Review Article

A Full-Scale Review on the Anticancer Potential of Pteridine Derivatives

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ABSTRACT

Cancer is considered as one of the major health challenges across the world; it impacts the quality of life and the treatment is associated with several side effects. Drug resistance, cost effectiveness and the adverse effects warrants the need of novel anticancer agents. Pteridines are aromatic compounds formed by fused pyrazine and pyrimidine rings. Pteridine, a privileged scaffold plays a vital role in various biological procedures as well as in cancer pathogenesis and it is recognized as a valuable compound in the treatment of cancer. Many pteridine derivatives have been designed and developed for their anticancer activity in the last few years. The present review aims to focus on the development of potent and efficacious anticancer drugs with pteridine scaffold.

Keywords: Pteridine, Pteridine derivatives, DHFR, Carbonic anhydrase, Anticancer activities.

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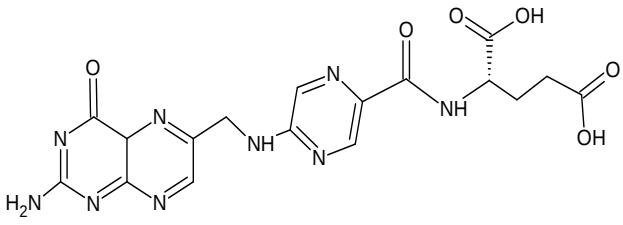
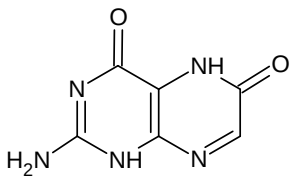
INTRODUCTION

Pteridine is an aromatic chemical compound which is composed of fused pyrimidine ring with pyrazine ring and the molecular formula is $C_6H_4N_4$. It is a worthy structure for enhancing probes of magnificent curative potentials. It is also a group of heterocyclic compounds containing wide variety of substitutions on its structure. The major substituted Pteridines are Pterins and Flavins that possess diverse biological roles. Natural compounds containing pteridines, such as erythropterin, xanthopterin, isoxanthopterin, lactic acid and leucopterin (fig 1), these all play a major role in growth processes, metabolism, biological colouration and in medicine as antiviral, anticancer, antibacterial and diuretic drugs[1]. Pteridine-based compounds have been reported to have various biological activities like anti-inflammatory activity, analgesic activity, potent inhibitors for hepatitis virus, immunosuppressive activity, and anti-nematode, glyoxylase inhibitory and antimicrobial activity. Naturally produced Pteridines are Pterins with amino and carbonyl group at ring positions 2 & 4 respectively. Many living organisms synthesize pteridines, where they act as enzymatic cofactors, pigments, or immune system activation molecules.

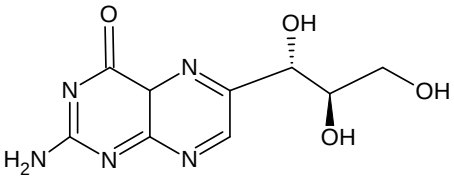
The pharmacological approach to neoplastic disease has made some spectacular procure since 1940 when the antileukemic activity of nitrogen mustard was come across during World War II. Cancer has been acknowledged as disease of anomalous cellular proliferation, with conventional cancer therapies pointing to make use of the proliferation mechanism. By its very nature, they indicate only partial refinement for tumour cells over normal cells in proliferation tissue in the gut and bone marrow. It is now generally accepted that a neoplastic transformation is related to genes alteration or oncogene activation, permitting advancement in the evolution of new treatments for malignant diseases, both by revealing the pathophysiology of the disease and the discovery of new drugs. Furthermore, the role of many proteins has been identified as novel targets in cancer therapy allowing the design of more selective agents[2]. The antitumor activity of pteridine-based compounds is one of the most studied and advanced therapeutic potentials, for which several molecular targets has been identified. In this review, we are focusing on the achievements of pteridine and pteridine based compounds for the treatment of cancer.



