

# Recent Advances in the Development of PI3K/mTOR-Based Anticancer Agents: A Mini Review

Ishan Panchal<sup>1</sup>, Archana Navale<sup>1</sup>, Ashish Shah<sup>2</sup>, Sandip Badeliya<sup>3</sup>, Rati Tripathi<sup>4</sup>

<sup>1</sup> Parul Institute of Pharmacy, Parul University, Vadodara, India

<sup>2</sup> Department of Pharmacy, Sumandeep Vidyapeeth, Vadodara, India

<sup>3</sup> Saraswati Institute of Pharmaceutical Science, Dhanap, Gandhinagar, India

<sup>4</sup> Department of Pharmaceutical Science, Assam University, Silchar, Assam, India

**Corresponding author:** Ishan Panchal, Parul Institute of Pharmacy, Parul University, Vadodara, India; E-mail: ishanpharma@gmail.com

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## Abstract

Cancer refers to the group of diseases characterized by uncontrolled growth of abnormal cells. It spreads throughout the body which makes this disease one of the huge global threats to mankind. Intensive research over the years has established deregulation of mammalian target of rapamycin pathway in cancer. This has led to the development of mammalian target of rapamycin inhibitors. Several inhibitors of the mammalian target of rapamycin are under preclinical and early clinical trials. Researchers have investigated a series of furoquinoline, phenyl sulphonylureas, 4-acrylamido-quinoline, pyrazolo-chalcones, imidazole [4,5-b] pyridine, thienopyrimidine, aminopyrimidin scaffolds in the last three years. This review provides comprehensive information and critical discussions on designing of novel selective inhibitors of mammalian target of rapamycin with superior activity in the treatment of cancer.

## Keywords

cancer, discovery, furoquinoline, phenylsulphonylureas, pyrazolo-chalcones

### Abbreviations used in the article

AGC: protein kinase A/protein kinase G/protein enzyme C

Akt: protein kinase B

HUVEC: human umbilical vein endothelial cells

MCF7: Michigan cancer foundation-7

mTOR: mammalian target of rapamycin

mTORC1: mammalian target of rapamycin complex 1

PI3K: phosphatidylinositol 3-kinase

PIK3CA2: phosphatidylinositol-4-phosphate 3-kinase catalytic

PC-3: prostate cancer cell

PTEN: phosphatase and tensin homolog

S6K: p70 ribosomal S6 kinase

SGK: serum and glucocorticoid protein kinase

## INTRODUCTION

Cancer is known as a group of diseases officially accountable for uncontrolled growth and spread of atypical cells. Many scientists have designed and synthesized compounds which act on breast cancer.<sup>1</sup> Breast cancer is one of the most frequent malignancies in women as around one in

eight women will develop breast cancer in their lifetime. In the United States, this comes close to more than 200,000 new cases of invasive breast cancer each year, which will result in approximately forty thousand deaths.<sup>2</sup> In age-adjusted terms, this represents a combined male and female incidence of about a quarter of that recorded in Western Europe.

According to the National Cancer Registry Programme of the India Council of Medical Research, more than 1300 Indians die every day due to cancer.<sup>3</sup> One of every two women newly diagnosed with carcinoma dies of cervical cancer every eight minutes in the Asian nation.<sup>4,5</sup>

Consequently, there is an exigent need to explore some newer classes of therapeutics with selective action against cancer cells. The edict of cell proliferation and apoptotic pathways related to cell death is known as an important tactic to understand nearly these cells.<sup>6,7</sup> The phosphatidylinositol-3-kinase (PI3K)/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) plays an important role in cell proliferation, advance, and angiogenesis.<sup>8</sup> mTOR is a critical signalling protein as it obliges as a cause of many pathways related to cell progress and means. This major pathway is deregulated: it can cause uninhibited activation of cancer cell progress and proliferation. This commonly results in malignancies that affect the kidney, breast and the neuroendocrine system. Deregulation of mTOR signalling is implicated in the development of several human diseases, including cancer, type 2 diabetes and obesity, highlighting the crucial role that mTOR plays in the maintenance of cellular homeostasis.<sup>9</sup> mTORC1 and mTORC2 are presented in Fig. 1.

