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In vitro assessment to evaluate the anti-thyroid potential of selected carbazole derivatives

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Abstract

Carbazole compounds provide substantial advantages in the quest for innovative and efficient anticancer therapies. Recently, scientists have successfully synthesized a range of carbazole molecules to develop potent medications for the treatment of cancer. The objective of this study was to assess the antithyroid properties of two carbazole derivatives, specifically 7-Chloro-1,4-dimethyl-9H-carbazole (26h/CDC) and N-[(1R)-6-chloro-2,3,4,9-tetrahydro-1H-carbazol-1-yl]. The compound -2-pyridine carboxamide (14h / CTCP) was subjected to in vitro testing on cell lines derived from anaplastic thyroid cancer (ARO and FRO) and papillary thyroid cancer (BHP 7-12 and TCP1). The study findings indicate that compound CDC is substantially more effective than propylthiouracil, a standard antithyroid medication. This is particularly evident in our in vitro studies, where compound CDC demonstrated IC50 values of 10.1 µg/ml, 5.8 µg/ml, 6.2 µg/ml, and 11.43 µg/ml against TPC1, BHP 7-12, ARO, and FRO cell lines, respectively. To establish a foundation for the development of effective therapeutic drugs based on this molecule, it will be essential to carry out further preclinical and clinical research.

Keywords:Antithyroid, Carbazole derivatives, Hyperthyroidism, MTT assay

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1. Introduction

Antithyroid drugs are largely thionamides and iodides. Propylthiouracil and methimazole are the most prescribed thionamides. They inhibit thyroid peroxidase, which makes T4 and T3. Methimazole is preferred to PTU because of its longer duration of action and fewer side effects, but congenital defects may require PTU in the first trimester. PTU slows peripheral T4 to T3 conversion, making it indicated in thyroid storms [1]. Preoperatively, potassium iodide reduces hormone release to shrink the thyroid gland and vascularity. They are quick to respond, which makes them excellent acute managers. Patients suffering from hyperthyroidism, such as toxic multinodular goiter, Graves' disease, and toxic adenoma, can be treated with antithyroid medicines. Over time, they ease symptoms and restore thyroid function [2]. Because they prevent the body from producing thyroid hormones, antithyroid medications are an essential component in the treatment of hyperthyroidism [1]. These pharmaceuticals, which include ethionamides like methimazole and propylthiouracil, as well as iodine-containing substances like potassium iodide, exert their effects by inhibiting the enzyme hydroperoxides, which is responsible for the production of thyroid hormones to begin with [2]. After oral administration, these pharmaceuticals are effectively absorbed, according to pharmacokinetic studies. However, their half-lives and peak plasma concentrations differ, which can have an impact on dosage regimens and the possibility of interactions with other medications. A better understanding of their mechanism of action and their effectiveness in inhibiting the generation of thyroid hormone can be gained through pharmacodynamic studies [3]. During the monitoring of efficacy, thyroid hormone levels and thyroid-stimulating hormone are evaluated to determine how well the medication is working and whether or not the symptoms have been resolved. Agranulocytosis, hepatotoxicity, and rash are some of the side effects that may be brought on by these medications [4]. However, these medications are not risk-free medicines. Patients are therefore required to undergo close monitoring, which may include routine blood testing, to identify and treat any potential issues that may arise. When it comes to

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pregnant women, in particular, extra considerations are required since the safety of antithyroid medications needs to be carefully evaluated to strike a balance between the health of the mother and the well-being of the unborn[5]. When it comes to the therapy of hyperthyroidism, making sure that antithyroid medicines are used in a way that is both safe and successful requires a full biological review[6]. Performing research on non-living subjects, typically through the utilization of isolated tissues, cells, or biochemical assays, is the process that is referred to as antithyroid medication evaluation in vitro [7]. In light of these findings, significant new insights into the pharmacological properties, mechanisms of action, and potential toxicity of antithyroid medications have been established [8].

