Nigerian Research Journal of Chemical Sciences **(ISSN: 2682-6054)**
Volume 10, Issue 1, 2022

Short Communication

NOVEL 1,2,3,4-TETRAHYDROISOQUINOLINE DERIVATIVES AS POTENTIAL ANTICANCER AGENTS: PRELIMINARY *IN SILICO* INVESTIGATION

[*1]Yusuf Hassan, [2]Gizem Tatar, [3]Tugba Taskin-Tok, [1]Aliyu Danmusa Mohammed

[1]Department of Chemistry, Umaru Musa Yar'adua University, Katsina, Nigeria

[2]Department of Bioinformatics and Computational Biology, Gaziantep University, Gaziantep, Turkey

[3]Department of Chemistry, Gaziantep University, Gaziantep, Turkey

*Corresponding Author: yusuf.hassan@umyu.edu.ng

ABSTRACT

The need for new anticancer agents continues to be of paramount importance due to the limitations of the existing drugs used for chemotherapy. Tetrahydroisoquinoline is one of the privileged heterocyclic moieties that show excellent promising activity in the *in vitro* studies of some cancer cell lines. In this short communication, the structures of five substituted derivatives were proposed and searched on the SciFinder and Reaxys databases which proved their structural novelty. Subsequently, molecular docking studies using CDOCKER subprotocol in the Discovery Studio 2017 R2 program were employed to study the interactions of the compounds against epidermal growth factor receptor (EGFR) as a potential target for cancer therapy. The findings revealed that the hydroxy-, methoxy phenyl substituted tetrahydoisoquinoline derivative demonstrated the lowest binding energy (-155.468 kcal/mol) and CDOCKER score of -31.456. Also there were favourable hydrophobic interactions with the five amino acid residues.

Keywords: Tetrahydroisoquinoline derivatives, epidermal growth factor receptor, Docking studies

INTRODUCTION

Cancer represents the second leading cause of death after cardiovascular diseases worldwide [1, 2]. However, the search for novel structures that can act as a more potent, selective, and reliable anticancer agent, remains one of the major challenges facing medicinal chemists [3]. This is because of the major limitations, such as lack of selectivity of the existing drugs for cancer cells, which bring about unwanted side effects, and acquisition of multiple-drug resistance by the

cancer cells [4]. Interestingly, it was found that the over expression of epidermal growth factor receptor (EGFR) in cancer cells leads to abnormal signal transduction and is closely related to the occurrence of cancer. As such it has become one of the most important protein targets for designing and developing kinase inhibitors that act ononcogenic EGFR [5].

EGFR is a member of the ErbB family of receptor tyrosine kinases that plays important role in cellular signaling pathways such as mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/Akt, as well as signal transducer and activator of transcription (STAT) pathways that regulate essential functions like survival, proliferation, differentiation, and apoptosis [6]. Structurally, EGFR is composed of an extracellular receptor domain, a single hydrophobic transmembrane region and an intracellular domain, which includes a juxta membrane domain [7], a tyrosine kinase (TK) domain and a C-terminal tyrosine-rich region [8]. The EGFR-mediated signaling pathways activation begins with EGF binding to the extracellular domain, which then activates the TK domain to phosphorylate at its C-terminal tail, and eventually, initiates downstream signaling pathways [9,10]. Therefore, targeting EGFR protein has been suggested as a promising strategy for targeted cancer therapy, since the EGFR is commonly overexpressed in common human cancers which includes head, breast, bladder and ovarian carcinoma [11,12].

Tetrahydroisoquinoline (THIQ) is a privileged heterocyclic scaffold that demonstrates a tremendous potential in anticancer drug design. A number of THIQ analogues have been shown to exhibit potent activity against various cancer molecular targets. However, some drawbacks have been noticed in terms of selectivity that needs addressing. The ease of the synthesis of THIQ core structure complimented with its reactivity makes it ideal for further structure-activity relationship studies [13]. Therefore, the aim of this study was to utilise molecular docking technique to explore interaction mechanisms of various novel derivatives of 1,2,3,4-tetrahydroisoquinolines and epidermal growth factor receptor (EGFR) as potential therapeutic agents.

MATERIALS AND METHODS

The human EGFR receptor was downloaded from the Protein Data Bank (PDB) and all compounds were drawn and optimization using DFT/ B3LYP / 6-31G* basic set with Gaussian

9.0 package program. The docking study was performed using CDOCKER subprotocol in the Discovery Studio 2017 R2 program [14].