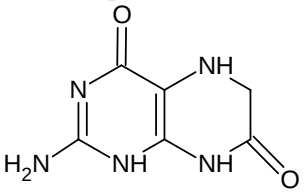
Folic acid



Xanthopterin



Neopterin



Isoxanthopterin

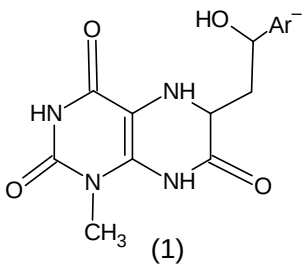
Figure 1

ANTI-CANCER ACTIVITIES

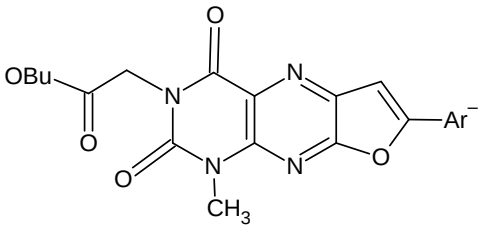
Pteridine derivatives as DHFR inhibitors

Dihydrofolate reductase (DHFR) is an enzyme required for the regeneration of tetrahydrofolate from dihydrofolate, which is formed under catalysis of thymidylate synthase (TS). Inhibition of the DHFR-catalytic activity results in reduction of intensity of abovementioned processes and consequently prevents DNA replication and cell division[3]. Thus, inhibition of DHFR is one of the possible mechanisms of the chemotherapeutic drugs activity. Most of "classical" (aminopterin, methotrexate, pemetrexed, lometrexol, raltitrexed, *etc.*) and "non-classical" (trimetrexate, trimethoprim, Iclaprim, *etc.*) DHFR inhibitors may be used as antibacterial, antimalarial or antitumor drugs.

Nosulenko *et al.,* synthesized pteridine and furo[3,2-g] pteridine derivatives[4]. They were evaluated for their inhibitory potential against DHFR enzyme. The DHFR-inhibitory activity of substituted 1-methylpteridine-2,4,7-triones (1,2,3) and 7-aryl-(hetaryl-)furo[3,2-*g*]pteridine-2,4(1*H*,3*H*)-diones was studied. It was established that 6-(2-hydroxy-2-aryl(hetaryl-)ethyl)-1-methylpteridine-2,4,7(1*H*,3*H*,8*H*)-triones(1) and butyl 2-(7-aryl-(hetaryl-)-1-methyl-2,4-dioxo-1,4-dihydrofuro[3,2-*g*]pteridine 3(2*H*)-yl)acetates(2) inhibited DHFR by 14.59–52.11%. The conducted primary *in vitro* screening revealed low or moderate DHFR-inhibiting activity of the synthesized compounds when compared to methotrexate. It was established that the introduction of aryl moiety with electron-accepting group, naphthyl substituent or electron-accepting heterocycle (furan, thiophene and benzofuran) caused an increase in the DHFR-inhibitory activity.



(1)



(2)

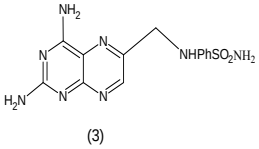
Pteridine derivatives as carbonic anhydrases inhibitor

CA isozymes IX, XII, and CA-related protein VIII are highly abundant intumors and are involved in tumorigenesis and tumor progression,7,8 and that has led to their validation as new therapeutic targets for cancer chemotherapy intervention[5].

Mechanism of action of carbonic anhydrase is catalyze the reversible hydration of carbondioxide to produce bicarbonate and a proton. multiple ca isoforms are implicated in a range of disease including cancer. In solid tumors, continuously dividing cells create hypoxic conditions that eventually lead to an acidic microenvironment.

Marques *et al.,* developed and evaluated novel MTX analogues, containing a pteridine moiety conjugated with benzenesulfonamide derivatives[5]. He reported the design and synthesis of several diaminopteridine-benzensulfonamide and benzene sulfonate conjugates. The inhibition studies were performed on a set of Carbonic anhydrases(CA) and DHFR. Their antiproliferative activities were tested on 2 cancer cell lines (A549 and PC-3).

