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ANTICANCER ACTIVITY OF PIPERAZINE PROPYL-4-OXO-3,4-DIHYDROQUINAZOLINE -2-CARBOXYLATE DERIVATIVES

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Abstract:

Cancer is one of the major causes of worldwide human mortality. A wide range of cytotoxic drugs are available on the market, and several compounds are in different phases of clinical trials. Many studies suggest that these cytotoxic molecules are also associated with different types of adverse side effects; therefore researchers around the globe are involved in the development of more efficient and safer anticancer drugs. In recent years, quinazoline and its derivatives have been considered as a novel class of cancer chemotherapeutic agents that show promising activity against different tumors. Due to the increase in knowledge about cancer pathways, there is a growing interest in finding novel potential drugs. Quinazoline is one of the most widespread scaffolds amongst bioactive compounds. A number of papers appear in the literature regarding the discovery and development of novel promising quinazoline compounds for cancer chemotherapy . Numerous quinazoline derivatives have been found to possess anticancer activity, which stimulated the research activity in this field. Quinazolines and its derivatives represent one of the most active classes of compounds. The purpose of this review was to collate literature work reported by researchers on Quinazoline derivatives for their anticancer activities and also reported recent efforts made on this moiety.

Key words: *Quinazoline moiety, Anticancer activity.*

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INTRODUCTION

Introduction and development of anticancer agents:

Cancer is one of the most common diseases worldwide and is the second leading cause of deaths in the world. Drug discovery has played an important role in the development of newer and safer anti-cancer agents that have a broader spectrum of cytotoxicity to tumour cells [1]. Most of the agents are important in therapy which is natural or synthetic organic compounds. The role of the medicinal chemist is to design and synthesize a drug structure that has the maximum beneficial effects with a minimum of toxic side effects. The organic molecules with increasingly specific pharmacological activities are clearly dominated. Development of new anti-cancer agents has grown beyond traditional synthetic methods. Cancer represents one of the most severe health problems worldwide, and the development of new anticancer drugs and more effective treatment strategies are fields of utmost importance in drug discovery and clinical therapy. Much of the research in these areas is currently focused on cancer-specific mechanisms and the corresponding molecular targets [2], but the search for improved cytotoxic agents still constitutes an important part of modern anticancer drug discovery. As the major types of solid human tumors (breast, lung, prostate, and colon), which represent most cancer cases today are multicausal in nature, there is a growing recognition that the treatment of solid tumors with "mechanism-based" agents alone is unlikely to be successful. Instead, improved treatment strategies are likely to involve combinations of signal transduction inhibitors with new and better cytotoxic drugs.

The aim of most cancer chemotherapeutic drugs currently in clinical use is to kill malignant tumor cells by inhibiting some of the mechanisms implied in cellular division. Accordingly, the antitumor compounds developed through this approach are cytostatic or cytotoxic. However, the knowledge of tumor biology has exploded during the past decades and this may pave the way for more active, targeted anticancer drugs [3]. Chemotherapeutic drugs are divided into several categories based on how they affect specific chemical substances within the cancer cells, which cellular activities or processes the drug interferes with, and which specific phases of the cell cycle the drug affects. These include DNA topoisomerase I and II inhibitors, antimitoticagents, antimetabolites, DNA interactive agents and miscellaneous agents. Unfortunately, the majority of drugs currently available on the market are not specific [4,5], which leads to the many common side effects associated with cancer chemotherapy

Objectives and Results of the Present Study:

MATERIALS AND METHODS:

Cell Cultures, Maintenance and Anti proliferative Evaluation.

The cell lines, HeLa (cervical), MDA-MB-231 (breast), PANC-1 (pancreatic), and A549 (lung carcinoma) which were used in this study were procured from American Type Culture Collection (ATCC), United States. The synthesized test compounds were evaluated for their *in vitro* anti proliferative activity in these four different human cancer cell lines. A protocol of 48 h continuous drug exposure was used and an SRB cell proliferation assay was used to estimate cell viability or growth. All the cell lines were grown in Dulbecco's modified Eagle's medium (containing 10% FBS in a humidified atmosphere of 5% CO_2 at 37 °C). Cells were trypsinized when sub-confluent from T25 flasks/60 mm dishes and seeded in 96-well plates in 100 µL aliquots at plating densities depending on the doubling time of individual cell lines. The micro titre plates were incubated at 37 °C, 5% CO_2, 95% air, and 100% relative humidity for 24 h prior to addition of experimental drugs and were incubated for 48 hrs with different doses (0.01, 0.1, 1, 10, ,100µM) of prepared derivatives**.** After 48 hours incubation at 37 °C, cell mono layers were fixed by the addition of 10% (wt/ vol) cold trichloroacetic acid and incubated at 4 °C for 1h and were then stained with 0.057% SRB dissolved in 1% acetic acid for 30 min at room temperature. Unbound SRB was washed with 1% acetic acid. The protein –bound dye was dissolved in 10mM Tris base solution for OD determination at 510 nm using a micro plate reader (Enspire, Perkin Elmer, and USA). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth was calculated at each of the drug concentrations levels. Percentage growth inhibition was calculated as:

[(Ti-Tz)/(C-Tz)] x 100 for concentrations for which Ti>/=Tz

[(Ti-Tz)/Tz] x 100 for concentrations for which Ti<Tz.

