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SYNTHESIS OF NEW PYRIMIDINE DERIVATIVES AS POTENTIAL ANTICANCER AGENT

Arpan Jadav [1]* and Sandip Singh[2]

[1]Research Scholar, C S J M University, Kanpur, India

[2]Associate Professor, Department of Chemistry, C S J M University, Kanpur, India

Abstract:

We have tried to synthesize a series of 5 derivatives of Pyrimidine. Synthesis was carried out according to reactions shown in Reaction Scheme. At first, 4th position of 2,4 dichloropyrimidne was substituted by Anthranilic acid to form Synthesis of 2-(2- chloropyrimidin-4-ylamino)benzoic acid 1[C]. 5amino-1,3,4-thiadiazole 2[B] was prepared using Synthesis of 2-(2-chloropyrimidin-4ylamino)benzoic acid 1[C] and Thiosemicarbazide as starting material. Further confirmation was carried out by IR which showed the presence of amino (-NH2) band ~3422.80 cm-1, 1H NMR spectra which revealed all the corresponding peaks at δ=4-8 ppm for aromatic protons. MASS spectrum showed M+1 peak at 305.4

Various Substituted Pyrimidine derivatives (3[B-1]-3[B-5]) were prepared from substituted aniline(3[A-1]-3[A-5]) by reacting with5-[2-((2-chloropyrimidine- 4yl)amino)phenyl)-1,3,4-thiadiazol-2-amine 2[B] .The reaction was monitored by Thin-layer chromatography using suitable mobile phase such as Chloroform: Methanol (9:1); n-haxane:ethyl acetate (5:5). The Rf values were compared and found that they were different from each others. The melting point of the derivatives was determined.

Spectral study of all the derivatives of substituted Pyrimidine derivatives was carried out using IR, 1H NMR, and MASS which leads us to believe that all the derivatives has been properly synthesized.

Key Words: ***Anticancer activity, synthesis, characterisation.***

Corresponding author:

Arpan Jadav,
Research Scholar,
C S J M University,
Kanpur,
India
**E-mail: arpanjadav@gmail.com Ph. (M) 09911626304*

QR code

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INTRODUCTION:

According to the World Health Organization (WHO), cancer associated mortality is predicted to continue rising, with an estimated 12 million yearly deaths by 2030 (WHO, 2011). In India, the International Agency for Research on Cancer estimated indirectly that about 635000 people died from cancer in 2008 and 395400 in 2010 representing about 8% of all estimated global cancer deaths and about 6% of all deaths in India The earlier sources of drugs were plants, animals and minerals, but due to the lack of potential action, definitive cure and sometimes more toxicity, the discovery of new drugs that are more potent and less toxic is essential. The synthesis of derivatives has been an important part and is aimed at modifying the action of drugs, particularly to reduce the side effects and to potentiate the drug action. Today more than 60% drugs used in practice are synthesized derivatives and day-by-day the scope of synthetic medicinal chemistry is broadening. There are 100 different types of cancer, and each is classified by the type of cell that is initially affected. Cancer harms the body when damaged cells divide uncontrollably to form lumps or masses of tissue called tumor (except in the case of leukemia where cancer prohibits normal blood function by abnormal cell division in the blood stream). Tumor can grow and interfere with the digestive, nervous and circulatory systems and they can release hormones that alter body function.

The 2,4-dichloropyrimidine-containing moieties in the anticancer drugs such as Pazopanib. Pazopanib is a potent and selective multi-targeted receptors tyrosine kinase VEGFR-1, VEGFR-2, VEGFR-3, Platelet-derived growth factor recptors. So, the new derivatives of 2,4-dichloropyrimidine can be developed to treat cancer.