As for the CA inhibition, some compounds presented low nanomolar activity, with compound (3) displaying the lowest IC50 value (2.1 µM) over CA IX, and selectivity for the cancer-related CA IX over the ubiquitous CA II rising up to 369 for compound (4). In terms of DHFR inhibition, most of the compounds presented activities in the low micromolar range, namely with 2.5 µM for (3) and 1.3 µM for (5).



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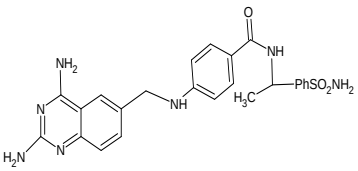

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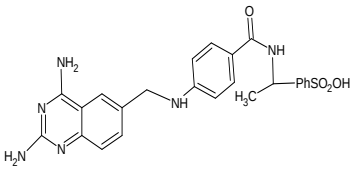


(5)

The antiproliferative properties of the new compounds against the two cell lines were more disappointing, with activities in the millimolar concentration range, probably due to deficiency of the inhibitor transport inside the cells. In general, the inhibitory profiles towards the CAs and

DHFR revealed good antitumor potential of these new bifunctional compounds, but apparently better cell permeability properties would be required to improve their efficacy.

Pteridine derivatives as monocarboxylate transporter 1 inhibitor

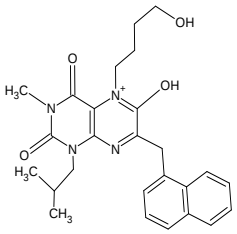
Highly glycolytic cells produce excessive amounts of lactate, the end product of glycolysis, which is actively transported out of the cell to normalize intracellular pH levels. Lactate homeostasis is maintained via a family of 12-membrane pass cell surface proteins coined monocarboxylate transporters (MCTs; also known as the SLC16a transporter family)[6].

Expression profiling studies have established that most aggressive tumor types express markedly elevated levels of MCT1, MCT4, or both.

Inhibition of MCT1 or MCT4 can kill tumor cells ex vivo and provoke tumor regression *in vivo*.

Hui Wang *et al.,* reported that the novel substituted pteridine-derived inhibitors of monocarboxylate transporter 1(MCT1), is an emerging target for cancer therapy[6].

The activity of these compounds as inhibitors of lactate transport was confirmed using a ^{14}C-lactate transport assay. Their potency against MCT-1 expressing human tumor cells was established using MTT assays. The four most potent compounds showed substantial anticancer activity (EC_{50}=37-150Nm) vs MCT1- expressing human Raji lymphoma cells are (6), (7), (8) and (9).



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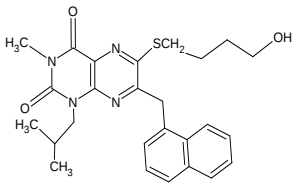

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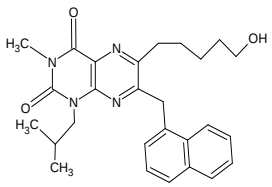

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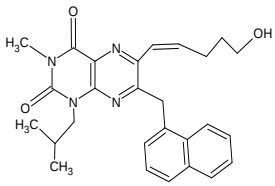

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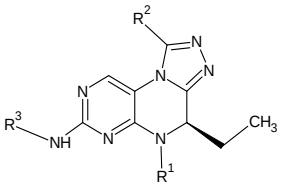
Pteridine derivatives as dual plk1/BRD4 inhibitor

Wang et al; synthesized derivatives of 4,5-dihydro-[1,2,4] triazolo[4,3-f] pteridine based on the structure of PLK1 inhibitor BI-2536[7]. From all those derivatives the most potent PLK1/BRD4 inhibitor was found to be (10) with good potency for both PLK1 (IC_{50}=20Nm) and BRD4 (IC_{50}=109Nm) and also it has got a good antiproliferative activity against a panel of cancer cell lines. (10) also exhibited favourable in vivo antitumor activity with 66% tumor growth inhibition (TGI) at a dose of 60 mg/kg.



