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Novel Organo Phosphonate-1,2,3 Triazole Derivatives: Molecular Properties Prediction

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Authors' contributions

This work was carried out in collaboration among all authors. All the authors contributed to the realization of this work and have knowledge of final version. All authors read and approved the final manuscript.

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ABSTRACT

In the present scenario drug discovery and development processes are expensive and time consuming. To resolve this, we utilised the Lipinski's rule (Ro5) methodology, which appears to be useful in defining drugability. In the present investigation, we reported the synthesis and evolution of antibacterial activity of title compounds and according to Rule of 5 series, twenty novel ((R)-dimethyl (hydroxy(4-((1-(2-nitrophenyl)-*1H*-1,2,3-triazol-4-yl)methoxy)phenyl)methyl)phosphonate-1,2,3-triazole derivatives were subjected to molecular properties prediction, drug likeness by Molinspiration (Molinspiration, 2020) and Molsoft (Molsoft, 2020) software.

Keywords: Organo phosphorous triazoles; azide-alkyne cycloaddition; molinspiration; molsoft.

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1. INTRODUCTION

In recent years, number of synthesized organic molecules with broad spectrum of antimicrobial activity have been reported, among which triazole derivatives exhibited most provocative inhibitory activity against microorganisms [1]. In this context, the widespread organo phosphorous compounds (A and B) (Fig. 1) (natural or synthesised) is found to be an integral part of many bioactive compounds which show various pharmacological properties [2-5]. On the other hand, out of a number of heterocyclic compounds, 1,2,3-triazole (C and D) (Fig. 1) is a structural motif of particular interest in the field of medicinal chemistry [6-8]. Besides displaying a range of biological activities, 1,2,3-triazoles show physicochemical properties such as planarity, dipole moment, H-bond acceptor properties, etc. similar to that of peptide bonds and therefore are considered to be isosteres of peptides. However, unlike peptide bonds, the stability of 1,2,3-triazole moiety under hydrolytic as well as reductive and oxidative conditions make this group a useful alternative to amide as a linker. In the light of the above stimulating properties, we designed the hybrid molecule E as depicted in Fig. 1 and recently we reported the synthesis, antibacterial properties of the title compounds, and the entire compounds showed moderate to good activity. Although, the candidates exhibiting interesting antimicrobial activity, further it is also important to investigate the druglikeness, absorption prediction, including molecular size and shape descriptors, hydrogen-bonding capabilities, and surface properties [9-10]. Hence, interest is being increased on Lipinski's rule to enhance oral bioavailability. It is assumed that all orally administered drugs should has high oral bioavailability. Good oral availability can be achieved by right balance between partitioning and solubility properties [11-14]. Thus, in order to achieve better analogues of organo phosphonate -1, 2, 3-triazole, we have performed computational investigations of all the synthesized compounds for the prediction of lipophilicity, solubility and Lipinski 'Rule of Five'.

2. METHODOLOGY

2.1 Synthetic Scheme and Experimental Section

2.1.1 General procedure for the preparation of terminal alkyne 3

To a mixture of aldehyde or ketone (8.1 mmol) and K_2CO_3 (2.2 g,16.2 mmol) in acetone (15 ml) (1.9 g,16.2 mmol) was added propargyl bromide slowly dropwise. The reaction was completed in 3-4 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was added to the crushed ice (30 g). The solid obtained was filtered and collected. When solid was not obtained after pouring the reaction mixture into the crushed ice, the mixture was extracted with ethyl acetate. The combined organic extract was washed with brine solution dried over anhydrous Na_2SO_4.

