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Novel Thiadiazole Derivatives as Bcr-Abl Tyrosine Kinase Inhibitors

Vijayakumar Subramanian[1, 2], Sulaiman Ali Muhammad[1], Kaveri Sundaram[1], Subban Ravi[1*]

[1]Pollachi Institute Of Engineering and Technology, Poosaripatti, Pollachi, Coimbatore-642205, India.
[2]Department of chemistry, Karpagam Academy of Higher Education, Eachanari Post, Coimbatore- 641021, Tamil Nadu, India.

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ABSTRACT

The present work mainly aims to discover novel small molecular inhibitors against important molecular target T3151 Abl mutant involved in leukemia. Five heterocyclic compounds **1-5** with N and S atoms (thiosemicarbazone, thiadiazole and thiazolidinoyl derivatives) were synthesised and characterised using spectral data. Docking study was carried out for **1-5** against the T315I Bcr-Abl mutant. The compounds **3-5** with phenothiazine pharmacophore showed promising docking score than with the derivatives having the coumarin pharmacophore **1** and **2.** So the compounds **3-5** were tested for their anticancer activity against leukemic K562 cell line by trypan blue, MTT and LDH assays. Compound **5** showed marked anticancer activity and exhibited an IC_{50} value of 11.12 and 50.66 µg/ml against trypan blue and MTT assay respectively. Further a dose-dependent increase in LDH release was observed, confirming the antiproliferative potential of the compounds.

INTRODUCTION

In the post-genomic period, rational anti-cancer drug discovery aims to discover small molecules that change the activity of key therapeutic targets responsible for carcinogenesis (William and Kaelin 1999). Computer- aided or *in silico* design is being used to expedite and facilitate the lead molecule identification (Ali Muhammad *et al.,* 2015). It reduces the volume of chemical space and allows to focus on more promising candidates for lead discovery and optimization (Kapetanovic, 2008). Chronic myelogenous leukemia (CML) is a hematological stem cell disorder caused by deregulated growth of myeloid cells in the bone marrow and the accumulation of excessive white blood cells. Abelson tyrosine kinase (Abl) is involved in cell growth and proliferation and is usually under tight control (Noronha *et al.,* 2008). However, a large number of CML patients have the Philadelphia chromosome in which ABL gene from chromosome 9 fused with the breakpoint cluster (BCR) gene from chromosome 22. This Philadelphia chromosome is responsible for the production of Bcr-Abl, a constitutively active tyrosine kinase that causes uncontrolled cellular proliferation. Imatinib is an Abl inhibitor and is currently used as first line therapy (Desogus *et al.,* 2015; Mughal *et al.,* 2013). However, during the long term treatment with imatinib a high percentage of clinical relapse has been observed (Noronha *et al.,* 2008). A majority of these relapsed patients has several point mutations in and around the ATP binding pocket of the ABL kinase domain in Bcr-Abel (Michele *et al.,* 2007; Jorge *et al.,* 2011). In order to address the resistance of mutated Bcr-Abl to imatinib, 2(nd) generation inhibitors like dasatinib, and nilotinib were developed and used for the treatment of CML patients who are resistant to imatinib (Karthigai Priya *et al.,* 2015; Muhammad *et al.,* 2015; 2016; Noronha *et al.,* 2008). All of the Bcr-Abl mutants are inhibited by the 2(nd) generation inhibitors with the exception of the T315I mutant. Several 3(rd) generation inhibitors are currently in progress to target the T315I mutation. 1,3,4-thiadiazolines nucleus is a biologically active heterocyclic ring, which is associated with a wide range of pharmacological activities (Katritzky and Rees, 1981). 1,3,4-thiadiazolines/thiadiazoles are shown to exhibit antibacterial, diuretic, antifungal, anti-inflammatory, herbicidal and antiviral activities.

* *Corresponding Author*
Ravi Subban, Department of chemistry, Karpagam Academy of Higher Education, Eachanari Post, Coimbatore- 641021, Tamil Nadu, India.
Email: ravisubban @ rediffmail.com