One of the most common in vitro methods involves the utilization of cell culture systems to subject thyroid cells or cell lines to antithyroid drugs and then subsequently evaluate the effect of these medications on the production and secretingof thyroxine [9]. In the case of thyroid follicular cells, for instance, researchers might make use of animal models or human cell lines such as FRTL-5 or TPC-1. Measures such as iodine absorption, thyroglobulin synthesis, and thyroid peroxidase activity are some of the things that researchers can monitor to evaluate the efficacy of antithyroid medicines and determine the mechanism of action by which they restrict theproductionofthyroid hormones [10].

One other method that is utilized in vitro to examinehow antithyroid drugs interact with specific molecular targets that are involved in the production of thyroid hormone is known as biochemical tests [11]. Antithyroid drugs, for instance, can inhibit thyroperoxidase, which is the enzyme responsible for iodating thyroglobulin [12]. " With the help of enzyme inhibition tests, researchers can evaluate this. By assessing the degree of enzyme inhibition, researchers can determine the efficacy and selectivity of several different antithyroid drugs [13].

The in vitro evaluations of antithyroid drugs are vital for assessing their safety profiles, in addition to

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the pharmacodynamics of these medications. To determine the extent to which cytotoxic antithyroid medicines are harmful to thyroid cells or other cell types that are important, cell viability experiments, for example, can be carried out [14]. In addition, the use of in vitro research, which provides essential information for risk assessment and mitigation strategies, might be utilized to discover off-target effects or unfavorable responses that are associated with antithyroid medications [15].

In vitro, evaluation of antithyroid pharmaceuticals offers a method that is both regulated and cost-effective for examining the pharmacological characteristics and safety profiles of these agents. This type of evaluation helps to complete the picture of the therapeutic potential and limitations that are associated with in vivo research [16].

One of the most obvious characteristics that can be observed in a variety of natural sites is the carbazole nucleus, which is also a trait that is shared by a large number of biologically active substances [17]. To induce apoptosis and halt the progression of the cell cycle, carbazole compounds have been shown to have powerful antiproliferative effects against a wide variety of cancer cell lines. In addition, certain medications that are used to combat cancer are composed of compounds that are derived from carbazole (19). In the search for novel and potent anticancer medicines, carbazole derivatives are useful agents that can be utilized [19]. A variety of carbazole hybrids have recently been created by researchers to develop them into anticancer medications that are extremely effective [20]. This review examines the advancements made in comprehending the anti-cancer properties, structure-activity relationships, and mechanisms of action of carbazole hybrids, with a specific emphasis on the period from 2016 to the present. This will lay the groundwork for the development of therapeutic medications that are both effective and efficient.

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2. Methodology

In the previous study,we investigated the ability of heterocyclic chemicals to regulate thyroid function. We have developed compounds that are designed to interact with targets involved in the generation and regulation of thyroid hormone by making modifications to existing heterocyclic scaffolds [21]. We utilized molecular docking simulations to assess the binding affinities of these drugs to thyroid receptors, specifically thyroid peroxidase (TPO) and thyrotropin receptor (TSHR). The compounds that were created had favorable interactions, indicating their potential as medicines that can counteract the effects of thyroid hormones. More precisely, compounds 26h and 14h exhibited a notable affinity for binding, which resulted in the inhibition of TPO's activity and a decrease in the generation of thyroid hormones.Furthermore, Compound 14h had a remarkable binding affinity of -10.6 kcal/mol on 1XZX, surpassing that of the ligand[22].

2.1 General Procedure for the Preparation of 7-chloro-1,4-dimethyl-3-nitro-9H-carbazole (CDC or 26h)

An indole derivative 1a solution in 10 mL of ethanol was gradually supplemented with 0.70 mL of acetylacetone (equivalent to 6.00 mmol) and p-toluene sulphonic acid (equivalent to 6.00 mmol), with constant stirring. In addition, the mixture was vigorously mixed on multiple occasions. I used a vacuum to condense the reaction mixture after subjecting it to reflux for six hours. A mixture of 7.25 mL of acetic anhydride and 0.27 mL of fuming nitric acid was slowly added to a cooled solution of 20 mL of dichloromethane that contained 4.35 mmol of 7-Chloro-1,4-dimethyl-9H-carbazole (4.35 g/mL). Pouring the reaction mixture onto crushed ice after five minutes allowed the pH level of the solution to drop to nine, followed by the addition of a solution containing one million sodium hydroxides, bringing the pH level down to eight. Flash chromatography was used to improve the purity of the crude product after it had been filtered. [23].