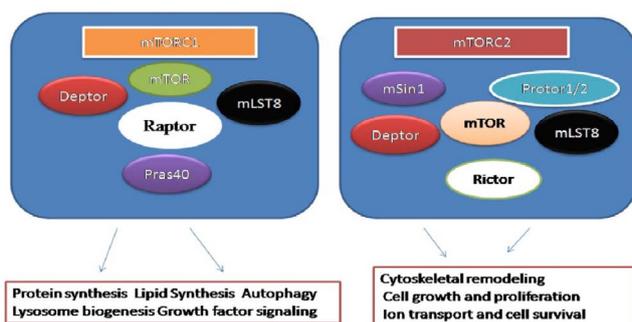


Figure 1. mTORC1 and mTORC2.

## PI3K/AKT/mTOR (PAM) pathway

Activation of the phosphoinositide three enzymes (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway is common in carcinoma. There is diagnostic evidence to support inhibition of the pathway, and phase I to III clinical trials involving inhibitors of the pathway have been and are being conducted in solid tumours and breast cancer.<sup>5</sup> mTOR is the catalytic subunit of two functionally and structurally distinct multiprotein complexes known as mTOR complex 1 (mTORC1) and 2 (mTORC2) that are defined by their necessary components Raptor (regulatory-associated protein of mTOR) and rapamycin-insensitive companion of mTOR (Rictor), respectively.<sup>10</sup> mTORC1 is a central regulator of protein blend, which is the most energy-unbearable infringement in the cell.<sup>11</sup> It is thus not unexpected that mRNA translation symbolizes a tightly

regulated route. mTORC1 senses mutagenic signals and nutrient readiness in cells, and stimulates protein synthesis, particularly at the initiation step of the mRNA form.<sup>12,13</sup> Data in solid tumours demonstrated that the mTOR signal is dysregulated in almost 30% of cancers and is one of the most frequently affected cascades in human cancers.<sup>14</sup>

## mTOR inhibitors in clinical trials

### LY3023414

LY3023414 is chemically (8-(5-(2-Hydroxypropan-2-yl)pyridin-3-yl)-1-((S)-2-methoxypropyl)-3-methyl-1H-imidazo[4,5-c]quinolin-2(3H)-one). Bendell JC et al. has reported pharmacokinetics demonstrating dose-dependent exposure with 90% target inhibition at doses of 150 mg. Drug-drug interaction analysis established LY3023414 to be a weak inhibitor of CYP3A4.<sup>15</sup> LY3023414 potently and by selection obstructs category I PI3K isoforms, DNA-PK, and mTORC1/2 with IC<sub>50</sub> of 6.07 nM, 77.6 nM, 38 nM, 23.8 nM, 4.24 nM and a hundred sixty-five nM for PI3K $\alpha$ , PI3K $\beta$ , PI3K $\delta$ , PI3K $\gamma$ , DNA-PK and mTOR, respectively. LY3023414 vigorously inhibits mTORC1/2 at low nanomolar concentrations.<sup>16</sup> Lan Zheng et al. and co-researchers have investigated autophagy inhibition sensitizes LY3023414-induced anti-glioma cell activity in vitro and in vivo (Fig. 2).<sup>17</sup>

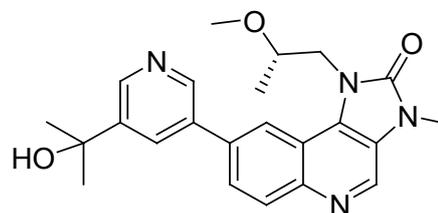


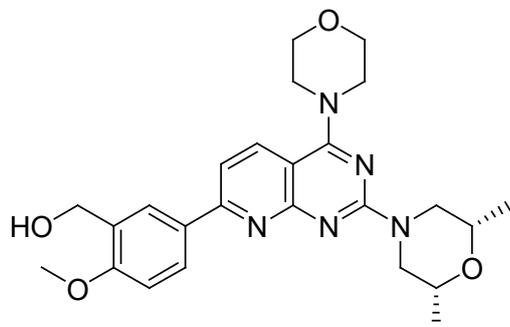
Figure 2. Structure of LY3023414.

