100 µL of dimethyl sulfoxide was added to each well followed by incubation for 15 minutes. The absorbance was read using a microplate reader at a wavelength of 490 and 630 nm. The absorbance readings were used to calculate the half maximal inhibitory concentration (IC50).

It is worth noting that all the experiments were carried out in a triplicate framework.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A. and Bray, F. (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **71**, 209-249. https://doi.org/10.3322/caac.21660

[2] Hjelmborg, J.B., Scheike, T., Holst, K., Skytthe, A., Penney, K.L., Graff, R.E., Pukkala, E., Christensen, K., Adami, H.-O., Holm, N.V., *et al.* (2014) The Heritability of Prostate Cancer in the Nordic Twin Study of Cancer. *Cancer Epidemiology, Biomarkers & Prevention*, **23**, 2303-2310. https://doi.org/10.1158/1055-9965.EPI-13-0568

[3] Dejous, C. and Krishnan, U.M. (2020) Sensors for Diagnosis of Prostate Cancer: Looking Beyond the Prostate Specific Antigen. *Biosensors and Bioelectronics*, **173**, Article 112790. https://doi.org/10.1016/j.bios.2020.112790

[4] Ziaran, S., Novakova, Z.V., Böhmer, D. and Danišovič, L. (2015) Biomarkers for Determination Prostate Cancer: Implication for Diagnosis and Prognosis. *Neoplasma*, **62**, 683-691. https://doi.org/10.4149/neo_2015_082

[5] Borley, N. and Feneley, M. (2009) Prostate Cancer: Diagnosis and Staging. *Asian Journal of Andrology*, **11**, 74-80. https://doi.org/10.1038/aja.2008.19

[6] James, N.D., Sydes, M.R., Clarke, N.W., Mason, M.D., Dearnaley, D.P., Spears, M.R., *et al.* (2016) Addition of Docetaxel, Zoledronic Acid, or Both to First-Line Long-Term Hormone Therapy in Prostate Cancer (STAMPEDE): Survival Results from an Adaptive, Multiarm, Multistage, Platform Randomised Controlled Trial. *The Lancet*, **387**, 1163-1177. https://doi.org/10.1016/S0140-6736(15)01037-5

[7] Hamdy, F., Donovan, J., Lane, J., Mason, M., Metcalfe, C., *et al.* (2016) 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *The New England Journal of Medicine*, **374**, 1415-1424. https://doi.org/10.1056/NEJMoa1606220

[8] Cooperberg, M.R. (2017) Re: 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *European Urology*, **71**, 492-493. https://doi.org/10.1016/j.eururo.2016.10.037

[9] Kyriakopoulos, C., Chen, Y., Carducci, M., Liu, G., Jarrard, D. *et al.* (2018) Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survval Analysis of the Randomized Phase 3 E3805 CHAARTED Trial. *Journal of Clinical Oncology*, **36**, 1080-1087. https://doi.org/10.1200/JCO.2017.75.3657

[10] Tiruye, T., Ettridge, K., O'Callaghan, M., Moretti, K., Jay, A., Higgs, B., Santoro, K., Kichenadasse, G., Roder, D. and Beckmann, K. (2023) Reporting Real-World Data on Prostate Cancer Treatment Outcomes to Consumers: The Prostate Cancer Report Card. *European Journal of Cancer Care*, **2023**, Article ID: 6660371. https://doi.org/10.1155/2023/6660371

[11] Withrow, D., Pilleron, S., Nikita, N., Ferlay, J., Sharma, S., Nicholson, B. and Lu-Yao, G. (2022) Current and Projected Number of Years of Life Lost Due to Prostate Cancer: A Global Study. *Prostate*, **82**, 1088-1097. https://doi.org/10.1002/pros.24360

[12] Sayan, M., Langoe, A., Aynaci, O., Eren, A., Eren, M., Kazaz, I., Ibrahim, Z., Al-Akelie, O., Al-Mansouri, L., Abu-Hijlih, R., Moningi, S., Abou Chawareb, E., El Hajj, A., Orio, P. and Mula-Hussain, L. (2024) Prostate Cancer Presentation and Management in the Middle East. *BMC Urology*, **35**, 2-5. https://doi.org/10.1186/s12894-024-01427-6

[13] Franlund, M., *et al.* (2018) Results from 22 Years of Follow Up in the Goteborg Randomized Population-Based Prostate Cancer Screening Trial. *The Journal of Urology*, **208**, 292-300. https://doi.org/10.1097/JU.0000000000002696