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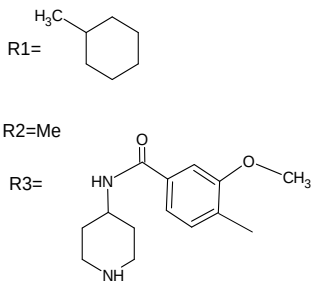
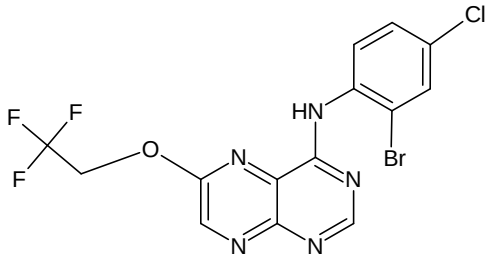


Pteridine derivatives as EGFR inhibitors

Jin Lin *et al.,* synthesized a series of novel pteridine derivatives bearing 2,2,2-trifluoroethoxy groups on position-6 and N-aryl amino or aryloxy groups on position-4[8]. Cellular anti-proliferative activities and inhibition activities on EGFR signalling of target compounds in vitro were determined. Among them compound (11) showed comparable antiproliferative activity and superior inhibition activity on p-EGFR and p-ERK. These observations confirmed that the proliferative activity of (11) against A549 was attributed to inhibition of EGFR phosphorylation and ERK phosphorylation in EGFR signalling pathway.

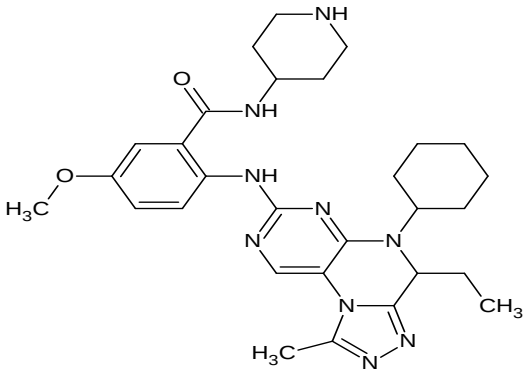


(11)

Pteridine derivatives as BRD4 inhibitors

Jian *et al.,* synthesized a series of 4,5-dihydro-[1, 2, 4] triazolo [4, 3-f] pteridine derivatives[9]. It used to establish 3*D*/2*D*-QSAR models and to discuss the relationship between inhibitor structure and activity. Four ideal models were established, including the comparative molecular field analysis (CoMFA: *q*2 *cv* = 0.574, *rncv*2= 0.947) model, comparative molecular similarity index analysis (CoMSIA: *q*2 *cv*= 0.622, *rncv*2 = 0.916) model, topomer CoMFA (*q*2 *cv* = 0.691, *rncv*2 = 0.912) model and hologram quantitative structure–activity relationship (HQSAR: *q*2 *cv*= 0.759, *r*2 *ncv*= 0.963) model. The analysis results are helpful to promote the modification of the inhibitor framework and to provide a reference for the construction of new and promising BRD4 inhibitor compounds.

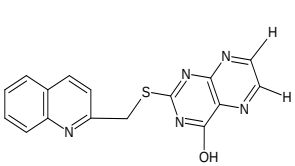
Ning *et al.,* designed and synthesized 4,5-dihydro-[1,2,4]triazolo[4,3-f]pteridine derivatives[10]. Subsequent targets affinity screen and antiproliferative activity test led to the discovery of the most potent dual PLK1/BRD4 inhibitor(12)with good potency for both PLK1 (IC_{50}= 22 nM) and BRD4 (IC_{50}= 109 nM) as well as favourable antiproliferative activity against a panel of cancer cell lines.



(12)

Other anti-cancer activities of pteridine derivatives

Chauhan *et al;* synthesized novel pteridine analogues and tested invitro against 3 cancer cell lines, MCF7 (breast), NCI-H460(lung) and SF-268(CNS). From this, compounds (13), (14), (15) and (16) shown some inhibiting effect on growth of cell lines. These pteridine analogues can serve as novel templates for anticancer chemotherapy and can be new leads in cancer chemotherapy.



