

# Monobactams as Anticancers: A Review Study

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## ABSTRACT

Cancer is a heterogeneous disease which categories as the second-leading cause of death worldwide. It is fatal to 42% of diagnosed patient every year. The ideal anticancer agents needed to be powerful, well tolerated in patients, with low side effect and high selectivity. Antibiotics on the other hand are efficient, well tolerated, with very low level of toxicity. Therefore, they continue to be the most important goal for new drugs invention. 2-Azetidinones ( $\beta$ -lactams) are most marketing drugs than any other antibiotics. The  $\beta$ -lactams provide unlimited choices of biological activities, and

they efficaciously used as anticancer agent's delivery system directly to the tumor sites as pro-drugs. These records indicate that the designation and synthesis of new monobactams will be favorable zone for improvement anticancer studying researches.

**Keywords:** Monobactams,  $\beta$ -lactams, 2-Azetidinones, Anticancer

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## INTRODUCTION

Cancer is a mixed disease and considered as the major threats for human health in 20<sup>th</sup> and 21<sup>th</sup> century, it classified as the 2<sup>nd</sup> trigger of death worldwide. Cancer described as the malignant cell progression that at the last leads to change the regular physiological activities (Kuhn D, *et al.*, 2004). Antimalignant agent investigation concentrates on reducing tumor cell growing rate and initiation of apoptosis in malignant cells. Programmed cellular death (apoptosis) is described as the capability of a cell to undertake a step-by-step self-suicide program without disturbing adjacent cells (Kuhn D, *et al.*, 2004; Dong J, *et al.*, 2019). Initiation of such apoptotic action in malignant cells is very necessary in cancer management process (Dong J, *et al.*, 2019).

The percentage of death in cancer diagnosed patient are high and it approximately about 42%. There for there is an urgent need to introduce new and safe anticancer agents, and this consider as an objective for medical research (Sharipova RR, *et al.*, 2019). However, nowadays the cancer treatments are almost as hazardous as the disease itself caused by incapability of the currently existing chemotherapeutic agents to target the cancer cells away from normal cells (Vento S and Cainelli F, 2003). Another drawback of cancer treatments is the critical unwanted effects of the anticancer agents as they weakening the immunity system cause by neutrophil cells decline (Vento S and Cainelli F, 2003; Tikhomirov AS, *et al.*, 2018). The ideal anticancer agents needed to be powerful, well tolerated in patients, with low side effect and high tumor cells selectivity.

The innovation of natural and synthetic antibiotics is one of the most significant medical discoveries in human history (Mehta PD, *et al.*, 2010). Antibiotics are efficient, mostly well tolerated in patients, with very low level of toxicity. This is why the antibiotics continue to be the main aim for drug invention (Basu S and Banik BK, 2017). 2-Azetidinones ( $\beta$ -lactams) are the most famous antibacterial compounds and they are most marketing antibiotics drugs (Basu S and Banik BK, 2017; Zhou P, *et al.*, 2018). The  $\beta$ -Lactams category including penicillins, cephalosporins, carbapenems, and monobactams, all with a rigid ring structure (Figure 1) (Zhou P, *et al.*, 2018).

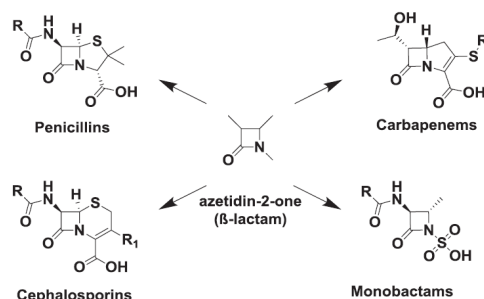


Figure 1: The  $\beta$ -Lactams categories

Their antimicrobial action is a result of inhibiting the peptidoglycan enzyme and thus inducing cell wall damage (Borazjani N, *et al.*, 2019). Around year 1981, couple of teams belongs to the Squibbs and Takeda Laboratories define and isolate the initial N-thiolated monobactams from natural resources. These monobactams were the first with the N-sulfonic acid substituent that attached directly to the nitrogen atom. They possess a flexible monocyclic structure.

## LITERATURE REVIEW

Nowadays,  $\beta$ -lactam compounds offer an extensive range of biological activities (Hammersley D and Signy M, 2017). The new drug with monobactam moiety Ezetimibe selectively inhibits intestinal cholesterol absorption (Hammersley D and Signy M, 2017; Chen D, *et al.*, 2008). Moreover, many studies indicate that several antibiotics are qualified to inhibit the growth of tumor cells. In addition to many antitumor antibiotics approved nowadays for cancer treatment, they interacted with DNA leading to inhibit tumor cell growth (Chen D, *et al.*, 2008; Tripodi F, *et al.*, 2018). Recently, a new class of N-thiolated monobactams was used to prompt apoptosis powerfully in specific manner in many lines of tumor cells but they do not do so in non-transformed cell lines (Tripodi F, *et al.*, 2018; Banik I, *et al.*, 2003). These records indicate that the designation and synthesis of new monobactams will be favorable zone for improvement anticancer researches

(Banik I, *et al.*, 2003).