### Ku-0063794

Ku-0063794 is chemically pyridopyrimidine derivative exactly (5-(2-((2R,6S)-2,6-dimethylmorpholino)-4-morpholinopyrido[2,3-d]pyrimidin-7-yl)-2-methoxyphenyl)methanol, act on mTOR which kindles cell progress by phosphorylating and associate initiation of AGC (protein kinase A/protein kinase G/protein enzyme C) family enzymes, for example, Akt (protein enzyme B), S6K (p70 ribosomal S6 kinase) and SGK (serum and glucocorticoid protein kinase). The minor molecule Ku-0063794, which frustrates both mTORC1 and mTORC2 with an IC<sub>50</sub> of ~10 nM.<sup>18</sup> Consistent with this possibility, temsirolimus, but not Ku0063794, decreased tumour angiogenesis in vivo, and decreased the viability of HUVEC (Human Umbilical Vein Endothelial Cells) cells in vitro at pharmacologically relevant concentrations.

Furthermore, expression levels of VEGF and PDGF were lower in Caki-1 and 786-O cells treated with temsirolimus than cells treated with Ku0063794.<sup>19</sup> García-Martínez JM

et al. epitomized the molecule Ku-0063794, which impedes both mTORC1 and mTORC2 with an IC<sub>50</sub> of approximately 10 nM, but does not suppress the activity of 76 other protein kinases or seven supermolecule kinases, including Class 1 PI3Ks (phosphoinositide 3-kinases) at 1000-fold higher concentrations. It is cell permeating, suppresses activation and hydrophobic phosphorylation of Akt, S6K and SGK, however, not RSK (ribosomal S6 kinase) (Fig. 3).<sup>20</sup>

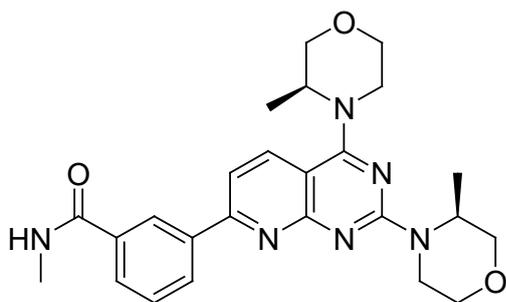


**Figure 3.** Structure of Ku-0063794.

### AZD2014

It is a small-molecule adenosine triphosphate competitive staple of mTOR that incumbents both mTORC1 and mTORC2 complexes and includes a finer repressive operate in contradiction of mTORC1 than the clinically approved rapalogs. Herein, AZD2014 has broad antiproliferative things diagonally numerous cell lines, including ER<sup>+</sup> breast models with attained conflict to hormonal remedy and cell lines with acquired resistance to rapalogs. It is chemically 3-(2,4-bis((S)-3-methylmorpholino)pyrido[2,3-d]pyrimidin-7-yl)-N-methylbenzamide act on the intonation of both mTORC1 and mTORC2 substrates, locked with its mechanism of action.<sup>21</sup>

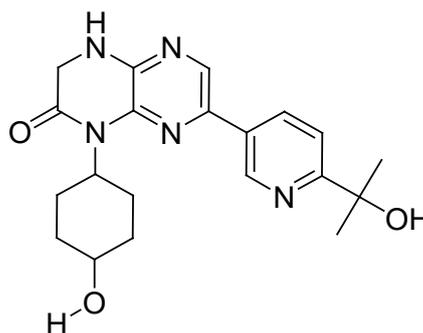
Included has broad antiproliferative effects across multiple cell lines, including ER(+) breast models with acquired resistance to hormonal therapy and cell lines with acquired resistance to rapalogs. The ability to dose AZD2014 intermittently, together with its ability to block signalling from both mTORC1 and mTORC2 complexes, makes this compound a superlative candidate for combining with endocrine therapies in the clinic. AZD2014 is currently in phase II clinical trials (Fig. 4).<sup>21</sup>