EXPERIMENTAL:

General method of synthesis of Pyrimidine

Synthesis of pyrimidines has been of great interest to organic chemists because of their varied biological and pharmacological activities. In 1818, Gasfare B.

isolated the first pyrimidine derivative, alloxan, by the oxidation of uric acid with nitric acid. The first example of principal pyrimidine synthesis was the synthesis of barbituric acid, in 1878, from malonic acid and urea. Since then synthesis and chemistry of pyrimidine have been discussed by Kenner in 1957, Ramage and Landquist in 1959. The most common route to such pyrimidine derivatives is through the principal synthesis involving the condensation of 1, 3-dicarbonyl compounds with bis nucleophiles like amidines. A number of such fruitful condensations have been effected with a host of 1, 3-dicarbonyl analogues to obtain appropriately substituted pyrimidines. The methods of synthesis of pyrimidines are classified on the basis of components employed in the pyrimidine cyclization. The classes are as follows: Thiadiazole compounds constitute one of the most important heterocyclic families. Their quite rich chemistry as well as the wide range of their application has generated a continued interest during the last two decades. The thiadiazoles have occupied an important place in drug industry. 24 Thiadiazole is a five membered diunsaturated ring structure having the structural formula C2H2N2S. Thiadiazole ring structure composed of one sulphur and two nitrogen atom. They occur in four isomeric form viz., 1,2,3-thiadiazole (1), 1,2,4-thiadiazole (2), 1,2,5-thiadiazole (3), 1,3,4thiadiazole (4).25 Thiadiazole moiety act as a “hydrogen binding domain”and “twoelectron donar system”.26 Thiadiazole and its derivatives are used for biological activities such as antiviral, antibacterial, antifungal, antitubercular27, antimicrobial27, anti- inflammatory, antioxidant28, anti cancer28,29, anticonvulsant30.

Experiment work

Step-1 1. Synthesis of 2-(2-chloropyrimidin-4-ylamino)benzoic acid 1[C]

Step-2 1. Synthesis of 5-[2-((2-chloropyrimidine-4-yl)amino)phenyl)-1,3,4thiadiazol- 2-amine 2[B]

Step-3 1. Synthesis of different substituted Pyrimidine Derivatives with different substituted Aniline Derivatives (3[B-1]-3[B-5])

The screening is a two stage process, beginning with the evaluation of all compounds against the 60 cell lines at a single dose of 10µM. The output from the single dose screen is reported as a mean graph and is available for analysis by the compare program. Compounds which exhibit significant

growth inhibition are further evaluated against the 60 cell panel at five concentration level.

Characterization of compounds

Among the synthesized compounds, 3 compounds (2[B], 3[A-1], 3[A-4],) were screened for in-vitro anticancer activity against 60 cell lines at NCI, U.S.A. Result of compound 2[B], 3[A-4], has been obtained. Compounds have shown good anticancer activity.

The compounds were screened for anticancer activity against various cancer cell lines at National cancer Institute (NCI, USA). All the selected compounds submitted to National Cancer Institute (NCI) for in vitro anticancer assay were evaluated for their anticancer activity. Primary in vitro one dose anticancer assay was performed in full NCI 60 cell panel representing leukemia, melanoma and cancers of lung, colon, brain, breast, ovary, kidney and prostate in accordance with the protocol of the NCI, USA.

The compounds were added at a single concentration (10-1M) and the culture was incubated for 48 hrs. End point determinations were made with a protein binding dye, Sulforhodam ine B. Results for each compound were reported as a mean graph of the percent growth of the treated cells when compared to the untreated control cells.

RESULT AND DISCUSSION:

The present work, which has under taken is bonafied, for the "SYNTHESIS OF NEW PYRIMIDINE DERIVATIVES AS POTENTIAL ANTICANCER AGENTS", A novel series of substituted pyrimidine analogs synthesized successfully from 5-[2-((2-chloropyrimidine-4-yl) amino) phenyl)-1,3,4-thiadiazol- 2amine and substituted different aniline derivatives. The yield of the synthesized compounds was found to be in range from 5075%. Three compounds were selected National Cancer Institute (NCI), USA for anticancer activity at a single high dose (10 -5 M) in full NCI 60 cell panel. All the newly synthesized compounds were characterized on the basis of their physical, spectral and analytical data. The IR spectra, 1H NMR spectra, and Mass spectra of the representative compounds were analyzed, studied and ascertained in the section of spectral studies in annexure. It was concluded that the synthesized substituted Pyrimidine derivatives have potential to act as an anticancer agents and the activity of various compounds varied according to the substituent attached. These preliminary encouraging results of biological screening of the tested compounds could offer an excellent framework in this field that may lead to discovery of potent anti- tumor agent.