The monobactams structural moiety has attracted a great deal of attention owing to their extensive biological activities (Trivedi AR, *et al.*, 2012; Pathak RB, *et al.*, 2012; Kumar A, *et al.*, 2007). In addition, many research indicating that these monobactams used in efficaciously manner as pro-drugs to deliver the anticancer agents directly to the tumor sites (Ojima I and Delalogue F, 1997; Hodge M, *et al.*, 2009; Mahmood AA, *et al.*, 2021).

Monobactam is a four-membered cyclic amide, at the second position of the ring there is an oxo group, with various substitutions on the amide nitrogen (N-1), on the carbon neighboring to the carbonyl group (C-3), and on the carbon next to the nitrogen (C-4) (Figure 2) (Kuhn D, *et al.*, 2004; El-Shorbagi AN and Chaudhary S, 2019).

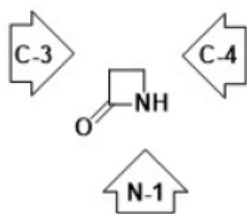


Figure 2: The chemical structure of monobactam

The monobactams reactivity can control, by varying the character of the electron withdrawing substituent (Kuhn D, *et al.*, 2004). From the mechanistic view, monobactam moiety acts as an electrophilic nucleus targeting serine-containing enzymes (El-Shorbagi AN and Chaudhary S, 2019).

Monocyclic  $\beta$ -lactams were diagnosed to have an anti-mycobacterial, anti-protozoal, anti-fungal, anti-HIV, anti-inflammatory, anti-tumor, anti-parkinsonianic, anti-diabetic and anti-depressant effects. They have been reported as cholesterol absorption inhibitors, vasopressin V1a antagonists, trypsin, chymase and thrombin inhibitors, human leukocyte elastase and carbonic anhydrase inhibitors, N-acetylthanolamine acid amidase inhibitors and also inhibitors of dengue and West Nile virus NS2B-NS3 protease (Trivedi AR, *et al.*, 2012; Pathak RB, *et al.*, 2012; Kumar A, *et al.*, 2007; Jain AK, *et al.*, 2012; Galletti P and Giacomini D, 2011; Decuyper L, *et al.*, 2018; Dražić T, *et al.*, 2019).

In recent years Tripodi F, *et al.* mention the ant malignant effect of 1,4-Diaryl-2-azetidiones caused by the stimulation of Adenosine Monophosphate Activated Protein Kinase (AMPK) leading to initiate an apoptotic response in colorectal cancer cell lines (Tripodi F, *et al.*, 2012; Valtorta S, *et al.*, 2014). Also they indicated these monobactams specifically for the Small Bowel Adenocarcinoma (SBA) and also for the Colorectal Cancer Diseases (CRC), as they all sharing comparable pathophysiology (Koch V, *et al.*, 2019; Carr M, *et al.*, 2010). In another study 1, 4-diarylazetidion-2-ones were present potent antiproliferative action against MCF-7 (Michigan Cancer Foundation-7), MDA-MB-231 (51-year-old caucasian female with a metastatic mammary adenocarcinoma) human breast carcinoma cell lines (Koch V, *et al.*, 2019; Banik BK, 2014; Chavan AA and Pai NR, 2007). Other monobactams act as effective antimalignant agents as they provoke DNA destruction and inhibit the replication of the Jurkat T cells DNA (Kamath A and Ojima I, 2012).

### Synthesis of monobactams

2-azetidione (monobactams) compounds are synthesized according to [2+2] ketene-imine cycloaddition (Staudinger cycloaddition reaction) (Tanaka T, *et al.*, 2007). In 1907, this reaction was first reported and defined as a [2+2] cycloaddition involving both a ketene (formed from acid chloride) and suitably substituted imines under basic conditions. This reaction stays as the most commonly used method for its flexibility and efficiency. The required imines were prepared by the reaction of the required

substituted benzaldehydes and the aromatic amines (Figure 3) (Tanaka T, *et al.*, 2007; Mahmood AA, 2021; Singh GS, 2003; Lima LM, *et al.*, 2020; Söderström TS, *et al.*, 2002).