**Figure 4.** Structure of AZD2014.

### CC-223

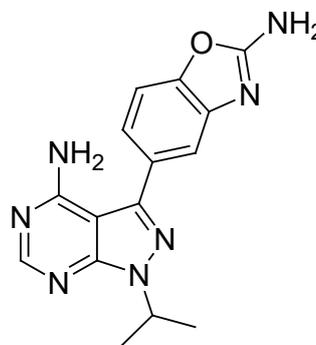
It is a dihydropyrazinopyrazin derivative which is chemically 3,4-dihydro-1-(4-hydroxycyclohexyl)-7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)pyrazino[2,3-b]pyrazin-2(1H)-one, impedes mTORC1 and mTORC2 in cellular organisms. Cellular mortification of the PI3K–mTOR pathway by CC-223 was first judged in PC-3 prostate cancer cells by Western blot analysis. CC-223 inhibited both mTORC1 (S6RP and 4EBP1) and mTORC2 [AKT (S473)] markers athwart the panel with IC<sub>50</sub> choices of 27 to 184 nmol/L for pS6RP, 120 to 1,050 nmol/L for p4EBP1 and 11 to 150 nmol/L for pAKT (S473) (Fig. 5).<sup>22</sup>



**Figure 5.** Structure of CC-223.

### TAK-228

It is a pyrazolopyrimidin derivative exactly (3-(2-amino-benzo[d]oxazol-5-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine). Researchers have developed TAK-228 on the PI3K/AKT/mTOR pathway in preclinical studies and the frequency of pathway alterations in chronic tumours, which is a rational therapy for bladder sarcoma. This clinical investigation was done by the scientists proved how deviations in the PI3K/AKT/mTOR pathway connect with treatment. In preclinical bladder cell line mock-ups and xenografts done in our lab, the synergistic effect has been seen with the combination with paclitaxel. It is an investigational oral dual TORC1/2 inhibitor: A phase I dose-escalation study in patients with relapsed or refractory multiple myeloma, non-Hodgkin lymphoma, or Waldenström's macroglobulinemia (Fig. 6).<sup>23</sup>

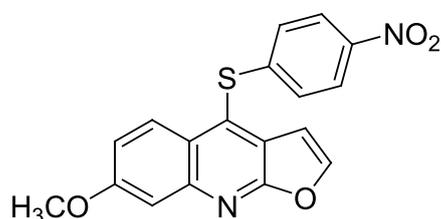


**Figure 6.** Structure of TAK-228.

## Discovery and development of mTOR inhibitors [2015-2019]

### Furoquinoline based analogues

Manoj V. Loharet et al.<sup>24</sup> has premeditated a sequence of furoquinoline centred inhibitors of multiple bulls in the PI3K/Akt-mTOR pathway. Most of the complexes were originated to show clear-sightedness toward PI3K/Akt-mTOR and were found to be moderately heady. 4-(4-nitrophenylthio)-7-methoxyfuro[2,3-b]quinoline turns out to be the most active multi-targeted PI3K 48  $\mu\text{M}$  and motor 49  $\mu\text{M}$  inhibitor of this furoquinoline sequences. The PI3K/mTOR inhibitory potency of it was further inveterate by Western blot analysis using the H-460 cell line for phosphorylation of Akt (PI3K) and 4E-BP1 (mTOR) at concentrations of 3 and 10  $\mu\text{M}$  (Fig. 7).