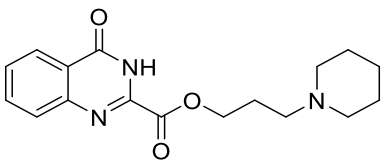
The dose response parameter, growth inhibition of 50 % (GI50) was calculated from [(Ti-Tz)/(C-Tz)] x 100 = 50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. Values were calculated for this parameter if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter was expressed as greater or less than the maximum or minimum concentration tested.

Effects of the compounds on the viability of human cancer cells:

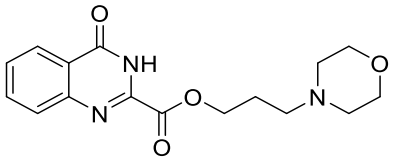
Anti-proliferative activity of the following compounds was evaluated against four human cancer cell lines He La (cervical), MIAPACA (pancreatic), MDA-MB-231 (breast) and IMR 32 (neuroblastoma) by the standard SRB assay method.[6,7] From the data reported in Table 1, most of the compounds showed significant anti-proliferative activity on the concerned cell lines. Among all the compounds only two compounds **8e** and **8g** showed potent anti proliferative activity with GI_{50} values of 0.02, less than 0.01 μM against MIAPACA human cancer cell line and some compounds showed significant activity within the range of 0.1-0.87 μM against human cancer cell lines. Potencies of all the compounds were comparable to the standard drugs Doxorubicin and Paclitaxel. As per the data from Table 1, we can examine **8a-g** series of the compounds were more potent.

The structure-activity relationship (SAR) study revealed that not only the electron accepting substituents on the quinazolinone moiety but also the quinazolinone with a propyl linker is required for inducing anti-proliferative activity against the MIAPACA as well as remaining human cancer cell line. The substituent at ring-B on quinazolinone moiety with propyl linker of ortho-fluoropiperazine (**8e**) and para-fluoropiperazine (**8g**) were associated with a potent increase in the growth inhibitory effect against MIAPACA. In conclusion, introduction of propyl linker and electron lacking groups on quinazolinone moiety played a major role in the evaluation of anti- proliferative activity.

Quinazoline piperazine hybrids:



8a



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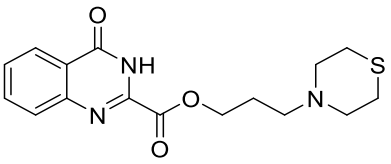

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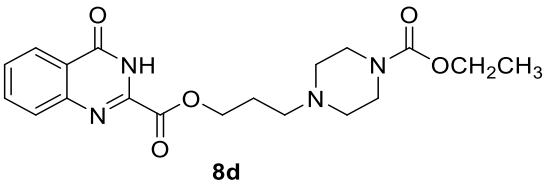
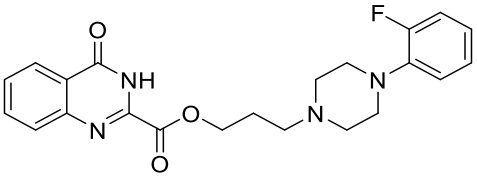
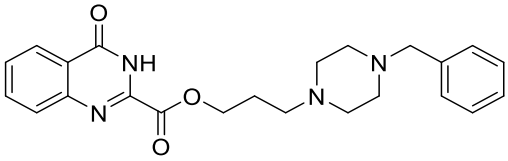


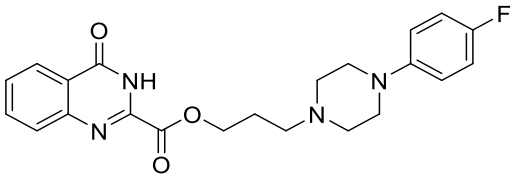
8d



8e



8f



8g

Table 1: (GI_{50}/µM) values of the tested compounds against four human cancer cell lines.

S.No	Compound	HeLa	MIAPACA	MDA MB 231	IMR 32
1.	**8a**	5.1±0.7	0.84±0.05	0.1±0.03	1.0±0.08
2.	**8b**	1.5±0.06	>100	0.88±0.05	0.2±0.03
3.	**8c**	1.0±0.03	>100	0.42±0.08	0.59±0.01
4.	**8d**	1.8±0.08	1.5±0.06	>100	1.2±0.03
5.	**8e**	1.6±0.09	1.5±0.06	22.3±0.6	1.5±0.06
6.	**8f**	16.8±0.9	61.7±0.53	68.1±0.2	5.0±0.09
7.	**8g**	1.1±0.55	1.7±0.2	5.1±0.1	0.19±0.04
	Doxorubicin	**0.074±0.003**	**0.082±0.001**	**0.065±0.0041**	**0.029±0.0023**
	Paclitaxel	**0.032±0.0012**	**0.059±0.0032**	**0.089±0.0052**	**0.073±0.005**

CONCLUSION:

In conclusion, the compounds **8e** and **8g** exhibited potent *in vitro* anti proliferative activity with GI_{50} values 0.02, less than 0.01 μM against MIAPACA human cancer cell line. Moreover, the compounds **8a, 8b, 8c, 8g, 8b, 8c, 8d, 8e, 8f** showed a significant *in vitro* anti proliferative activity against MIAPACA, MDA MB-231 and IMR-32 human cancer cell lines with GI_{50} values ranging from 0.1-0.87μM. Introduction of carbon chain in the series **8a-g**. This study gives valuable information for further development of more potent anticancer agents.

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