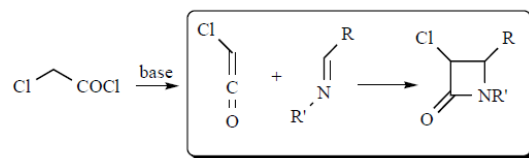


Figure 3: The Staudinger [2+2] ketene-imine cycloaddition reaction

### Monobactams as anticancers

The general chemical structure for the 2-azetidiones with the possible substitutions on each monobactam corner is clarified in Figure 4:

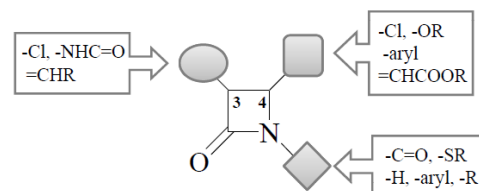


Figure 4: The general chemical structure for the 2-azetidiones with the possible substitutions

In early 2000, some studies indicate that the N-thiolated  $\beta$ -lactams capable to induce apoptotic reaction in tumor cell by causing DNA destruction and without affecting the normal body cells (Kazi A, *et al.*, 2004; Cainelli G, *et al.*, 2003). They found that the N-methyl-thio group is very important for such apoptosis-inducing activity (Cainelli G, *et al.*, 2003). Another study indicates that 4-alkylidene- $\beta$ -lactams could be as inhibitor for matrix Metalloproteinases-2, and Metalloproteinases-9 (MMP) (Chin JR, *et al.*, 1985), both were a classes of mammalian proteases, which playing a very critical role in cancer propagation by promoting neovascularization needed for tumor growing (Hojilla CV, *et al.*, 2003). MMPs activated specifically in malignant cells, and not in normal cells (Chin JR, *et al.*, 1985; Wilhelm SM, *et al.*, 1987; Malig TC, *et al.*, 2018).

Banik I, *et al.* described a class of poly aromatic imine  $\beta$ -lactams (the 4-alkylideneazetidion-2-ones). Many of these compounds were verified *in vitro* for their preventing action against MMP-2 and -9 and human leukocyte elastase (LE) (Zhuang C, *et al.*, 2017). They conclude that monobactams bearing phenanthrene and chrysene substituents dedicate excellent activity. While naphthalene, anthracene, and pyrene substituents cause no cytotoxic activities (Zhuang C, *et al.*, 2017).

Kuhn D, *et al.* describe some of synthetic N-methylthio- $\beta$ -lactams that provoke apoptosis in many tumor cell lines as the breast cancer (MCF-7 and MDA-MB-231) human leukemia Jurkat T cells, head-and-neck (Human Prostatic Carcinoma cell line-13 (PCI-13)) and Prostate Carcinoma cell line (PC-3 and DU-145) (Frezza M, *et al.*, 2008). They finally conclude several key points that to be considered in upcoming purpose and synthesis of monobactams as an anticancer (Figure 5):

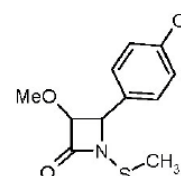


Figure 5: The structure of N-methylthio- $\beta$ -lactams by Kuhn D, *et al.*, 2004

- 1) The N-methyl-thio group must maintain as it is without any addition.
- 2) All substitutions on ortho, meta and para of the phenyl ring retain the apoptotic effect, and the most potent are on the ortho position.
- 3) The bigger groups in the ortho position will cause the powerful apoptotic-inducing activity.

Frezza M, *et al.* studied the effects of C3 and N1 substitutions on  $\beta$ -lactams moiety for their apoptotic effect with Structure-Activity Relationship (SAR). They mentioned couple of  $\beta$ -lactam compounds, both bearing a branched-chain moiety on C3, they exhibit a potent apoptosis-inducing activity. They concluded that any substituents on the N1 or C3 atoms of the monobactam will further potentiate such an effect (Arya N, *et al.*, 2014).

Based on the studies, that mentions the anticancer activity of the combretastatin analogues with OH and OMe groups at C-3 (Sun L, *et al.*, 2004; Carr M, *et al.*, 2010; Meegan MJ, *et al.*, 2008). Also the potent anticancer action of monobactams compounds that contain methyl group at C-3 (Martelli G, *et al.*, 2020; Pettit GR, *et al.*, 1987; O'Boyle NM, *et al.*, 2010) studied the anti-proliferative action of a novel synthesized series of inflexible analogues of natural combretastatin which bearing the 1,4-diarly-2-azetidinone (monobactams) instead of the regular ethylene link existing in the natural combretastatin stilbene compounds. Moreover, these new compounds substituted with an aryl ring at position 3 on monobactam moiety. Also the 3,4,5-trimethoxyphenyl moiety introduced at the N-1 atom and the 4-methoxyphenyl ring is hosted at the C-4 atom (Figure 6) (Cerić H, *et al.*, 2010).

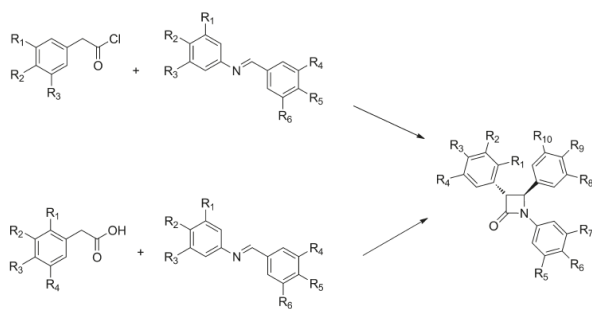


Figure 6: The structure of monobactams by O'Boyle NM, *et al.*, 2010

First, these compounds were estimated for their anticancer effect against the MCF-7 human breast cancer cell line, and then the most powerful agents were tested versus the MDA-MB-231 cell line.