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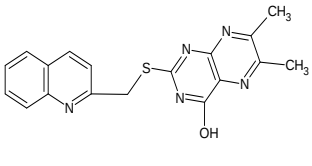

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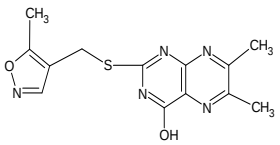

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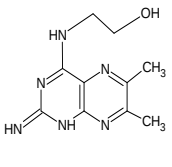
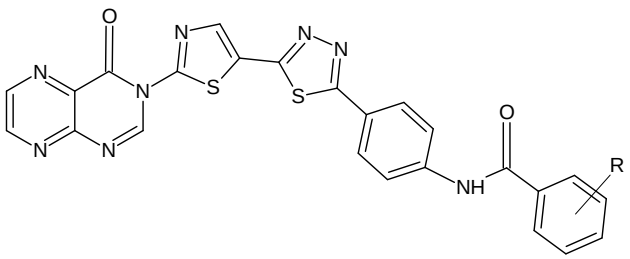


(16)

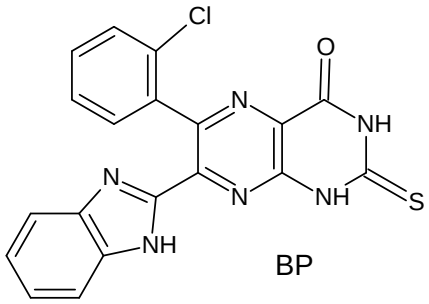
Eeduri et al; designed and synthesized a series of amide derivatives of pteridones[11].

These derivatives were tested for their anticancer activity on 4 human cancer cell lines including MCF-7(breast), A549 (lung), Colo-205(colon) and A2780(ovarian), Etoposide is used as the positive control. Among them 5 compounds namely (17), (18), (19), 920) and (21) showed the most promising activity than the Etoposide.



17:R-3,4,5-trimethoxy.
18:R-4-methoxy
19:R-4-nitro
20:R-3,5-dinitro
21:R-3-nitro-4-chloro

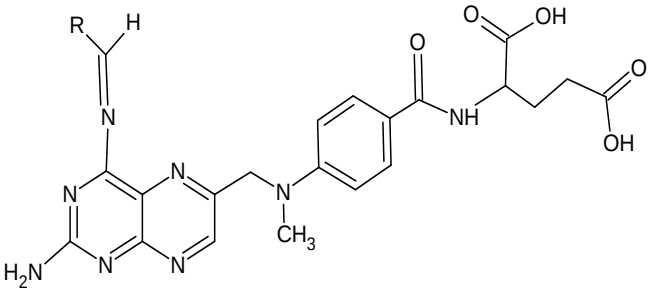
Mirgorodskaya et al; synthesized new conjugated derivative of pteridine and benzimidazole[12]., i.e; 7-(benzimidazol-2-yl)-6-(2,4-dichlorophenyl)-2-thioxo-2,3-dihydropteridin-4(1H)-one [BP] (22). It was shown that the liposome with encapsulated BP have cytotoxicity toward M-Hela tumor cells at the level of commercial doxorubicin drug, but are less toxic (37 times) to the normal Chang liver cell line.



BP

(22)

Aifa Nemat *et al.,* developed active MTX Schiff base derivatives by treating MTX with several aldehydes viz 2-chlorobenzaldehyde, 3-nitrobenzaldehyde, 5-chloro-2-hydroxybenz-aldehyde, 2-hydroxy-5-nitrobenzaldehyde, 2-thiocarboxyaldehyde, trans-2-pentenal and glutaraldehyde[13]. Newly synthesized derivatives were evaluated for their anticancer potential against human malignant glioma U87(MG-U87) cell lines at different concentrations of 200 µM, 100 µM, 50 µM, 25 µM, 12.5 µm, 6.25 µm and 0µM. MTX derivatives with 2-Chlorobenzaldehyde (IC_{50}=100 µM) (23), 2-Thiocarboxyaldehyde (IC_{50}< 200µM) (24) and 2-Pentenal (IC50 = 250 µM) (25) showed much better activity at 100 µM compared to 400 µM concentration of MTX.