**Figure 7.** Structure of 4-(4-Nitrophenylthio)-7-methoxyfuro[2,3-b]quinolone.

### Phenylsulfonylurea derivatives

Bingbing Zhao and co-workers have studied a chain of novel phenylsulfonylurea derivatives as PI3K/mTOR dual actions. The pharmacological results concentrated that most of the compounds showed a cytotoxicity sign alongside the cancer cell lines. Most of the compounds were found to

display discernment toward PI3K/mTOR dual inhibitors. In particular, the cellular activity of the potent compounds 19a and 23b against MCF-7 cell was equal to the positive control sorafenib, through the IC<sub>50</sub> value of  $2.88 \pm 0.58$  and  $6.55 \pm 0.81$ , respectively. Structure-activity relationships (SARs) specified that the introduction of the methoxyl scaffold in 4-anilinoquinoline scaffold was new auspicious than the introduction of halogen to the cellular stir.<sup>25</sup>

### Imidazole [4,5-b] pyridine derivatives

Lingzhi Zhang et al. investigated a sequence of novel 3H-imidazole [4,5-b] pyridine derivatives as discriminating mTOR inhibitors. In general, compounds 10d and 10n with nanomolar motor inhibitory motion also established attractive potency against the tested cell lines, comprising MCF-7 and A2780.<sup>25</sup> Fig. 8 shows the structures of phenylsulfonylurea derivatives and imidazole [4,5-b] pyridine derivatives.

### Thienopyrimidine derivatives

Herein WZ et al. has designed and develop a series of novel thienopyrimidine derivatives bearing chromone moiety as mTOR/PI3Ka inhibitors. Some of the target facilities exhibited moderate to admirable mTOR/PI3Ka kinase inhibitory activity and cytotoxicity. The most promising compound 16i showed good inhibitory activity against mTOR/PI3Ka kinase and worthy antitumor potency for H460 and PC-3 cell lines with IC<sub>50</sub> values of  $0.16 \pm 0.03$  mM,  $2.35 \pm 0.19$  mM,  $1.20 \pm 0.23$  mM and  $0.85 \pm 0.04$  mM, which were 8.6, >5, 7.9, and 19.1 times supplementary active than I ( $1.37 \pm 0.07$  mM, >10 mM,  $9.52 \pm 0.29$  mM,  $16.27 \pm 0.54$  mM), distinctly.<sup>26</sup>

Miao Z et al. studied novel morpholine substituted thienopyrimidines as potential Class I PI3K/mTOR dual inhibitors. Dysfunctional signalling of the PI3K/AKT/mTOR pathway in cancer and its grave role in cell growth and survival has made it abundantly anticipated mark for cancer

Compound	R1	R2	R3	IC <sub>50</sub>			
				HepG2	A549	PC-3	MCF-7
19a	pivalonitrile	-F	-Br	33.28	38.52	66.52	3.88
23b	-OCH <sub>3</sub>	Treat-butyl	-OCH <sub>3</sub>	2.71	7.47	>100	6.55

Compd	R	R1	R2	%Inhibition	IC <sub>50</sub> (nM)
10d	n-Pr	Me	H	33	290
10n	Et	Me	Me	30	332

**Figure 8.** Structures and IC<sub>50</sub> of (a) phenylsulfonylurea derivatives (b) imidazole [4,5-b] pyridine derivatives.

therapeutics. Among them, compound 14o was identified as a dual Class I PI3K and mTOR kinase activity, which had an approximately 8-fold improvement in motor shyness relative to the class I PI3K inhibitor 1 (pictilisib, GDC-0941). Western blot analysis confirmed the 14o mechanistic variety of the cellular PI3K/AKT/mTOR pathway through inhibiting phosphorylation of both AKT and S6 in human cancer cell lines. Besides, 14o demonstrated momentous usefulness in SKOV-3 and U87MG tumor xenograft models without causing weighty weight loss and toxicity.<sup>27</sup> Scaffolds of thienopyrimidine derivatives are presented in **Fig. 9**.