They indicate that the highest effective compounds in this groups were establish in those with tiny, polar substituents such as (4-fluorophenyl), (4-hydroxyphenyl), (3-hydroxyphenyl), and (4-aminophenyl). The SAR studies indicate that the replacement of the  $\beta$ -lactam carbonyl group with the thione resulted in a decrease of the antiproliferative activity (Cerić H, *et al.*, 2010).

Galletti and Giacomini in their review reported that Banik and its colleague established a new series of N-polyaromatic-azetidinones with antitumor actions. Their SAR study exposed that the aromatic structural requirement for cytotoxicity must contain three aromatic rings as a minimum in an rangy configuration (compounds with chrysenes substituents established activity, while naphthalene, anthracene or pyrene substituents with no activities (Banik BK, *et al.*, 2010; Tripodi F, *et al.*, 2012). Their results reveals that the inhibition of the growth are not equal against all tumor lines, suggesting that there are specificity in the targeting process. In addition, the existence of a OH group on C3 enhanced the activity or even it may switch inactive compound into active ones (Figure 7) (Banik BK, *et al.*, 2010).

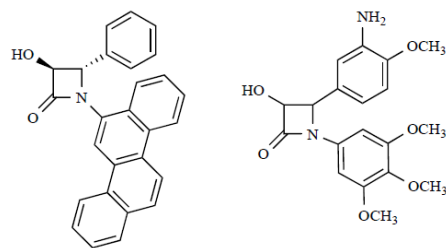


Figure 7: The structure of monobactams by Banik I, *et al.*, 2003

Tripodi F, *et al.* considered four series of compounds. One with a 3,4,5-trimethoxyphenyl moiety at position 1 accompanied by a 4-methoxy-3-hydroxyphenyl moiety at 4 position of the monolactam ring and also a OH or HH2 group at position number 3. The other series with 3,5-dimethoxyphenyl moiety accompanied by a 4-methoxyphenyl group at position number 4 of the monobactam ring. The third and fourth series were with the inverted aryl moieties of the first and second series respectively (Figure 8) (Petrovski G, *et al.*, 2011). All the synthesized products evaluated against HeLa cells (cervical adenocarcinoma), and also against the breast cancer cell line MCF-7, as well as against several colon cancer cell lines (SW48, SW480, SW620, T84) and finally against the neuroblastoma cell line (SK-N-BE) in order to estimate their antiproliferative activities (Petrovski G, *et al.*, 2011; Kondratyuk TP, *et al.*, 2011).

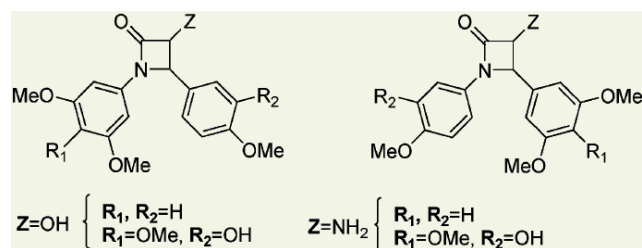


Figure 8: The structure of monobactams by Tripodi F, *et al.*, 2012

The results indicate that the water solubility of the tested compounds were enhanced by the presence of a OH group at position number 3 of the monobactam ring (Kondratyuk TP, *et al.*, 2011; Meegan MJ, *et al.*, 2001). Also compounds bearing the 3,4,5-trimethoxy or 3,5-dimethoxyphenyl substituents at position 1 (N atom) of monobactam ring represent efficient activity comparing to those with polymethoxylated substituents at C-4 position (Kondratyuk TP, *et al.*, 2011).

Greene TF, *et al.* studied the SAR for a new family of 3-phenoxy-1,4-diary-lazetidin-2-ones (Olazaran FE, *et al.*, 2017; Fu DJ, *et al.*, 2017; Barrett I, *et al.*, 2010), that finally led to synthesize a group of active anticancer compounds involving trans-4-(3-hydroxy-4-methoxyphenyl)-3-phenoxy-1-(3,4,5-trimethoxyphenyl)azetidin-2-one and trans-4-(3-amino-4-methoxyphenyl)-3-phenoxy-1-(3,4,5-trimethoxyphenyl) azetidin-2-one (Barrett I, *et al.*, 2010). The anticancer activities were tested against MCF-7 breast cancer cells (targeting tubulin polymerization process) (Barrett I, *et al.*, 2010; Greene TF, *et al.*, 2016). Their results indicate that these compounds targeted tubulin effectively, and that the monobactams synchronize within the colchicine-binding site of the  $\beta$ -tubulin. In addition, and by studying the X-ray crystallography for a number of chosen compounds, the results indicating that the torsional angle among the aryl rings at N-1 and C-4 of the monobactams considered to be essential for effective anticancer effects (Figure 9) (Barrett I, *et al.*, 2010; Deep A, *et al.*, 2016).