RESULTS AND DISCUSSION

A total of five 1,2,3,4-tetrahydroisoquinoline derivatives (Figure 1) which could be obtained via Pictet-Spengler methodology [15] were flexibly docked with EGFR receptor (Figure 2). This resulted in ten poses for ten tetrahydroisoquinoline derivatives and the best pose of each ligand was found to be Compound **3**. Compound **3** possessed the lowest binding energy of -155.468 kcal/mol and CDOCKER score of -31.456. Furthermore, the best five favorable amino acids were found to be Val 702, Leu 802, Ala 719, Thr 766 and Lys 721 in the docking analysis. The hydrophobic interactions were observed more frequently than hydrogen bonding in the total interactions (Figure 4).

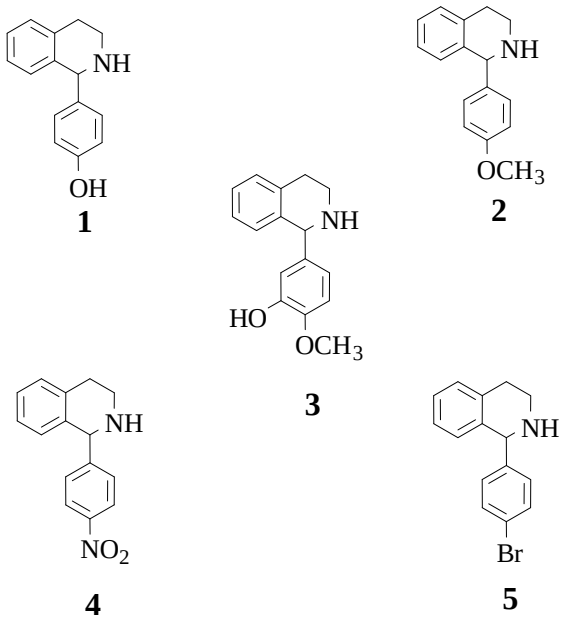

Figure 1: Structures of Novel 1.2.3.4-Tetrahydroisoquinoline Derivatives

