Indian Journal of Heterocyclic Chemistry
Vol. 32 - Number 02 (Apr-Jun 2022) 209-216
DocID: https://connectjournals.com/01951.2022.32.209

ISSN (Print) : 0971-1627
ISSN (Online) : 2456-4311

Synthesis, Anticancer, and Molecular Docking Studies of 3-Benzyl-*N*-aryl-1*H*-1,2,4-triazol-5- amines

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ABSTRACT Six new triazole analogues (**4a-f**) and the antiproliferative activity of four analogues have been described in this study. The triazoles were synthesized in three steps starting from aromatic anilines. A series of six triazoles were synthesized, and their structures (**4a-f**) were confirmed using nuclear magnetic resonance and mass spectral data, followed by anticancer testing of four compounds at 10 μM against nine different panels of human cancer cell lines using the National Cancer Institute (NCI US) standard protocol. All the four compounds were found to have moderate to low antiproliferative activity. 3-Benzyl-*N*-(2,5-dimethoxyphenyl)-1*H*-1,2,4-triazol-5-amine (**4d**) was discovered to have significant antiproliferative activity with higher sensitivity toward NCI-H522, MOLT-4, PC-3, HL-60(TB), HT29, CCRF-CEM, UO-31, UACC-257, and A549 cell lines with percent growth inhibitions (GIs) of 32.59, 26.53, 23.03, 21.84, 19.81, 17.97, 12.70, 12.29, and 12.19, respectively. The binding affinities of the title ligands (**4a-f**) against the colchicine binding site of tubulin were investigated using a molecular docking simulation. All of the ligands had similar types of binding interactions (H-bond interaction between the residue Ala317 and NH function of triazole), with the exception of ligand **4d**, which had two H-bonds (Asn258; NH function of triazole and secondary amine function) and a π-cationic interaction with the residue Lys254 and triazole ring.

KEY WORDS Anticancer Activity, Cytotoxicity, Cancer Cell Lines, Single Dose Assay, Triazoles.

How to cite this article: Bhatia, S., Yusuf, M., Garg, S.K., Salahuddin, Bakht, M.A., Sharma, N., Ahsan, M.J. Synthesis, Anticancer, and Molecular Docking Studies of 3-Benzyl-N-aryl-1*H*-1,2,4-triazol-5- amines. *Indian J. Heterocycl. Chem.*, **2022**, *32*, 209–216. (*DocID: https://connectjournals.com/01951.2022.32.209*)

INTRODUCTION

Cancer is one of the most dreadful diseases, surpassing cardiovascular disease as the leading cause of death now a day.[1] In 2020, an estimated 19.3 million new cancer cases and nearly 10.0 million cancer deaths occurred worldwide. By 2040, the situation is expected to worsen, with an estimated 28.4 million new cancer cases.[2] Lung cancer is the most common type of cancer, followed by female breast cancer and colorectal cancer.[3] For the year 2020, India's cancer patient population is expected to be 1,392,179.[4] Cancer diagnosis and treatment were hampered in 2020 due to the

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8.38 (1H, s, ArNH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.32, 156.11, 142.37, 136.21, 131.31, 129.12, 129.02, 128.61, 126.51, 125.71, 123.84, 123.79, 33.94, 17.61; Anal. calc. for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20; found: C, 72.67; H, 6.13; N, 21.24%. EIMS *m/z* = 265.10 $[M+1]^+$.

3-Benzyl-*N*-(4-methylpheyl)-1*H*-1,2,4-triazol-5-amine (4f)

IR (KBr): 3298 (NH), 1450 (C=N) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (3H, s, CH_3), 3.32 (2H, s, CH_2), 4.61 (1H, s, NH), 6.92 (2H, d, *J* = 6.0 Hz, ArH), 7.18-7.31 (5H, m, ArH), 7.36 (2H, d, *J* = 6.0 Hz, ArH), 8.38 (1H, s, ArNH); Anal. calc. for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20; found: C, 72.68; H, 6.12; N, 21.25%. EIMS *m/z* = 265.14 $[M+1]^+$.

Anticancer activity

The compounds (**4a-f**) were evaluated for anticancer activity against nine panels of 60 cancer cell lines. To test the anticancer activity at one dose (10 μM), the National Cancer Institute (NCI) protocol was followed.[36-39]

Molecular docking

The 3D X-ray crystallographic structure of tubulin (PDB ID: 1AS0) with resolution 3.58 Å and r-value 0.233 (obs.) was accessed from protein database.[40] The molecular docking was performed as per the reported method.[41,42]

CONCLUSION

All the compounds were synthesized in good yields and confirmed by spectral data. Some of the compounds displayed significant anticancer activity in single dose assay (at 10 μM). The compound **4d** was found to be the most promising compound exhibited significant anticancer activity. The molecular docking simulation was performed against the colchicine binding site of tubulin (PDB ID: 1AS0) to characterize the binding affinities of these ligands (**4a-f**). The docking scores were found ranging between -6.584 and -6.942 kcal/mol showed an efficient binding against the active site of tubulin and a plausible mechanism of action of the title compounds (**4a-f**). All of the ligands (**4a-f**) had similar types of binding interactions (H-bond interaction between the residue Ala317 and NH function of triazole), with the exception of ligand **4d**, which had two H-bonds (Asn258; NH function of triazole and secondary amine function) and a π-cationic interaction with the residue Lys254 and triazole ring. The present work is expected to potentiate the future anticancer drug discovery program.

ACKNOWLEDGMENT

The current research is supported by Taif University Researchers Supporting Project number (TURSP - 2020/293), Taif University, Taif, Saudi Arabia.

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Received: 07 Feb 2022; Accepted: 15 Mar 2022