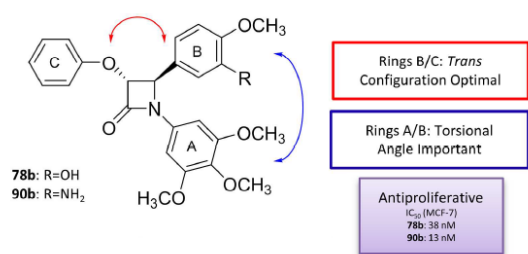


Figure 9: The structure of monobactams by Greene TF, *et al.*, 2016

Deep A, *et al.* synthesized another series of monobactams derivatives in 2016 from hippuric acid (Figure 10), they assessed the *in vitro* anticancer activities for these compounds against an estrogen receptor positive human breast adenocarcinoma MCF-7 (ATCC HTB-22) cancer cell line. The results showed a regular anticancer potential possessed by these compounds, and the best compound was N-[2-(3-chloro-2-oxo-4-styrylazetid-1-ylamino)-2-oxoethyl] benzamide (Deep A, *et al.*, 2016).

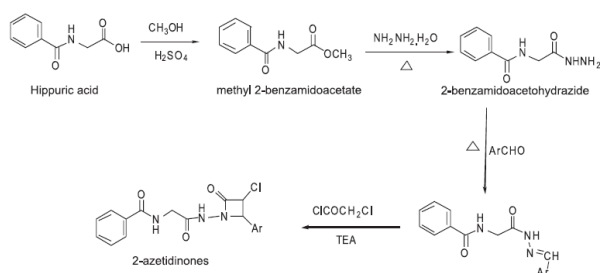


Figure 10: The structure of monobactams by Deep A, *et al.*, 2016 (A)

The SAR studies indicate that the existence of electron releasing groups on benzylidene portion will improve the anticancer activity. Cinnamaldehyde derivatives were categorized as the most effective compounds (Deep A, *et al.*, 2016). These findings summarized in Figure 11.

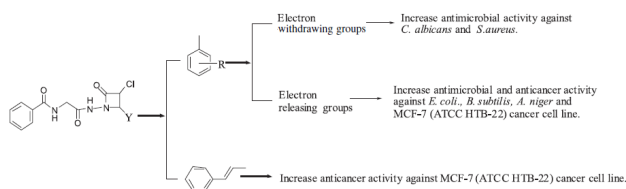


Figure 11: The SAR studies of Deep A, *et al.*, 2016 (A)

Another study for Deep A, *et al.* (2016) in which they synthesized another monobactam series from hydrazone and chloroacetyl chloride in dimethylformamide (Figure 12). The anticancer activity of synthesized compounds was tested against human breast cancer cell line (MCF-7). Their results indicated that the synthesized compounds exposed weak anticancer activity against breast cancer cell line (MCF-7) comparing to standard drug (Deep A, *et al.*, 2016).

The SAR studies indicate that the presence of electron releasing groups will improve the anticancer activity against human breast cancer cell line (MCF-7) (Figure 13) (Deep A, *et al.*, 2016).

Also in another research, Deep A, *et al.* design and synthesis a new series of 4-thiazolidinone derivatives, and evaluate their *in vitro* antimicrobial and anticancer activities. The anticancer study results revealed that N-(2-(5-(4-hydroxybenzylidene)-2-(4-methoxyphenyl)-4-oxothiazolidin-3-ylamino)-2-oxoethyl) benzamide was the most powerful anticancer agent (Zhang Y, 2010).

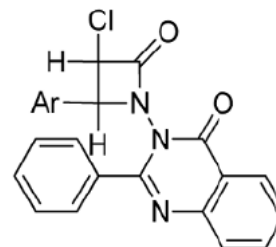


Figure 12: The structure of monobactams by Deep A, *et al.*, 2016 (B)

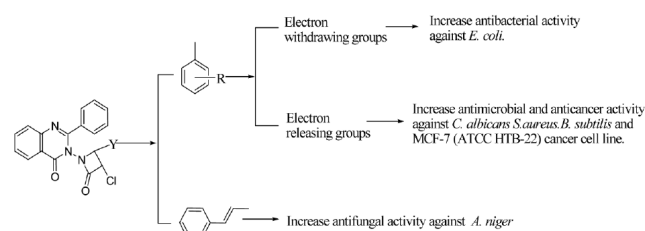


Figure 13: The SAR studies of Deep A, *et al.*, 2016 (B)

Geesala R, *et al.* synthesized a new monobactams by introducing allyl moieties in stead of aromatic ring on the N1 atom of 1,4-diazylazetid-2-ones, indicating that these allyl (isothiocyanate and disulfide compounds) will give a potent anticancer effect (Geesala R, *et al.*, 2016).