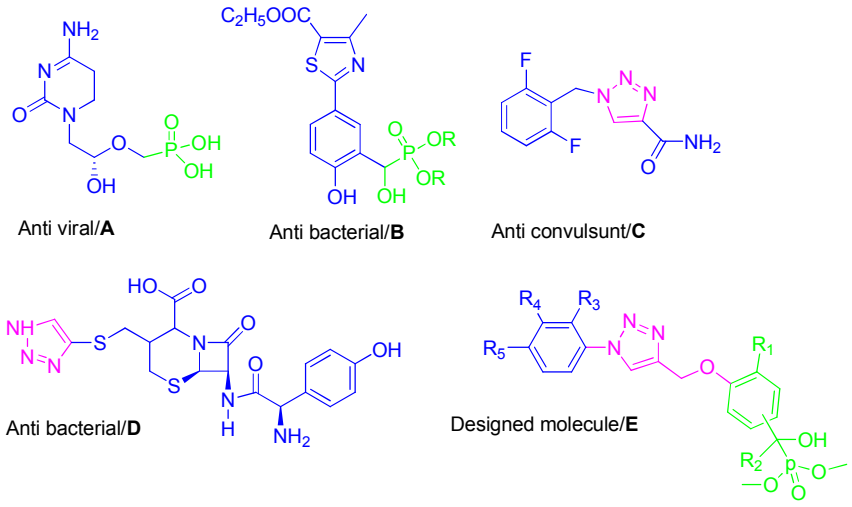


Fig. 1. Design of hybrid molecule

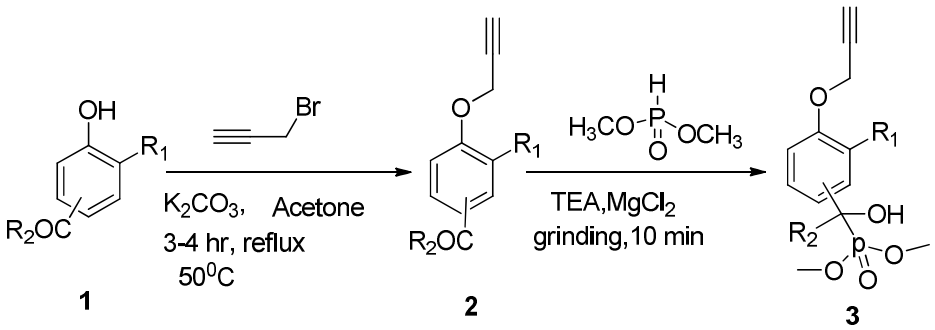
Anhydrous magnesium chloride (0.1 g, 1mmol), triethyl amine (0.3 g, 3 mmol) terminal alkyne (0.106 g, 1 mmol) and dimethylphosphite (0.136 g, 1.1 mmol) was taken in a mortar. The mixture was grinded in mortar with pestle after 5-10 min the reaction was monitored by TLC, indicated that the reaction was completed after 5 minutes. The product formed was extracted three times with 5 ml EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to isolate white solid. The crude compound was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent (Scheme-1).

2.1.2 General procedure for the preparation of aromatic azide 4

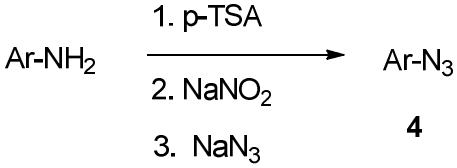
Organic azides 4 have been prepared from aromatic primary amines by following the earlier reported procedure (Nemati and Elhampour 2012) (Scheme-2).