Table 1: Mean graph of the one dose screening for the compound 3[A-4]

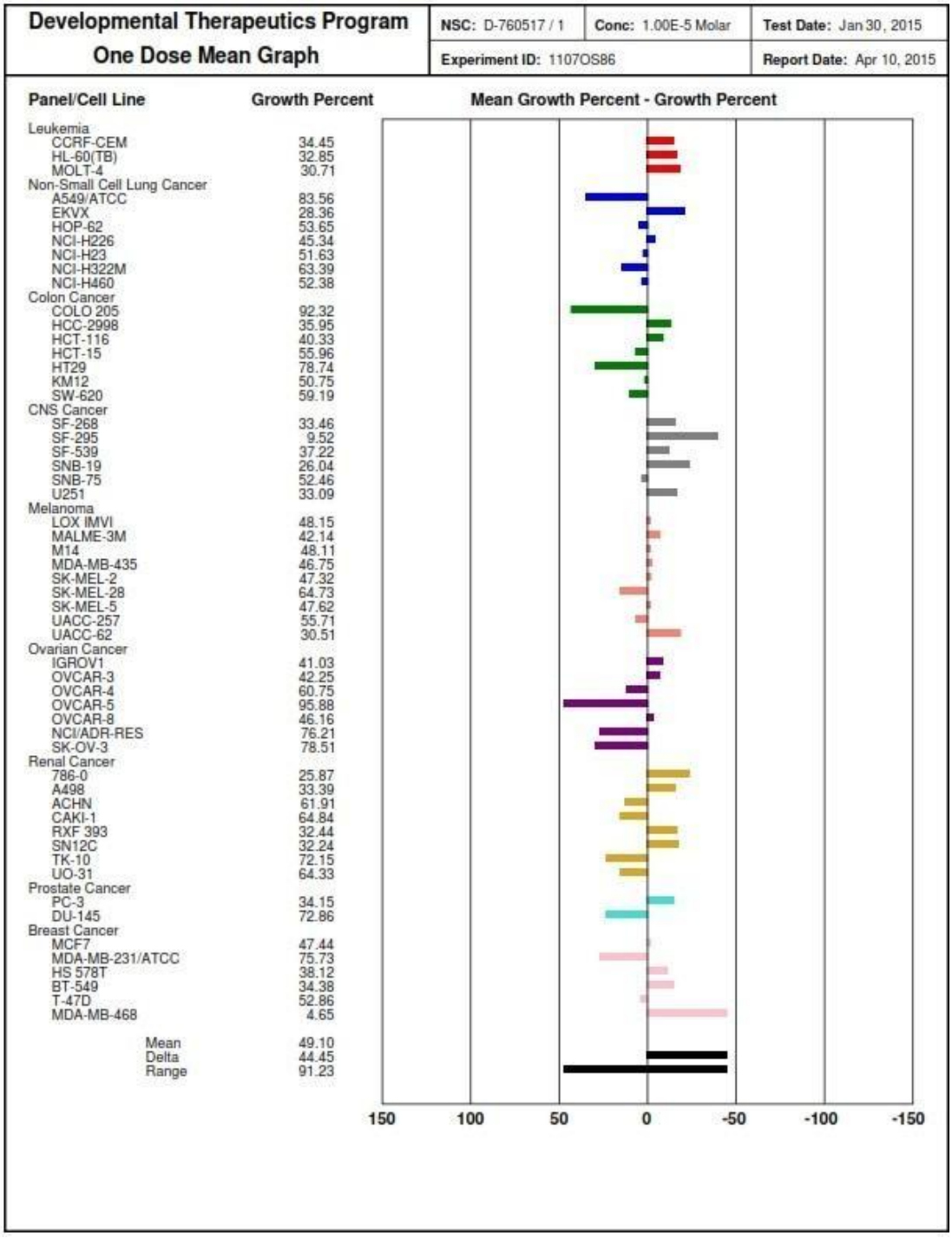
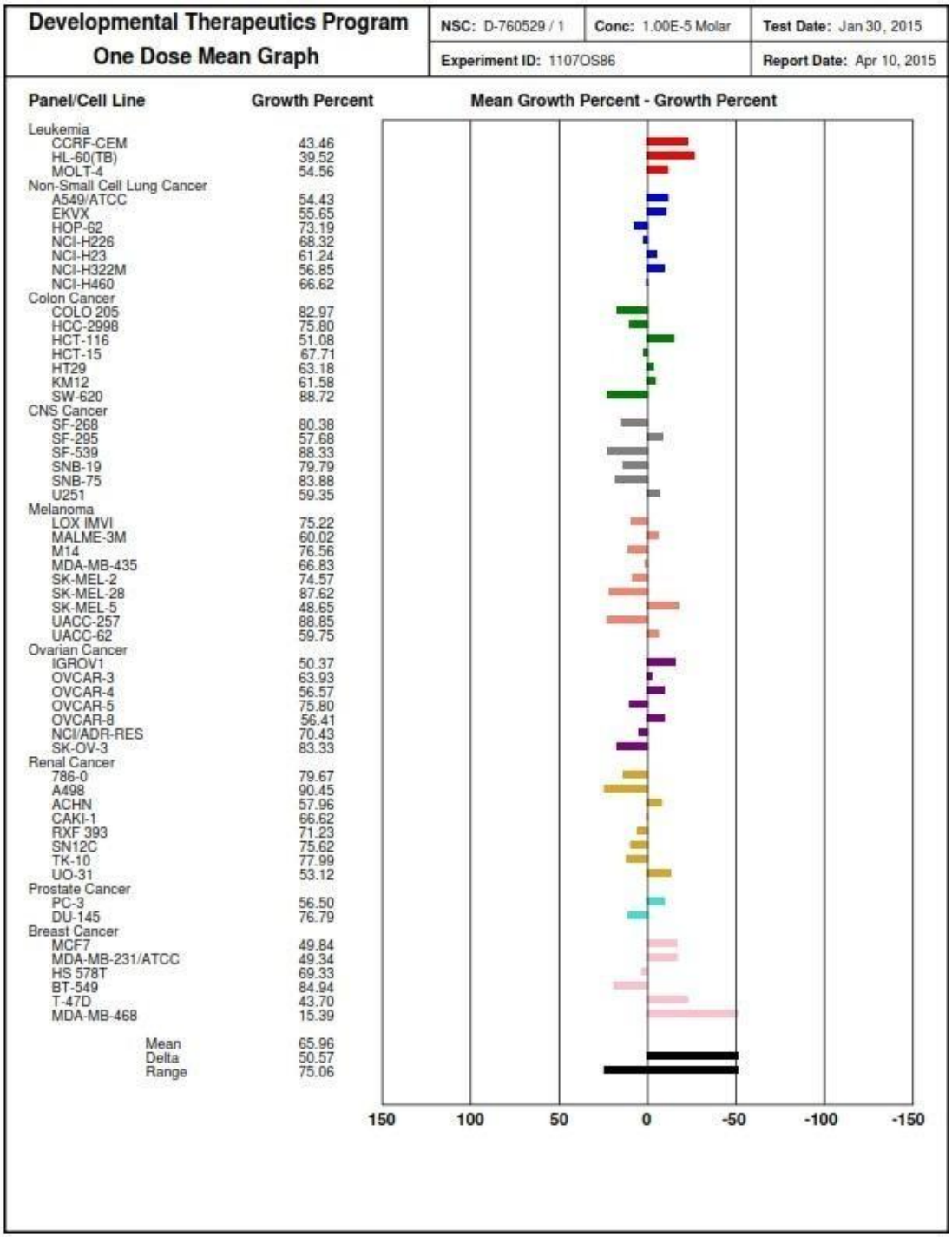


Table 2: Mean graph of the one dose screening for the compound 2[B]



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