### Aminopyrimidin derivatives

In this Wei Penget et al. has examined a chain of 2-(2-aminopyrimidin-5-yl)-4-morpholino-N-(pyridin-3-yl)quinazolin-7-amines as novel PI3K/mTOR inhibitors and anticancer mediators. Their PI3Ka inhibitory activities, antiproliferative happenings against seven cancer cell lines, namely, PC-3, DU145, MCF-7, BT474, SK-BR-3, U937 and A431, were assessed in vitro. 4-(trifluoromethyl)-5-(7-substituted-4-morpholinoquinazolin-2-yl)pyridin-2-amine proved to be a likely drug aspirant with high PI3Ka embarrassment activity (IC<sub>50</sub> ¼ 4.2 nM) and good antiproliferative activity. The 3-(methylamino)pyridine-2-carbonitrile substituted compound 17f was also tested for its inhibitory activities against other kinases, such as PI3Kb, PI3Kg, PI3Kd and mTOR, its effects on p-Akt (S473) and cell cycle. These results suggested that compound 17f could significantly inhibit the PI3K/Akt/mTOR pathway as a potential PI3K inhibitor and anti-cancer agent.<sup>28</sup>

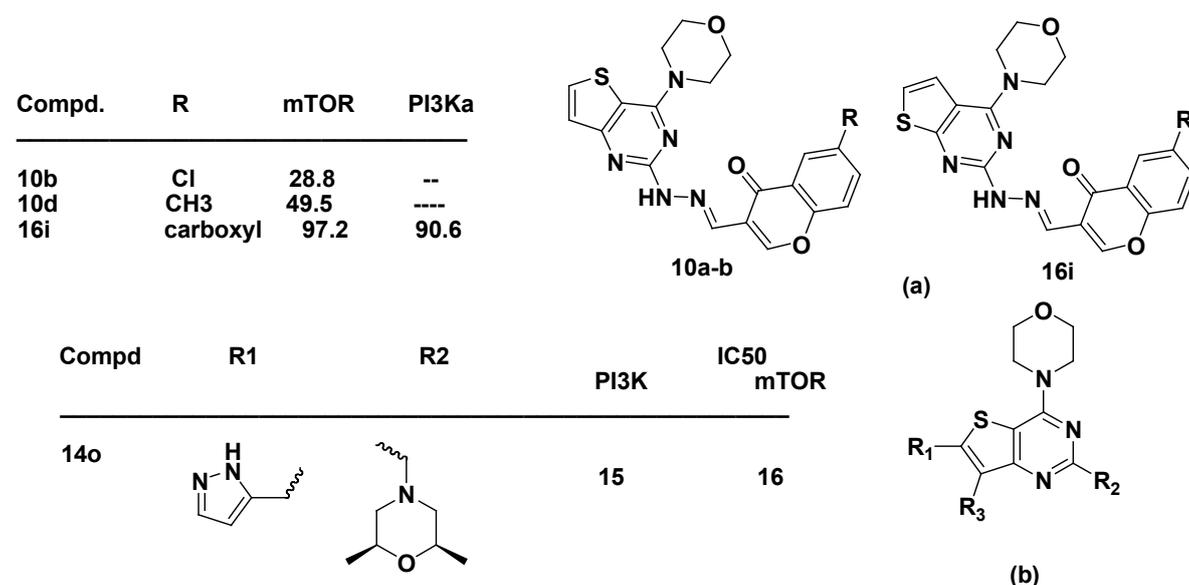
### 4-Acrylamido-quinoline derivatives

Xiaodong Ma et al. has described novel 4-acrylamido-quinoline derivatives as effective PI3K/mTOR dual inhibitors. A novel structural series of quinoline derivatives were de-

