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Title of the project: **Synthesis, Characterization and Anticancer Activity Study of Some Novel Synthetic Heterocyclic Compounds**

Keywords: Docking study, Heterocyclic compounds, organic synthesis, anticancer activity

Introduction: Study of anticancer activity of organic compounds has developed significant attention in the drug discovery research in recent years owing to the growing cases of cancer of various types in human being. Change in lifestyle, change in agricultural cultivation and environmental issues are responsible for the increased cases of cancer patients. Heterocyclic compounds are important structural components of many of the anti-cancer drugs available on the market today. In fact, amongst those novel anti-cancer agents approved by the FDA between 2010 and 2015, almost two-thirds contained heterocyclic rings in their structures.

Heterocyclic compounds are defined as cyclic compounds containing ring member atoms of carbon and at least one other element (such as nitrogen, oxygen and sulfur). Heterocycles are common in biology, featuring in a wide range of structures from enzyme co-factors through to amino acids and proteins. They play a vital role in the metabolism of all living things, and are utilized at almost every stage of the many biochemical processes necessary to sustain life.

(a) Origin of the research problem:

The heterocyclic compounds show a broad range of interactions with living system they are involved with which is possible due to the physicochemical properties of their heteroatom that can behave as either acids or bases, depending on the pH of their environment [1]
The heterocycles have a unique ability to engage in a wide variety of intermolecular interactions. It includes hydrogen bond donor/acceptor capability, pistacking interactions, metal co-ordination bonds as well as van der Waals and hydrophobic forces. This allows them to bind with enzymes in a multitude of ways. In addition, heterocycles comes in a broad range of shapes and sizes which enhances scope for structural permutations which allows them to match the equally diverse structural range of enzyme binding pockets.
With the functional versatility of heterocycles and their extremely common occurrence in nature along with involvement in large numbers of biological pathways there is high scope for investment in research on synthesis of heterocyclic-based anticancer drug design. This area of synthetic organic chemistry will justify its place to overcome one of the world's most devastating diseases.

(b) Interdisciplinary relevance: The study of synthetic organic compounds for anti cancer activity gives a idea of the structural features which can make a compound as possible precursor for drug development. The study requires a strong support of computation softwares for docking studies. The positive results obtained docking is used to design a compound with probable biological activity. Once synthesized, the compound is screened on cancer cell line by the experts from the field of biochemistry.

(c) Review of Research and Development in the Subject:

Review of the earlier work carried out at global level shows that anti-cancer drug designing is a crucial area of pharmaceutical domain across the world. Many of the heterocyclic compounds and their derivatives are already a part of well marketed drugs. The heterocyclic compounds bearing pyrazole show a diverse chemotherapeutic action [2–5]. Drugs based on heterocyclic compounds bearing 1,2-diaryl substituted pyrazole are in the list of best selling pharmaceutical products. The important pyrazole based drugs available in the market are apixaban, celecoxib, fipronil, remogliflazone etabonate, lonazolac, tolpiprazole, deracoxib and many more. Crizotinib and ruxolitinib are important pyrazole tethered anticancer drug [6]. Pyrazole derivatives show anticancer activity due to their inhibition of various targets such of topoisomerase II [7–9]. Hence, incorporation of the pyrazole moiety is an important synthetic strategy in rational drug development process. This study is aimed to synthesize new organic compounds which will show potential anticancer activity against some of the important cell lines. Earlier work carried out by this worker has showed that a series of pyrazole derivatives has potential for further exploration as an anticancer compound.

The present study focuses on the design strategies and the structure activity relationship of different derivatives bearing the nitrogen, sulphur and/or oxygen containing ring. These scaffolds play an important part in the activity of organic compounds which are likely to show anticancer activity against different human cancer cell lines through apoptosis, cell

cycle arrest, inhibiting kinases, angiogenesis, disruption of cell migration, modulation of nuclear receptor responsiveness and others [10].
Nitrogen-based heterocyclic compounds are of particular importance in anti-cancer drug design. Almost three fourth of the heterocyclic anticancer agents approved by the FDA between 2010 and 2015 are nitrogen heterocycles. Of all the nitrogen heterocycles, indoles are the most important class of compounds. Research showed that they demonstrate a very good ability to induce cell death in a number of cancer cell lines [11].

Oxygen-containing heterocyclic compounds are also prominent in many anti-cancer drugs. Paclitaxel, which contain an oxetane ring, is a early drug in cancer therapy from the family of oxygen heterocyclic anti-cancer drugs. Its mode of action is based on the depolymerisation of microtubule polymers, resulting in progression inhibition of mitosis in cancer cells. It results in the retardation of cancer cell division, ultimately halting cancer in its tracks, which is similar in mode of action taken by viblastine.
Despite its benefits, there are some of systemic side effects correlated to the drug, which includes hypersensitivity, hematological issues and neurotoxicity. As a result, much effort has been made to find alternative therapies that have less adverse effects without compromising the strong therapeutic potential of paclitaxel.
Recently-developed oxygen-containing heterocyclic anti-cancer drugs include microtubule inhibitors cabazitaxel and eribulin which are used to treat prostate and metastatic breast cancer respectively. Cabazitaxel is a tubulin-stabiliser, but is thought to be of particular interest for the treatment of multidrug-resistant tumours due to its resistance to cellular efflux by the p-glycoprotein efflux pump, expressed by a number of resistance cancer cells [12–13].

Sulfur is a key component in several vitamin cofactors, sugars and nucleic acids. It plays important role in regulating translation via the sulfuration of transfer RNA. Looking at the significance of sulfur in biological systems, sulfur-containing heterocyclic compounds are used in development of anti-cancer drugs, much like their oxygen- and nitrogen-based counterparts.