The synthesized monobactams were tested by the 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) cell viability assay against human breast cancer cell lines MCF-7 (Estrogen Receptor+(ER+)/Progesterone Receptor+(PR+)/Human epidermal growth factor receptor 2-(Her2-), Luminal type) and MDA MB-231 (ER-/PR-/Her2-, Basal type) and also against non-transformed normal human Mammary Epithelial Cells (MEpIC) (Meenakshisundaram S, *et al.*, 2016). The results represent that when fluorine located at the p-position of 3-methoxy-2-oxo-4-phenylazetid-2-ones will be more active than chlorine or bromine atoms at the same location in the phenyl acrylonitrile derivatives. In addition, the presence of methyl moiety at the p-position on the same derivatives was noticed to enhance the antiproliferative activity. It is worth noting that when the methyl moiety located on the m-position and also when the second and fifth location occupied by methoxy groups and chlorine located on the p-position of these derivatives the activity will decrease. Also they mention that the methyl-phenyl acrylate compounds of 3-methoxy-2-oxo-4-phenylazetid-2-ones bearing either nitro or tri-fluoro methyl group or chlorine atom at m-position were ineffective (Figure 14) (Meenakshisundaram S, *et al.*, 2016).

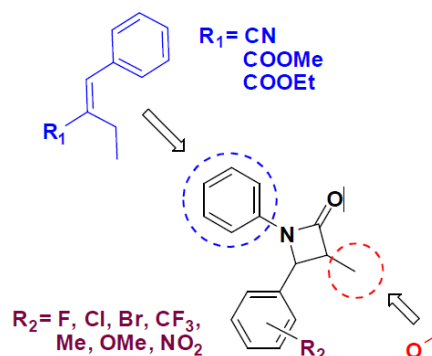


Figure 14: The structure of monobactams by Geesala R, *et al.*, 2016

In another study, Meenakshisundaram S, *et al.* synthesize and evaluate *in vitro* inhibitory activities of new monobactams group against three human cancer cell lines (cervical HeLa, renal ACHN and breast MDA-MB-231). In this study, the dimeric Schiff bases were prepared from terephthalaldehyde and groups of amines (Kayarmar R, *et al.*, 2017). Another group of Schiff bases were created by the reaction of the isophthalaldehyde with other amines. Then the monobactams were synthesized from these Schiff bases (Figure 15) (Kayarmar R, *et al.*, 2017).

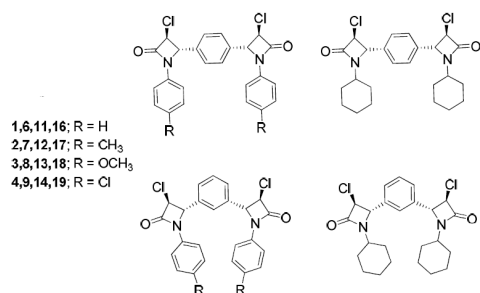


Figure 15: The structure of monobactams by Meenakshisundaram S, *et al.*, 2016

The results indicates that the 1,3-positional isomers of 3-chloroazetidines revealed strong anticancer activity, and also the 4-methyl derivative exhibited potent cytotoxic activity (Kayarmar R, *et al.*, 2017).

In 2017, a novel group of N-substituted monobactams were synthesized by Kayarmar R, *et al.* by the reaction of chloroacetyl chloride with 4-arylidene hydrazino-1-isobutyl-1H-imidazo[4,5-c]quinolines compounds. Also by substitute imidazoquinoline at the 4-position they create a group of 3-chloro-4-arylsubstituted-1-[(1-isobutyl-1H-imidazo[4,5-c]quinolin-4yl)amino] azetid-2-ones (Figure 16), and then they examined the antimicrobial and anticancer activities of these compounds (Mohamad-zadeh M and Zarei M, 2021).

R
4-Chloro phenyl
Biphenyl
2,4-Dimethoxy phenyl
2,4-Dimethoxy-5-nitro phenyl
4-Hydroxy-3- methoxy-5-nitro phenyl
6-Methoxy naphthyl
4-Hydroxy phenyl
2,4- Dichloro phenyl

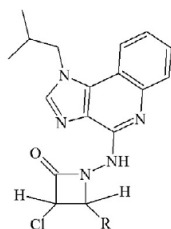


Figure 16: The structure of monobactams by Kayarmar R, *et al.*, 2017

The anticancer activities against the HeLa cancer cell line for the synthesized compounds were compared with cyclophosphamide as standard drug. Compounds with 4-OH phenyl and 2,4-Dichloro phenyl represent a highest anticancer activity against HeLa cells (Mohamad-zadeh M and Zarei M, 2021).

In early 2020, Mohamad-zadeh and Zarei synthesize new groups of monobactams having anthraquinone moiety with several substituents (Figure 17), and then they evaluate their antitumor activities. The results showed that many of these monobactams represent reasonable to significant antitumor activity against Prostate Carcinoma (PC3), colon carcinoma (HCT116), breast carcinoma (MCF7) and neuroblastoma (SK-N-MC) cell lines *via* MTT assay. Due to the structure similarity, the reference compound was Doxorubicin (Zhou P, *et al.*, 2016).