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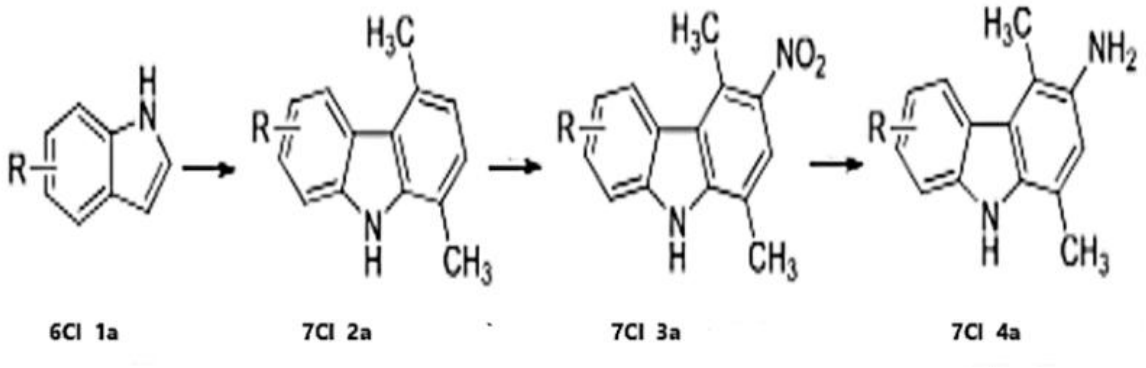

Figure 1: Synthesis of 7-Chloro-1,4-dimethyl-9*H*-carbazole (CDC)

2.2General Procedure for the Preparation of N-[(1R)-6-chloro-2,3,4,9-tetrahydro-1H-carbazol-1-yl]-2-pyridinecarboxamide (14h / CTCP)

The synthesis is particularly notable for the separation of the 2-picolinic acid salt of (1R)-6-chloro-2,3,4,9-tetrahydro-1Hcarbazol-1-amine. Using 1-propylphosphonic acid cyclic anhydride (T3P) in the straightforward synthesis of amides from the two salt components allows for the production of a significant amount of product 14h / CTCP. The research process consists of several stages that ultimately lead to the synthesis [24]. The resolution method involves a racemic synthesis as the initial step, followed by chiral supercritical fluid chromatography as the subsequent phase. Utilizing Ru(II) complexes of N-[(1S,2S)-2-amino-1,2-diphenylethyl] as catalysts enables the achievement of enantioselective reductive amination through chiral transfer hydrogenation.