In a recent screening study, thiophene derivatives were assessed for their antiproliferative activity against human breast adenocarcinoma cells, with a number of compounds found to show promising inhibitory effects. These findings can provide a basis by which future tyrosine kinase inhibitors, with fewer side-effects, may be designed.[14]
Thiadiazole and thiazole structures also show important anti-cancer activity. Number of thiazole based nitrogen mustard heterocyclic compounds has been shown to exhibit strong inhibitory activity towards a panel of human cancer cell lines. Dabrafenib is a thiazole-containing anti-cancer drug molecule that was approved by the FDA in 2013 for use in patients with cancers associated with the mutated version of the BRAF gene.
It is evident from this development that heterocyclic compounds of many different species continue to form the basis of successful anti-cancer treatments.
Therefore, the heterocyclic compounds and their extensions continue to be a unexplored treasure in the world of drug therapy for anti-cancer treatment.□

International status / National Status:

There is a strong competition amongst global researchers in the field of synthetic organic chemistry and pharmaceutical chemistry to come up with novel drugs as potential anti-

cancer agents. Many of the giant pharmaceutical companies are funding and encouraging such research for anti-cancer drug development.

(e) Significance of the study: Any small step forward in the direction of a probable potential anti-cancer drug draws immediate attention of the global scientific fraternity. Though, it is a long process to call an organic molecule, a potential drug. But the idea of a skeleton structure for potential molecule triggers development of a series of compounds, few of which may be of further use. At national level, ACTREC of Tata Memorial Centre, Mumbai is providing support by offering a paid facility to screen the novel organic compounds for probable anti-cancer activity. This has really helped the screening of compounds in our earlier anti-cancer study on Hep-G2, liver cell line. We expect to screen the compounds synthesized henceforth in the same centre by utilizing their paid facility.

(iii) Objectives: Objective of the study is to synthesize novel organic compounds with probable anti-cancer activity. This will only be a primitive step towards identifying a particular organic skeleton which will fit into the cavity of enzyme. The extensions (organic functional groups) will be incorporated to see the change in activity. Based on this study, the compounds will be synthesized for in vitro anti-cancer study on various cell lines.

(iv) Methodology : The organic compounds with various functional groups will be identified through literature to be probable active compounds. Such skeleton compounds, with combination of functional groups will be drawn in chemdraw and the .cdx files so obtained will be converted into .mol and .mol2 files subsequently. The .mol2 file will be subjected to activity study on target (.pdb) file of the protein from the cancer cell. This interaction will be studied through docking study and the results obtained will help to assess the activity of compounds based on functional groups and shape. This helps in dropping down the actual number of molecules to be synthesized in laboratory. Such active compounds will be synthesized in laboratory on small scale and purified. After complete characterization of the compounds through IR, NMR, MS, EA the formation of the compound will be ascertained. To know the in depth structural features of the compounds, some of the compounds may be studied for single crystal X ray. After this, the compounds will be sent for anti-cancer activity to the Advanced Centre for Treatment, Research and Education in Cancer (ACTREC). It is the state-of-the-art R&D satellite of the Tata Memorial Centre which provides facility for screening of the synthesized compounds against various cancer cell lines from various tissues.

(v) Year-wise Plan of work and targets to be achieved: The study will begin with screening of compounds and getting down to actual number of compounds to be synthesized in laboratory. The synthesis and characterization of compounds of about two series of studies will take 8 to 10 months duration. The anti-cancer screening of compounds will take about 9 months. This study is totally dependent on the ACTREC, Navi Mumbai. The usual time for study claimed by the authorities from this centre is 6-8 months. Once, the reports are obtained from the ACTREC, the results will be communicated to some reputed journal indexed in SCI/WoS/Scopus.

Earlier experience of our group for synthesis and complete study of anti-cancer properties of one such series of compounds suggests that the entire study of one series takes 2 years. But two such series of compounds can be taken as task in parallel and both the reports can be worked in tandem.

(b) Institutional and Departmental facilities available for the proposed work:

Department of Applied Chemistry of the institute has a laboratory with basic facility for synthesis of organic compounds at micro scale. It has adequate facilities for synthesis and crystal growth of compounds. The laboratory has adequate glassware and microwave oven for energy efficient synthesis of organic compounds at small scale. A double beam spectrophotometer is also there for UV Visible study of the compounds in solution state.

12. Any other information which the investigator may like to give in support of this proposal.
One student has submitted PhD thesis from the same laboratory under my supervision in Gondwana University in the month of September 2018.

It is obligatory for us to acknowledge the facility of ACTREC for anti-cancer facility of that centre. Along with that, we need to acknowledge the other agencies from where we will seek help for facility of spectral analysis like IR, NMR, EA, MS & single crystal X-Ray.
Therefore, we seek your permission to acknowledge any other source, along with funding from this university, if this project proposal is sanctioned.

To certify that:

a. ~~The college is approved under Section 2(f) and 12(B) of the UGC Act and is fit to receive grants from the UGC.~~
b. General physical facilities, such as furniture/space etc., are available in the Department/College.
c. The PI shall abide by the rules governing the scheme in case assistance is provided to me from the university
d. The PI will complete the project within the stipulated period. If he/she fail to do so and if the university is not satisfied with the progress of the research project, the university may terminate the project immediately and ask for the refund of the entire amount (with interest) released by the university
e. The above research Project is not funded by any other agency.

Principal Investigator

Principal/Director
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