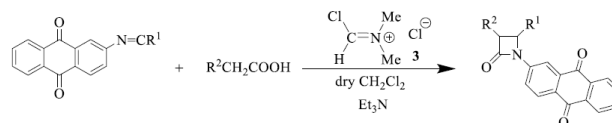


Figure 17: The structure of monobactams by Mohamad-zadeh M and Zarei M, 2021

The SAR study reveals that when 2-naphthoxy or methoxy groups substituted on C-3, there will be a higher activity than when substituted at N1, C2 or C4. Little activity also noticed with chloro, azido and phthalimido. Reasonable activity is shown by 3-thiolated or -sulfonated derivatives. In addition, cytotoxicity decreased with the replacement of methylthio by methylsulfonyl. The potent cytotoxicity against all cell lines were noticed when 2-azetidioneanthraquinone hybrids substituted at location 4 by 4-(dimethylamino) phenyl moiety. They concluded that monobactams could be used as antitumor because it's low toxicity and their potent anticancer activities (Zhou P, *et al.*, 2016).

Another study done by Giolito MV, *et al.* and they described the *in vitro* activity estimation of 35 novel chemical compounds against two negative murinmammary adenocarcinoma tumors. The selection involves two compounds which are  $\beta$ -lactams: PGC22i (penicillin) and CIT171B3 (monobactam) (Figure 18). Both penicillin and monobactams are having antitumor activity (Nam NH, 2003; Giolito MV, *et al.*, 2020).

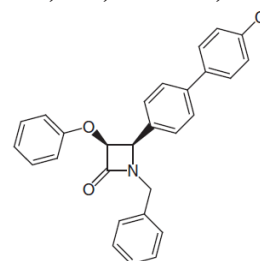


Figure 18: The structure of monobactams by Giolito MV, *et al.*, 2020

They found that the monobactam compound cause promotion of apoptosis and lower clonogenic capacity. They also decreased the migratory capacity of tumor cells. The results propose the possibility of their future utilization as antitumor and/or antimetastatic agents (Leite TH, *et al.*, 2020).

Grabrijan K, *et al.* in their patent overview mentioned the patent from 2011 (WO201107321) in which the authors designate synthetic monobactams derivatives of combretastatin as anti-cancer agents (Grabrijan K, *et al.*, 2021). The rigid beta lactam ring catches the compound in the preferred stereochemistry. The synthesized compounds strongly look like combretastatin, with trimethoxybenzyl at N-1 position, and 2-methoxyphenol at C-4 position. Different groups were presented on C-3 position (Figure 19). The anticancer effect was tested against MCF-7 breast cancer cell line. The reported IC<sub>50</sub> values for all compounds were in nanomolar range. In addition, some compound was shown to inhibit the growth of human chronic myeloid leukaemia K562 cells and human promyelocytic leukaemia HL-60 cells, their IC<sub>50</sub> were in the nanomolar or sub-nanomolar scope. They conclude that the possibility of using of such compounds as anti-cancer agents would inhibit angiogenesis and metastases (Patil SA, *et al.*, 2021).

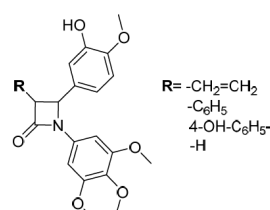


Figure 19: The structure of monobactams by Grabrijan K, *et al.*, 2021

Recently, Patil SA, *et al.* in their coumarins review study mentioned many bioactive coumarins holding azetidinone and thiazolidinone moieties, which found with a wide range of therapeutic characteristics, including anticancer activities. Azetidinone moieties were added to the positions three, four, six and seven of the coumarin skeleton (Figure 20) (Keri RS, *et al.*, 2010).

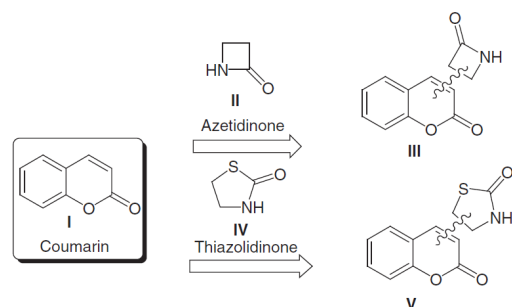


Figure 20: The structure of monobactams by Patil SA, *et al.*, 2021

The review mention the synthesis of a new series 3-chloro-4-[4-(2-oxo-2Hchromen-4-ylmethoxy)phenyl]-1-phenylazetidin-2-ones by Keri RS, *et al.* Compounds 33, 36, 38, 40 and 43 exposed powerful anticancer activity against *Artemia salina* (Figure 21).