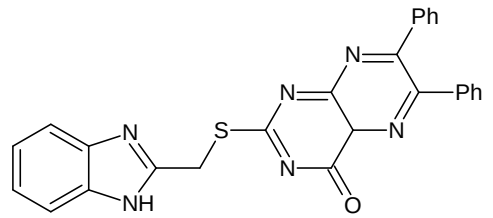
(25)

(23):R=2-Chlorobenzaldehyde

(24):R=Thiophenecarboxyaldehyde

(25):R=Trans-2-Pentenal.

Mahmoud Ali *et al.,* synthesized a series of new 2-Het-arylsulfanyl 6,7-diphenylpteridin-4(3*H*)-one[14]. The newly synthesized compounds were tested in vitro on human breast cancer cell line (MCF7) and colon cancer cell line (HCT116). Compounds (26), (27) and (28) exploited potent antitumor activity, with IC50 between 6.2-8.0 µg/mL. These results suggested that the thioether moiety attached to methylene group is preferred than that attached directly to the heterocyclic compounds



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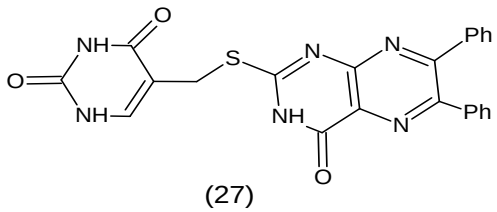

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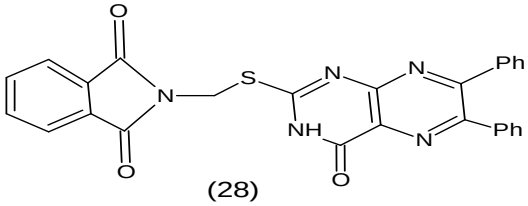
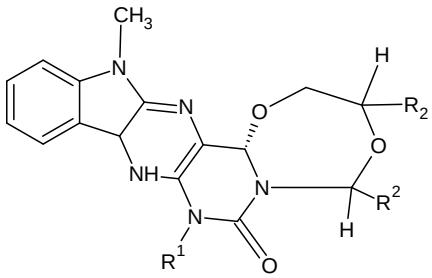


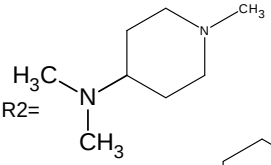
(28)

Kalman *et al.,* synthesized 3,5-Dialkylamino substituted *8H,lOH,15b(S)-2,3,6,7-tetrahydro-l,5,3-dioxazepino [3,2-c]indolo[3,2-*g]pteridine-7-one derivatives[15] (29-33). Preliminary results showed that they were active as inhibitors of the growth of murine Leukemia L1210 cells in vitro with IC_{50}-values of 4 to 24 µM. Ellipticine was used as the positive control.

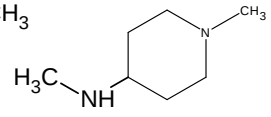
Compound	IC_{50}
29	16
30	6
31	24
32	4
33	20
Ellipticine	0.5



29 R1=H, R2=$CH_2N(CH_2CH_3)_2$
30 R1=CH_3, R2=$CH_2N(CH_2CH_3)_2$
31 R1=CH_3,R2=$CH_2N(CH_3)(CH_2)_3N(CH_3)_2$



32 R1=CH_3, R2=



33 R1=CH_3, R2=

CONCLUSION

Pteridine-derived compounds are important selector of many physiological and pathological processes, as evidenced from various literatures, over the past several years. The conservation of pterin structure throughout prokaryotic and eukaryotic cells leads to the probability of new and not yet discovered roles for these molecules.

As shown in this review, the range of target molecules of pteridine-based compounds are increasing and thus, the corresponding range of applications as anti-cancer agents is currently enlarging. In this consideration, although not many potent drugs having pteridine structure have reached clinical trials and pharmaceutical use, it is also obvious that, in recent years, several investigations have made important contributions in the field of research.

The accumulated evidence on the anti-cancer activity of the pteridine-derivatives reviewed here shows that the development of new synthetic methods and novel potent derivatives will guarantee remarkable proceedings in the pharmacological application of these compounds.

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