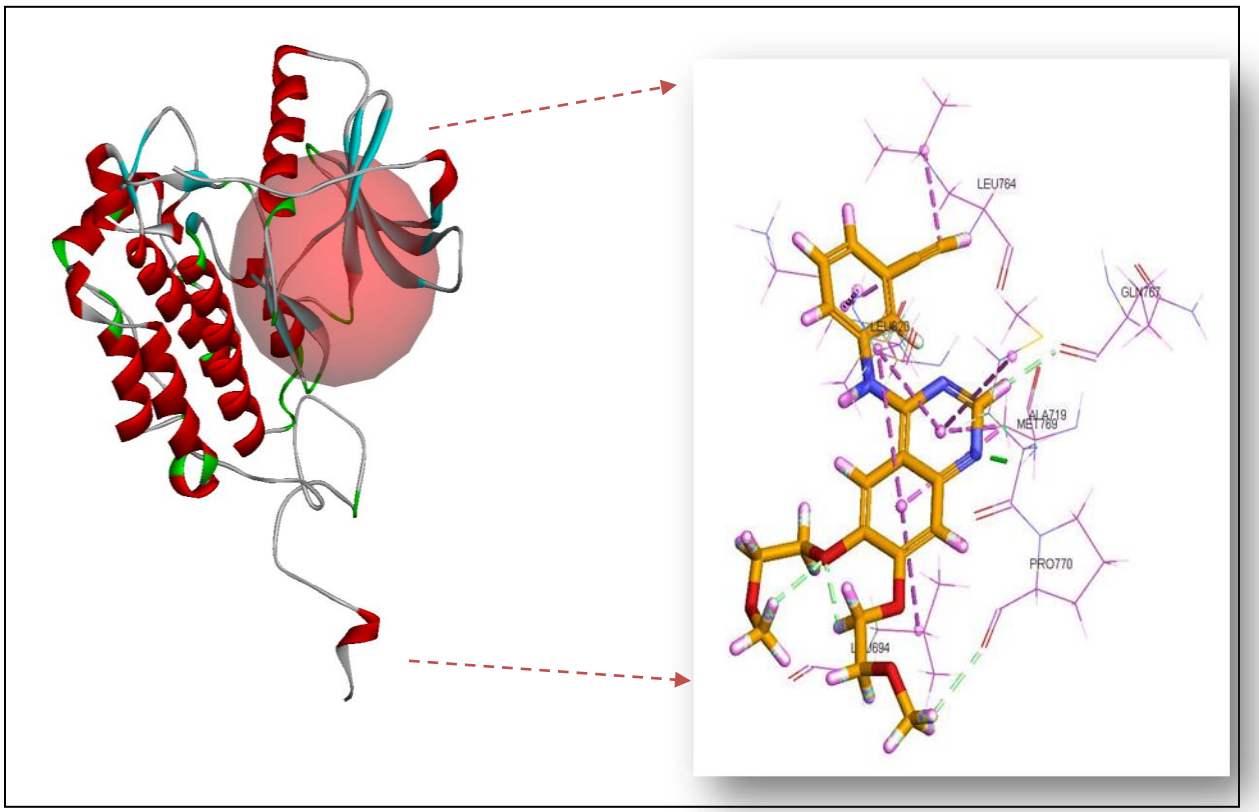

Figure 2: 3D Structure of EGFR and its Active Sites.

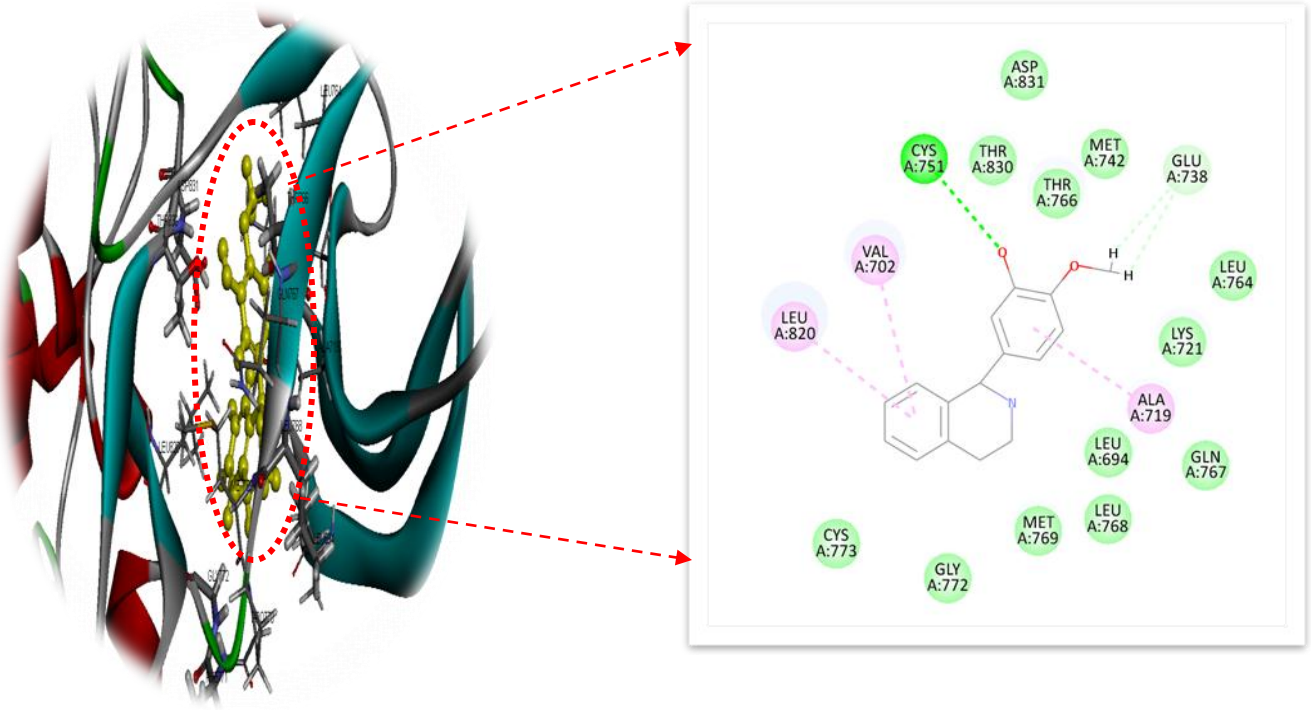

Figure 3: 2D and 3D interaction results of Compound **3** with EGFR.

CONCLUSION

A molecular modeling technique was employed to evaluate the potential of five novel tetrahydroisoquinoline derivatives as anticancer agents. This was achieved by docking the compounds against epidermal growth factor receptor (EGFR) which is a favourable target for cancer cell inhibition. The findings revealed that Compound **3** demonstrated the best properties in terms of binding energy, hydrogen bonding, and hydrophobic interactions with the EGFR active site. This signified that the compound could serve as a template for the discovery of new tetrahydroisoquinoline-based anticancer compounds.