[14] Mottet, N., van den Bergh, R.C., Briers, E., Van den Broeck, T., Cumberbatch, M.G., De Santis, M., Fanti, S., Fossati, N., Gandaglia, G., Gillessen, S., Grivas, N., Grummet, J., Henry, A.M., van der Kwast, T.H., Lam, T.B., Lardas, M., Liew, M., Mason, M.D., Moris, L. and Cornford P. (2021) EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer 2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *European Urology*, **79**, 243-262. https://doi.org/10.1016/j.eururo.2020.09.042

[15] Bhattacharya, A.K., Raut, D.S., Rana, K.C., Polanki, I.K., Khan, M.S. and Iram, S. (2013) Diversity-Oriented Synthesis of α-Aminophosphonates: A New Class of Potential Anticancer Agents. *European Journal of Medicinal Chemistry*, **66**, 146-152. https://doi.org/10.1016/j.ejmech.2013.05.036

[16] Alonso, E., Alonso, E., Solis, A. and Pozo, C.D. (2000) Synthesis of N-Alkyl-(α-Aminoalkyl)Phosphine Oxides and Phosphonic Esters as Potential HIV-Protease Inhibitors, Starting from α-Aminoacids. *Synlett*, **5**, 698-700. https://doi.org/10.1002/chin.200034183

[17] Allerberger, F. and Klare, I. (1999) *In-Vitro* Activity of Fosfomycin Against Vancomycin-Resistant Enterococci. *Journal of Antimicrobial Chemotherapy*, **43**, 211-217. https://doi.org/10.1093/jac/43.2.211

[18] Maier, L. and Spori, H. (1991) Organic Phosphorus Compounds. Resolution of 1-Amino-2-(4-Fluorophenyl)Ethylphosphonic Acid as Well as Some Di- and Tripeptides. *Phosphorus, Sulfur, and Silicon and the Related Elements*, **61**, 69-74. https://doi.org/10.1080/10426509108027339

[19] Bhattacharya, A., Rana, K., Pannecouque, C. and De Clercq, E. (2012) An Efficient Synthesis of a Hydroxyethylamine (HEA) Isostere and Its α-Aminophosphonate and Phosphoramidate Derivatives as Potential Anti-HIV Agents. *ChemMedChem*, **7**, 1601-1611. https://doi.org/10.1002/cmdc.201200271

[20] Kafarski, P. and Lejczak, B. (1991) Biological Activity of Aminophosphonic Acids. *Phosphorus, Sulfur, and Silicon and the Related Elements*, **63**, 193-215. https://doi.org/10.1080/10426509108029443

[21] Amira, A., Aouf, Z., K'tir, H., Chemam, Y., Ghodbane, R., Zerrouki, R. and Aouf, N. (2021) Recent Advances in the Synthesis of *α*-Aminophosphonates: A Review, *Chemistryselect*, **6**, 6137-6149. https://doi.org/10.1002/slct.202101360

[22] Al Quntar, A.A. and Srebnik, M. (2006) Direct Cyclopropanation of 1-Alkynylphosphonates by Cp_2ZrCl_2/2EtMgBr/2$AlCl_3$ to Afford Cyclopropylmethylphosphonates. *The Journal of Organic Chemistry*, **71**, 730-733. https://doi.org/10.1021/jo052157l

[23] Al Quntar, A.A., Dweik, H. and Dembitsky, V.M. (2020) Facile Synthesis of 2-Aminocyclobutenylphosphonates. *Russian Journal of Organic Chemistry*, **56**, 137-142. https://doi.org/10.1134/S1070428020010212

[24] Al Quntar, A.A., Dweik, H., Jabareen, A., Gloriozova, T.A. and Dembitsky, V.M. (2020) An Aminopyrrolidinyl Phosphonates—A New Class of Antibiotics: Facile Synthesis and Predicted Biological Activity. *International Journal of Organic Chemistry*, **10**, 170-181. https://doi.org/10.4236/ijoc.2020.104013

[25] Al Quntar, A.A., Abasy, I., Dweik, H., Maffei, M. and Dembitsky, V.M. (2023) Aminated (Cyclopropylmethyl)Phosphonates: Synthesis and Anti-Pancreatic Cancer Activity. *International Journal of Organic Chemistry*, **13**, 129-136. https://doi.org/10.4236/ijoc.2023.134010