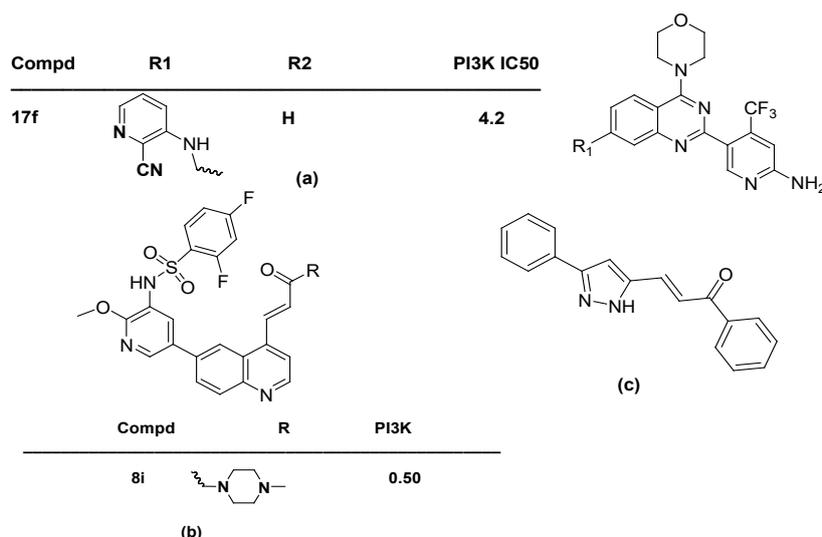
signed, synthesized and biologically evaluated as PI3K/mTOR dual inhibitors upon the incorporation of C-4 acrylamide fragments. Subsequently, all of them exerted remarkable inhibition against PI3Ka with IC<sub>50</sub> values ranging from 0.50 to 2.03 nM. In subsequent outlining, 8i is a piperazine derivative a representative compound throughout these sequences, also significantly inhibited other class I PI3Ks and mTOR. In PC3 cells, it remarkably down-regulated the essential biomarkers of PI3K/Akt/mTOR signalling, including phos-Akt (Ser473), phos-Akt (Thr308), phos-S6ribosomal protein (Ser235/236), and phos-4E-BP1 (Thr37/46), at a concentration as low as 5 nM. A further in vivo pharmacokinetic (PK) study proved 8i possessed suitable oral exposure, peak plasma concentration, and elimination half-life.<sup>29</sup>

### Pyrazolochalcones derivatives

Anver BS et al. has inspected a sequence of novel pyrazolochalcones as potential modulators of PI3K/Akt/mTOR pathway and inducers of apoptosis in breast cancer cells. In the present study, they synthesized forty pyrazolochalcone conjugates and explored their cytotoxic activity against a panel of sixty cancer cell lines. Fifteen conjugates of the series showed excellent growth inhibition (13b-e, 13h-j, 14c-d, 15 a, 15c-d, 16b, 16d and 18f; GI50 for MCF-7: 0.4-20 µM). Conjugates 13b, 13c, 13d, 16b and 14d were also estimated for their cytotoxic action in human breast tumor cell line (MCF-7). The auspicious candidates' induced cell cycle arrest, mitochondrial membrane depolarization and apoptosis in MCF-7 cells in a 2 µM concentration. Furthermore, inhibition of PI3K/Akt/mTOR pathway-regulators such as PI3K, p-PI3K, p-AKT, and mTOR were observed; as well as upregulation of p-GSK3β and tumor-suppressor protein, PTEN.<sup>29</sup> **Fig. 10** describes the examples of (a) aminopyrimidin derivatives (b) 4-acrylamido-quinoline derivatives (c) pyrazolochalcones derivatives.



**Figure 9.** Scaffolds of thienopyrimidine derivatives.



**Figure 10.** Examples of (a) aminopyrimidin derivatives (b) 4-acrylamido-quinoline derivatives (c) pyrazolochalcones derivatives.