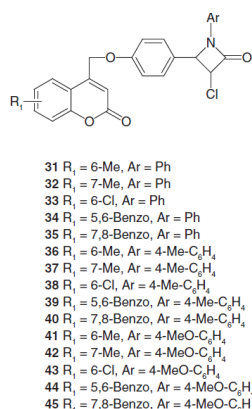


Figure 21: The structure of monobactams by Keri RS, *et al.*, 2010

In the same review, another study by Deepika P, *et al.* mentioned the design and synthesis of new azetidin-2-one coumarin derivatives (96-99) as anticancer drugs (Figure 22) (Deepika P, *et al.*, 2020). The docking scores indicated that out of all compounds docked, 96 had the powerfull binding affinity with protein 1XJD. Furthermore, all coumarin azetidinones exhibited good cytotoxic effects against HeLa cancer cell lines. They indicate that these series could be considered to be future leads for anticancer therapy (Głowacka IE, *et al.*, 2021).

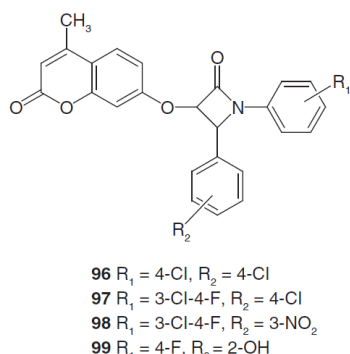


Figure 22: The structure of monobactams by Deepika P, *et al.*, 2020

A new family of N-substituted 3-aryl-4-(diethoxyphosphoryl)azetidin-2-ones was synthesized by Głowacka IE, *et al.* by reacting the N-methyl- or N-benzyl- (diethoxyphosphoryl)nitron (compounds 12 and 13) with the 14a-14f aryl alkynes (Figure 23) (Fram RJ, *et al.*, 1986).

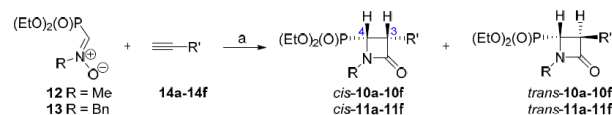


Figure 23: The structure of monobactams by Głowacka IE, *et al.*, 2021

The 50% cytostatic Inhibitory Concentration (IC<sub>50</sub>) was estimated against 9 cancerous cell lines: Capan-1 (pancreatic adenocarcinoma), Hap1 (chronic myeloid leukemia), HCT-116 (Colorectal Carcinoma), DND-41 (acute lymphoblastic leukemia), HL-60 (acute myeloid leukemia), NCI-H460 (lung carcinoma), MM.1S (multiple myeloma), K-562 (chronic myeloid leukemia), normal retina (non-cancerous) cells (Human Telomerase Reverse Transcriptase Retinal Pigment Epithelial-1 (hTERT RPE-1)), as well as Z-138 non-Hodgkin lymphoma. Some monobactams represent reasonable cytostatic effect concerning Capan-1, Hap1 and HCT-116 cells (Fram RJ, *et al.*, 1986).

Also Głowacka IE, *et al.* mentioned number of compounds and studies that resemble their work as synthesis of 4-(2-chlorophenyl)-3-methoxy-1-(methylthio)azetidin-2-one which stop proliferation and provoke apoptosis in human solid cell lines, like prostate and breast (Chimento A, *et al.*, 2013). Similarly, 1,4-diaryl-3-chloroazetidin-2-ones which documented as effective compounds against human breast cancer (Smith DM, *et al.*, 2002). Another group of 1,4-diarylazetidinone with methoxyphenyl moiety were synthesized and then evaluated for their cytotoxicity effect (Smith SR, *et al.*, 2014; Malebari AM, *et al.*, 2020). Many of them showed antiproliferative effect against MCF-7 and MDA-MB-231 human breast carcinoma cells with nanomolar value. Furthermore, the fluorinated compounds revealed substantial antitumor effects against HT-29 colon cancer cells (Smith SR, *et al.*, 2014; Malebari AM, *et al.*, 2020).

## CONCLUSION

Cancer considered as one of the major hazards to human health. It described as the malignant cells evolution that finally ended with the interference with ordinary physiological works. Anticancer drug investigation concentrates on reserve of tumor cell development and induction of apoptosis in the malignant cells, without disturbing adjacent cells. However, the low selectively and the serious chemotherapeutic drugs side effects are the major drawbacks of the current antitumor agents. Therefore there is an urgent need to develop appropriate (safe and selective) chemotherapeutic drugs.

Antibiotics are efficient, mostly well tolerated in patients and have very low level of toxicity. Thus, it may be an attractive target for antitumor agent's invention. There are now lots of antitumor antibiotics accepted as anticancer agents. In addition to that, and by varying the character of the electron withdrawing substituent of the monobactams, there is an excellent chance get a safe and effective antitumor monobactams. These records indicate that the designation and synthesis of monobactams represent a talented area for promoting improvement in anticancer fields.

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