2.1.3 General procedure for the preparation of compound 5

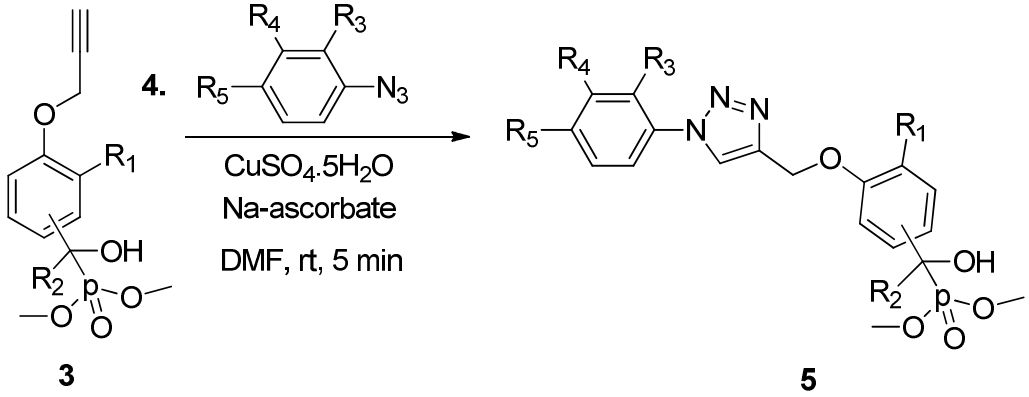
A mixture of an appropriate terminal alkyne 3 (0.53 mmol), azide 4 (0.53 mmol), $CuSO_4$•$5H_2O$ (65 mg, 0.26 mmol) and sodium ascorbate (52 mg, 0.26 mmol) in DMF (5 ml) was stirred vigorously for 5 min, at room temperature. The progress of the reaction was monitored by TLC at a regular interval. After completion of the reaction the mixture was poured into crushed ice (30 g). The solid separated was filtered, dried and purified by column chromatography on silica gel using petroleum ether /ethyl acetate (Scheme-3).



Scheme-1. Synthesis of terminal alkyne 3



Scheme-2. Synthesis of aromatic azide 4



Scheme-3. Synthesis of organo phosphonate triazole 5

Table 1. List of the compounds

S.NO	CODE	R_1	R_2	R_3	R_4	R_5
1	5a	H	H	NO_2	H	H
2	5b	H	H	H	NO_2	H
3	5c	H	H	OCH_3	H	H
4	5d	H	H	H	OCH_3	H
5	5e	H	H	H	H	OCH_3
6	5f	H	H	NO_2	H	H
7	5g	H	H	H	NO_2	H
8	5h	H	H	OCH_3	H	H
9	5i	H	H	H	OCH_3	H
10	5j	H	CH_3	H	H	OCH_3
11	5k	H	CH_3	NO_2	H	H
12	5l	H	CH_3	H	NO_2	H
13	5m	H	CH_3	OCH_3	H	H
14	5n	H	CH_3	H	OCH_3	H
15	5o	H	CH_3	H	H	OCH_3
16	5p	OCH_3	H	NO_2	H	H
17	5q	OCH_3	H	H	NO_2	H
18	5r	OCH_3	H	OCH_3	H	H
19	5s	OCH_3	H	H	OCH_3	H
20	5t	OCH_3	H	H	H	OCH_3

3. RESULTS AND DISCUSSION

3.1 Molecular Properties Prediction

Physicochemical parameters play a vital role in generation and determination of bioactivity of any compound. Molinspiration, web-based software, was used to explore the various parameters such as miLogP, TPSA, MW, and drug likeness. As the absorption of a drug molecule is linked with molecular weight, increasing the molecular weight will decrease the absorption. Keeping less molecular weight is an essential one in the drug development process. Analysis of molecular weight of the available drugs has pointed out that the 80% of drugs have solubility (logS) property of a drug in aqueous solution affect absorption and distribution characteristics. Good bioavailability can be achieved with an appropriate balance between solubility and partitioning properties. Thus in order to achieve good oral drugs we have subjected a series of twenty novel dimethyl (hydroxy(4-((1-(2-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)methyl)phosphonate-1,2,3-triazole derivative for the prediction of lipophilicity, solubility and Lipinski 'Rule of Five' The rule of five acts as a filter for drug like properties and status that a potential molecule is orally active. The number of rotatable bonds and polar surface area were determined using the molinspiration programme. All the derivatives (5a-t) under study have numerous hydrogen bond acceptors≤12 and numerous hydrogen bond donors≤1 as shown in Table 2. TPSA is molecular polar surface area and it characterizes the transport properties of a drug. This property is defined by polar atoms and predicted using different methods of classical 3D PSA and summation of tabulated surface contributions of polar fragments. The compounds (5a-t) under study Exihibit their conformational flexibility volume, percentage of absorption (%ABS) molecular polar surface area. The results are presented in Table 2. Magnitude of absorption is expressed by percentage of absorption and is calculated by the expression %ABS=109-0.35* PSA. Drug likeliness is a qualitative means of analysis to check whether the given molecule has drug-like properties, and it is defined as a complex balance of various molecular properties and structural features. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size, and flexibility and presence of various pharmacophoric features, influence the behaviour of a molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, and metabolic stability.

