JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS
https://doi.org/10.1080/07391102.2023.2222833

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New sulfonamide derivatives based on 1,2,3-triazoles: synthesis, *in vitro* biological activities and *in silico* studies

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Communicated by Ramaswamy H. Sarma

ABSTRACT

Eight new hybrid constructs containing a series of sulfonamide and 1,2,3-triazole units were designed and synthesized. Anticancer, antioxidant and cholinesterase activities of these hybrid structures were investigated. In our design, the Cu(I)-catalyzed click reaction between N,4-dimethyl-N-(prop-2-yn-1-yl)benzenesulfonamide (**6**) and aryl azides **8a–h** was used. Antioxidant activity values of **9f** (IC_{50}: 229.46 ± 0.001 μg/mL) and **9h** (IC_{50}: 254.32 ± 0.002 μg/mL) hybrid structures were higher than BHT (IC_{50}: 286.04 ± 0.003 μg/mL) and lower than Ascorbic acid (IC_{50}: 63.53 ± 0.001 μg/mL) and α-Tocopherol (IC_{50}: 203.21 ± 0.002 μg/mL). We determined that the cytotoxic effects of hybrid constructs **9d** (IC_{50}: 3.81 ± 0.1084 μM) and **9g** (IC_{50}: 4.317 ± 0.0367 μM) against A549 and healthy cell line (HDF) are much better than standard cisplatin (IC_{50}: 6.202 ± 0.0705 μM). It was determined that the AChE inhibitory activities of all synthesized compounds were much better than Galantamine used as a standard. In particular, **9c** (IC_{50}: 13.81 ± 0.0026 mM) had ten times better activity than the standard Galantamine (IC_{50}: 136 ± 0.008 mM). The ADMET properties of the molecules have been thoroughly examined and met the criteria for drug-like substances. They also have a high oral absorption rate, as they can effectively cross the blood–brain barrier and are easily absorbed in the gastrointestinal tract. *In vitro* experiments were confirmed by *in silico* molecular docking studies.

ARTICLE HISTORY
Received 2 February 2023
Accepted 2 June 2023

KEYWORDS
Triazole; Alzheimer; *in silico*

1. Introduction

Alzheimer's disease (AD) is the most common chronic neurodegenerative disease faced by the increasing elderly population due to prolonging the human lifespan (Bag et al., 2015). It is estimated that the number of dementia patients in the world is 50 million at present, of which 30–35 million are Alzheimer's patients. The disease's occurrence depends on genetic and environmental risk factors (Kung et al., 2001). The most significant known risk factor is age; As you age, the likelihood of disease progression increases, but it is not an inevitable part of aging. While memory initially deteriorates, attention, language, visuospatial skills, perception, and problem-solving decline. In addition, personality changes and behavioral and psychiatric symptoms (delusions, hallucinations, affective disorders, etc.) are added. Eventually, the disease progresses to loss of bodily function and, ultimately, death (Davis, 1976; Martin Prince et al., 2015). To treat Alzheimer's disease, inhibition of the enzyme acetylcholinesterase (AChE) is an important target, and AChE inhibitors are the primary drugs for treating this disease. Current AD drugs such as enzyme inhibitors donepezil, rivastigmine, and Galantamine, currently used for therapeutic purposes, provide symptomatic relief by increasing acetylcholine levels and inhibiting acetylcholinesterase (AChE). Still, they also give various side effects such as peripheral side effects, hepatotoxicity, and gastrointestinal system disorders (Luo et al., 2016; Singla & Piplani, 2016). To overcome this situation, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) enzyme inhibition studies of new molecules should be performed. Recent studies have stated that some molecules, as newly synthesized sulfonamide derivatives, exhibit AChE inhibition at very low concentrations (Hamedi et al., 2020; Köksal et al., 2019; Turkan et al., 2018).

Cancer is a non-communicable disease and is the second leading cause of death after cardiovascular disease (Malani et al., 2017). The increased mortality in patients affected by cancer is due to the failure of traditional therapeutic tools such as radiation therapy and surgical approaches (Kamal et al., 2008). Therefore, chemotherapeutic strategies often involve the development of small molecule anticancer agents that can be administered *via* bloodstream action targeting both cancers and metastasized colonies (Liu et al., 2016; Penthala et al., 2015). Therefore, great emphasis has been placed on reliable drug evaluation based on anticancer agents. Anticancer activities of natural compounds or new organic molecules are being studied. Due to the ineffective chemotherapy caused by drug resistance in cancer treatment and the inability of many drugs to differentiate between

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