ACKNOWLEDGEMENT

Funding by the Tertiary Education Trust Fund (TETFund), Nigeria under the Institution-Based Research (IBR) grant is gratefully acknowledged.

REFERENCES

[1] Gibbs, J. B. (2000). Mechanism-based target identification and drug discovery in cancer research. *Science*, 287(5460):1969-1973.

[2] Unger, C. (1997). New therapeutic approaches in cancer treatment. *Drugs of the Future*, *22*(12):1337-1345.

[3] Heffeter, P., Jakupec, M. A., Körner, W., Wild, S., von Keyserlingk, N. G., Elbling, L., Zorbas, H., Korynevska, A., Knasmuller, S., Sutterluty, H., Micksche, M., Keppler, B. K., & Berger, W. (2006). Anticancer activity of the lanthanum compound [tris (1, 10-phenanthroline) lanthanum (III)] trithiocyanate (KP772; FFC24). *Biochemical Pharmacology*, 71(4), 426-440.

[4] Menta, E. & Palumbo, M. (1997). Novel antineoplastic agents. *Expert Opinion on Therapeutic Patents*, 7(12), 1401-1426.

[5] Wee, P. & Wang, Z. (2017). Epidermal Growth Factor Receptor Cell Proliferation Signaling Pathways. Cancers 9, 52.

[6] Holbro, T. & Hynes, N.E. (2004). ErbB receptors: Directing key signaling networks throughout life. *Annual Review of Pharmacology and Toxicology*,44, 195–217.

[7] Choowongkomon, K., Carlin, C. R., & Sonnichsen, F.D. (2005). A structural model for the membrane-bound form of the juxtamembrane domain of the epidermal growth factor receptor. *Journal of Biological of Chemistry*,280, 24043–24052.

[8] Flynn, J. F., Wong, C., & Wu, J.M. (2009), Anti-EGFR Therapy: Mechanism and Advances in Clinical Efficacy in Breast Cancer. *Journal of Oncology*,2009, 526963.

[9] Seshacharyulu, P., Ponnusamy, M. P., Haridas, D., Jain, M., Ganti, A. K., & Batra, S.K. (2012). Targeting the EGFR signaling pathway incancer therapy. *Expert Opinion on Therapeutic Targets*, 16, 15–31.

[10] Fitzgerald, T. L., Lertpiriyapong, K., Cocco, L., Martelli, A. M., Libra, M., Candido, S., Montalto, G., Cervello, M., Steelman, L., Abrams, S. L., & McCubrey, J. A. (2015). Roles of EGFR and KRAS and their downstream signaling pathways in pancreatic cancer and pancreatic cancer stem cells. *Advances in Biological Regulation*, 59, 65–81.

[11] Ogiso, H., Ishitani, R., Nureki, O., Fukai, S., Yamanaka, M., Kim, J. H., Saito, K., Sakamoto, A., Inoue, M., Shirouzu, M. & Yokotama S. (2002). Crystal structure of the complex of human epidermal growth factor and receptor extracellular domains. *Cell*, 110, 775–787.

[12] Yang, C. H., Chou, H. C., Fu, Y. N., Yeh, C. L., Cheng, H. W., Chang, I. C., Liu, K. J., Chang, G. C., Tsai, T. F., Tsai, S. F. & Liu, H. P. (2015). EGFR over-expression in non-small cell lung cancers harboring EGFR mutations is associated with marked down-regulation of CD82. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease,* 1852, 1540–1549.

[13] Faheem, Karan K. B., Venkata, G. C. S. K., Chander, S., Kunjiappan, S. & Murugesan, S. (2021). 1, 2, 3, 4-Tetrahydroisoquinoline (THIQ) as privileged scaffold for anticancer de novo drug design. *Expert opinion on drug discovery*, 16(10), 1119-1147.

[14] Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Mennucci, B., & Petersson, G. A. (2016). Gaussian 09, Revision A.02, Gaussian Inc., Wallingford CT.

[15] Nishihachijo, M., Hirai, Y., Kawano, S., Nishiyama, A., Minami, H., Katayama, T., Yasohara, Y., Sato, F., & Kumagai, H. (2014). Asymmetric synthesis of tetrahydroisoquinolines by enzymatic Pictet–Spengler reaction. *Bioscience, Biotechnology, and Biochemistry*, *78*(4), 701-707.