Table 2. Lipinski parameters and drug likeness properties of compounds 5a-5t

Compd	miLogP	TPSA	natoms	MW	nON	nOHNH	nviolations	Nrotb	Volume	DI Drug score
5a	1.75	141.54	30	434.35	11	1	1	9	357.32	0.12
5b	1.77	141.54	30	434.35	11	1	1	9	357.32	0.12
5c	1.84	104.95	29	419.37	9	1	0	9	359.53	-0.05
5d	1.87	104.95	29	419.37	9	1	0	9	359.53	-0.04
5e	1.68	104.95	29	419.37	9	1	0	9	359.53	-0.31
5f	1.72	141.54	30	434.35	11	1	1	9	357.32	-0.04
5g	1.75	141.54	30	434.35	11	1	1	9	357.32	-0.08
5h	1.82	104.95	29	419.37	9	1	0	9	359.53	-0.13
5i	1.84	104.95	29	419.37	9	1	0	9	359.53	-0.21
5j	1.66	104.95	29	419.37	9	1	0	9	359.53	-0.14
5k	2.19	141.54	31	448.37	11	1	1	9	373.56	-0.36
5l	2.22	141.54	31	448.37	11	1	1	9	373.56	-0.49
5m	2.29	104.95	30	433.40	9	1	0	9	375.77	-0.53
5n	2.31	104.95	30	433.40	9	1	0	9	375.77	-0.65
5o	2.13	104.95	30	433.40	9	1	0	9	375.77	-0.84
5p	1.34	150.78	32	464.37	12	1	1	10	382.87	-0.10
5q	1.36	150.78	32	464.37	12	1	1	10	382.87	-0.02
5r	1.43	114.19	31	449.40	10	1	0	10	385.08	-0.13
5s	1.46	114.19	31	449.40	10	1	0	10	385.08	-0.03
5t	1.27	114.19	31	449.40	10	1	0	10	385.09	-0.05

miLogP: logarithm of compound partition coefficient between n-octanol and water; TPSA: topological polar surface area; MW: molecular weight; nON: number of hydrogen bond acceptors; nOHNH: number of hydrogen bond donors; Nrotb: number of rotable bonds, DI: Drug likeness

3.1.1 Molinspiration calculations

All the derivatives 5a-5t under examination have various hydrogen bond acceptors (≤11) and hydrogen bond donors (1) as appeared in Table 2. Number of rotatable bonds (nrotb) is an essential pointer for atomic adaptability and conformational change. It is uncovered that the criteria for nrotb ought to be ≤10. The derivatives under investigation display a high number of nrotb (9–10) showing their conformational adaptability, volume and molecular polar surface area (PSA) for the derivatives 5a-5t are introduced in Table 2.

3.1.2 Molsoft calculations

Druglikeness is a qualitative concept used in drug design for how druglike a substance is with respect to factors like bioavailability. The large the value of the druglikeness score is the higher is also probability that the Particular molecular will be active. Among the tested compounds the compounds 5a and 5b are having the higher value i.e, 0.12 wil be active compounds.

