Research Article **Mahapatra *et al.*, 10(1): Jan., 2019:6013-6015]**
CODEN (USA): IJPLCP **ISSN: 0976-7126**

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES
(Int. J. of Pharm. Life Sci.)

Exploring the anti-breast cancer (against MCF-7 Cell Line) potentials of uracil substituted hippuric acid based 1,3,4-thiadiazole compound

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Abstract

In the previous research done, uracil moiety substituted hippuric acid containing 1,3,4-thiadiazole scaffold was rationally designed, synthesized, and screened for anti-diabetic activity using the streptozotocin-induced hyperglycemic method in Swiss albino rats. In the current research, the same compound *N*-((5-(((2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyl)amino)-1,3,4-thiadiazol-2-yl)methyl)benzamide was screened against MCF-7 breast cancer cell line utilizing the Sulforhodamine B (SRB) assay and further the IC_{50} value was established in comparison with capecitabine, the standard drug. The study highlighted a notable anti-breast cancer activity against breast cancer cell line MCF-7 by the uracil substituted hippuric acid based 1,3,4-thiadiazole compound. The activity of the compound was although not analogous to the positive control drug capecitabine, as indicated by the IC_{50} value. The combination of hippuric acid, 1,3,4-thiadiazole, and uracil produced synergistic activity which arrested cell proliferation. The study will certainly open new avenues and provide direction towards anti-proliferative research by the rational hybridization of small molecules.

Keywords: 1,3,4-thiadiazole, Hippuric acid, Uracil, Anticancer, Hybrid, MCF-7

Introduction

Cancer is the second leading cause of death among the global population after cardiovascular disease. Breast and cervical cancer are the most prominent cause of death among females[1]. WHO has predicted a great pace in the appearance of new cancer cases after a defined interval of time. Even all the active international databases and organizations related to cancer demography and treatment have put breast cancer at high alert[2].

Earlier; surgical, chemotherapy, radiotherapy were the only options for the treatment or rather management to some extent, but not an absolute cure. Even in the majority of the pharmacotherapeutic regimen, long duration of chemotherapy by USFDA approved popular drugs leads to resistance conditions[3].

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This leads to an emerging need for a new series of drugs with high potency and lower toxicity. In the principle of drug discovery, exploration of unexplored chemical classes from both natural and synthetic sources with noticeable anti-proliferative activity, particularly anti-breast cancer activity, will be an attractive approach for the drug development [4]. Exploring synthetic heterocyclic compounds coupled with several small molecules, in other words, development of molecules by hybridization approach will be the most impressive way[5]. Thiadiazole is a very privileged scaffold in medicinal chemistry known to exhibit diverse pharmacological activities such as anti-convulsant, anti-trypanosomal, anti-cancer, anti-viral, anti-bacterial, anti-oxidant, anti-tubercular, anti-fungal, anti-leishmanial, anti-ulcer, anti-inflammatory, etc.[6]. Uracil is an imperative component of the human body which has prime role in the formation of DNA. It has several applications in the therapeutic area as anti-herpes, anti-cancer, anti-HIV-1, anti-Epstein-Barr, anti-varicella zoster,

anti-hepatitis B, etc. [7]. In the previous research done, uracil moiety substituted hippuric acid containing 1,3,4-thiadiazole scaffold was rationally designed, synthesized, and screened for anti-diabetic activity using the streptozotocin-induced hyperglycemic method in Swiss albino rats[8].

In the current research, the same compound *N*-((5-(((2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyl)amino)-1,3,4-thiadiazol-2 yl)methyl)benzamide (**Figure 1**) was screened against MCF-7 breast cancer cell line utilizing the Sulforhodamine B (SRB) assay and further the IC_{50} value was established in comparison with capecitabine, the standard drug.

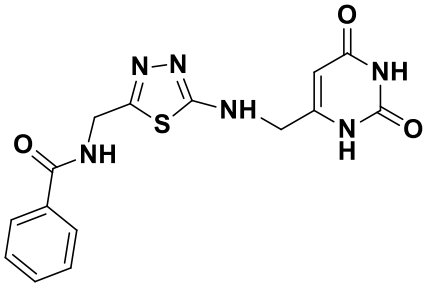

Fig. 1: Uracil substituted hippuric acid based 1,3,4-thiadiazole

Material and Methods

Chemicals and Instrumentation

The chemical reagents, analytical grade solvents, and miscellaneous entities were obtained from HiMedia Ltd., India through a local vendor. The screening molecule was synthesized and characterized previously by our research group [8]. Microplate reader of BioTek Instruments Inc., USA make was employed for the SRB assay.

Anti-cancer screening

The anti-proliferative perspective of the thiadiazole molecule against breast cancer MCF-7 cell line was screened by exploiting the SRB assay method given by Padole *et al*. The cancer cells were cultured in RPMI1640 media containing 10% fetal bovine serum under 5% CO_2 atmosphere at a temperature of 37°C. The cultured cells were further harvested on a 96-well plate and concurrently, the cells were plated. Furthermore, the cancer cells were made in contact with the thiadiazole molecule and then treated with 10% trichloroacetic acid solution at 4°C temperature. The harvested cells were washed with distilled water and stained with SRB solution (0.4%). After the lapse of 15 min, glacial acetic acid solution was treated at room temperature thoroughly for completely removing the unbound stain fractions in the wells. The prepared content was entirely dried and the bound stain was wholly solubilized by using tris-base (tris(hydroxymethyl)aminomethane) solution. The optical density was estimated at 540 nm using the microplate reader and the IC_{50} value was determined in comparison to capecitabine, the standard control [9].

Results and Discussion

Anti-proliferative activity

The thiadiazole compound presented a notable anti-proliferative activity with an IC_{50} value of 52.33 µM. The positive control (capecitabine) showed an IC_{50} value of 6.84 µM which concluded that the experimental compound was not analogous in terms of biological activity (**Table 1**). The combination of hippuric acid, 1,3,4-thiadiazole, and uracil produced synergistic activity which arrested cell proliferation. The carbonyl groups and the nitrogen-containing moieties have been known to exhibit target modulatory activity in the cancer cells. A free-radical scavenging activity by the compound may be predicted.

Table 1: MCF-7 screening of uracil substituted hippuric acid based 1,3,4-thiadiazole compound

Compounds	IC_{50} value (µM)
Thiadiazole derivative	52.33
Capecitabine	6.84

Conclusion

The study highlighted a notable anti-breast cancer activity against breast cancer cell line MCF-7 by the uracil substituted hippuric acid based 1,3,4-thiadiazole compound. The activity of the compound was although not analogous to the positive control drug capecitabine, as indicated by the IC_{50} value. The combination of hippuric acid, 1,3,4-thiadiazole, and uracil produced synergistic activity which arrested cell proliferation. The study will certainly open new avenues and provide direction towards anti-proliferative research by the rational hybridization of small molecules.

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How to cite this article
Mahapatra D.K., Dadure K.M. and Haldar A.C.G.M. (2019). Exploring the anti-breast cancer (against MCF-7 Cell Line) potentials of uracil substituted hippuric acid based 1,3,4-thiadiazole compound. *Int. J. Pharm. Life Sci.*, 10(1):6013-6015.
Source of Support: Nil; Conflict of Interest: None declared

Received: 05.12.18; Revised: 22.12.18; Accepted: 20.01.19