## CONCLUSIONS AND FUTURE PERSPECTIVES

Herein, researchers have reported the design, synthesis, evaluation, and molecular docking of a sequence of different series of heterocycles as mTOR inhibitors with for the treatment of innumerable cancers. Most of the composites were originated to exhibit inhibitory potencies in the micromolar to sub-micromolar kind. The series of compounds was found to be selectively active in contradiction of PI3K/Akt/mTOR isoform. Last 3 years have perceived an exhaustive exploration of mTOR/PI3K inhibitory contours of various chemical scaffolds in early stages of improvement. Variability's PI3K/Akt/mTOR inhibitors are under clinical trials. Researchers have also investigated a novel series of furoquinoline, phenylsulphonylureas, 4-acry-

lamido-quinoline, pyrazolochalcones, imidazole [4,5-b] pyridine, thienopyrimidine, aminopyrimidin scaffolds were designed and developed.

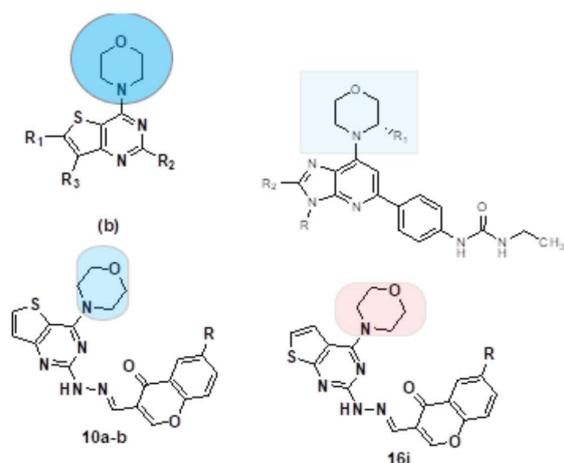
As per **Fig. 11** supreme of the compounds contain morpholine group is common. Based on our critical research, we observed that there still exist several shortcomings concerning advanced computational and experimental pharmacological studies to achieve prolific results. More significantly, the medicinal chemists and readers will gain evidence of various newly established PI3K/Akt/mTOR scaffolds and their development possibilities. The comprehensive evidence and critical negotiations provided herein will hopefully rush concepts for designing novel selective mTOR inhibitors with superior activity frameworks and inflict more caution in the verdict making process in the anticancer discovery.

## Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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**Figure 11.** Scaffolds containing morpholine groups.

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# Современные достижения в разработке противораковых лекарственных препаратов на основе PI3K / mTOR: мини-обзор

Ишан Панчал<sup>1</sup>, Арчана Навале<sup>1</sup>, Ашиш Шах<sup>2</sup>, Сандип Баделя<sup>3</sup>, Рати Трипати<sup>4</sup>

<sup>1</sup> Институт фармации Парул, Университет Парул, Вадодара, Индия

<sup>2</sup> Кафедра фармации, Sumandeep Vidyapeeth, Вадодара, Индия

<sup>3</sup> Институт фармацевтических наук Сарасвати, Дханап, Гандинагар, Индия

<sup>4</sup> Кафедра фармацевтических наук, Университет Ассама, Силчар, Ассам, Индия

**Адрес для корреспонденции:** Ишан Панчал, Институт фармации Парул, Университет Парул, Вадодара, Индия; E-mail: ishanpharma@gmail.com

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## Резюме

Рак относится к группе заболеваний, характеризующихся неконтролируемым ростом аномальных клеток. Он распространяется по всему телу, делая эту болезнь одной из величайших глобальных угроз человечеству. Углублённые исследования на протяжении многих лет установили нарушение регуляции целевого белка рапамицина у млекопитающих с раком. Это привело к разработке целевого белка ингибиторов рапамицина у млекопитающих. Несколько ингибиторов целевого белка рапамицина у млекопитающих прошли доклинические и ранние клинические испытания. За последние три года учёные изучили ряд структур фуорохинолина, фенилсульфонилмочевины, 4-акриламидо-хинолина, пиразологалконов, имидазол [4,5-b] пиридина, тиенопиримидина, аминопиримидина. В этом обзоре представлена подробная информация и критическое обсуждение разработок недавно представленных селективных ингибиторов целевого белка рапамицина у млекопитающих с лучшей активностью при лечении рака.

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## Ключевые слова

рак, открытие, фуорохинолин, фенилсульфонилмочевины, пиразологалконы

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