4. CONCLUSION

In summary we reported the target products and these analogues were subjected to their molecular properties prediction by employing Molinspiration and Molsoft toolkits and the designed analogues were exhibited suitable drug like properties and are expected to present good bioavailability profile. These studies revealed that most of the compounds behave as an oral absorption drugs. The antibacterial activities of all the triazole phosphonate derivatives synthesized were then examined using four bacterial strains including one Gram-positive and three Gram-negative species. Thus, we have chosen *Staphylococcus aureus* (+ve) as gram +ve, whereas *Klebsiella pneumoniae* (−ve), *Pseudomonas aeruginosa* (−ve) and *Escherichia coli* (−ve) were chosen as gram (-ve). All the synthesized compounds exhibited good antibacterial activity against both Gram-positive, Gram-negative bacteria. Compounds 5b, 5c, 5i, 5j, 5n, 5p and 5q displayed best activity against all the Gram-positive and Gram-negative bacterial strains.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Jalal Hasan M, Medicinal and biological importance of 1,2,3-triazoles in click chemistry. Int. J. Innov. 2015;5(2):2348–7968.
2. Aksinenko AY, Sokolov VB, Goreva TV, Makhaeva GF. Synthesis of o-phosphorylated 1-substituted 2,2,2-trifluoroethanols, serine hydrolase inhibitors. Russ. Chem. 2010;59(1):102–106.
3. Perera S, Naganaboina VK, Wang L, Zhang B, Guo Q, Rout L, Zhao CG. Organocatalytic highly enantioselective synthesis of β-formyl-α-hydroxyphosphonates. Advanced Synthesis & Catalysis. 2011;353(10): 1729–1734.
4. Sampath C, Harika P, Revaprasadu N. Design, green synthesis, anti-microbial, and anti-oxidant activities of novelα-aminophosphonates via Kabachnik-Fields reaction.“Phosphorus Sulfur Silicon Relat Elem”. 2015;191(8):1081–1085.
5. Waterbeemd HVD, Camenisch G, Folkersand G, Raevsky OA. 1-Hydroxy-1-(2-hydroxyphenyl)ethyl]phosphonates and-phosphinates: Convenient synthesis through intramolecular Abramov reaction and protective activity against influenza A. Tetrahedron Lett. 2013;16:11109-11115.
6. Naveen K, Jhonsee T, Venkanna B, Suresh N, Jaya Shree A and Sarbani P Novel benzoxepine-1,2,3-triazole hybrids:

Synthesis and pharmacological evaluation as potential antibacterial and anticancer agents. Med. Chem. Commun. 2015;(6): 1612–1619.

7. Sarbani P, Naveen K, Jhonsee T, Venkanna B, Jaya Shree A. Synthesis, characterization, antibacterial and anticancer activity of some novel triazolyl chromenone derivatives. Der Pharma Chemica. 2017;9(23):1-7.
8. Naveen K, Jhonsee T, Venkanna B, Balasubramanian S, Anireddy JS, Pal S. Design, synthesis and antibacterial evaluation of compounds based on new benzoxepine-oxime-1,2,3-triazole hybrid. mini rev. Med. Chem. 2018;18:803-809.
9. Clark DE, Pickett SD. Computational methods for the prediction of drug-likeness. LETT DRUG DES DISCOV. 2000;5:49-58.
10. John R, Proudfoot. Drugs, leads, and drug-likeness: an analysis of some recently launched drugs. Bioorg Med Chem Lett. 2002;(12):1647-1650.
11. Sunil Kumar Lakavath. Novel delivery system used for oral bioavailability enhancement of poorly water soluble drugs. J. Drug Deliv. Ther. 2020;10: 139-144.
12. Sietsema WK. The absolute oral bioavailability of selected drugs. International Journal of Clinical Pharmacology. Therapy, and Toxicology. 1989;27(4):179-211.
13. Yvonne C. Martin. A Bioavailability Score. J. Med. Chem. 2005;48(9):3164–3170.
14. Lipinski CA, Lombardo FB, Dominy BW, Feeney P, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. J. Adv. Drug Deliv. Rev. 1997;23(3):3-25.

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