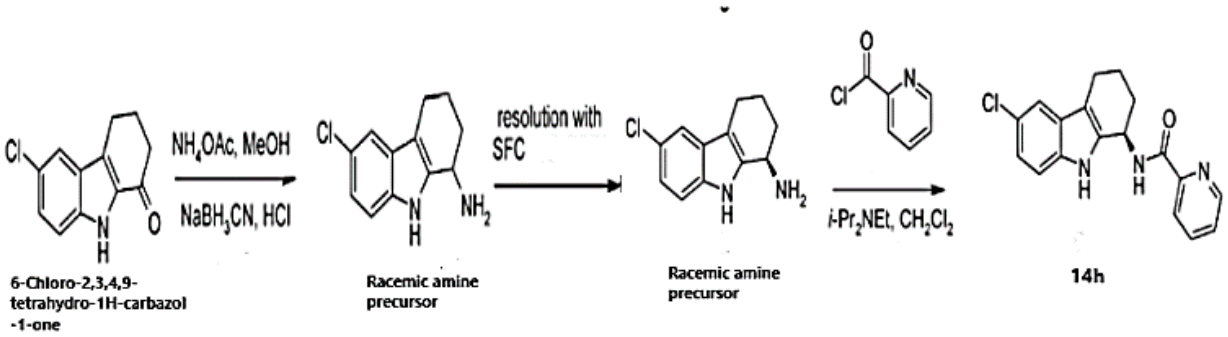

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Figure 2:Synthesis of N-[(1R)-6-chloro-2,3,4,9-tetrahydro-1H-carbazol-1-yl]-2-pyridine carboxamide (14h / CTCP)

2.3In-vitro cytotoxic activity using MTT assay

Tetrazolium dye-based tests are used to measure the cytotoxic or cytostatic effects of therapeutic bioactive substances or hazardous chemicals. Due to the light sensitivity of the MTT reagent, it is standard practice to perform assays in a dark setting. Both benign and malignant cell lines were cultured in a medium containing inactivated fetal bovine serum (FBS) at a concentration of 10%, coupled with 100µl/ml streptomycin and 100µl/ml penicillin. The specimen was placed in a moist incubator and subjected to incubation at a temperature of 370 degrees Celsius, within an atmosphere containing 5% carbon dioxide. After the cell attained a convergence of 70%, it was then moved to a solution containing 0.25% trypsin, following rigorous sanitary standards [25-27]. The chemicals and the standard were prepared as stock solutions in DMSO with a concentration of micromoles per milliliter. Later, the medium was used to create dilutions of 1µM, 10µM, 20µM, 50µM, and 100µM per ml. Cells were distributed onto 96-well plates by placing 5×103 cells in each well, with a volume of 100µl per well. Upon examining the growth parameters of each cell line, the density of each cell line was computed. After an incubation period of eight hours, three sets of wells were exposed to different concentrations of synthesized compounds, ranging from 0.1 to 1000µg/ml, for a duration of three days. After three days of treatment, the medium was substituted with 3µl of MTT solution, which had a concentration of 5mg/ml. The incubation period was subsequently prolonged to 4 hours [26]. The metabolic activity of cells was compared to untreated controls by employing the mitochondrial conversion of 3-(4, 5-dimethylthiazol-2-yl) 2, 5 diphenyltetrazolium bromide (MTT) to generate formazan crystals. The proportion of cells that were metabolically active was compared to the proportion of cells that were not treated. Once the formazan crystals were dissolved in DMSO, the absorbance of the crystals was measured using a microplate reader (BIO-RAD) at a wavelength of 570

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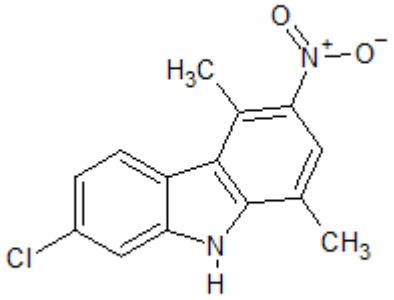
nm [26]. The synthesized compounds were evaluated for their anticancer activities using propylthiouracil. The MTT assay was conducted on the ARO and FRO cell lines, associated with anaplastic thyroid cancer, and the BHP 7-12 and TCP1 cell lines, associated with papillary thyroid cancer, as part of the investigation of medicinal treatments.

3. Results and Discussion

The current work produced the carbazole derivatives 2a using the method outlined by Cranwell and Saxton. The compounds were derived from the indoles 1a, which were readily accessible on the market. The intermediates were converted into the nitro derivatives 3a with a high yield of 81%. However, the yield was subsequently reduced using stannous chloride. Therefore, the compound 7-Chloro-1,4-dimethyl-9H-carbazole (CDC) was generated. Compound 26h, known as 7-Chloro-1,4-dimethyl-9H-carbazole (CDC) in scientific terms, was discovered via molecular docking modeling. This chemical exhibited a notable affinity for binding, resulting in the inhibition of TPO's activity and a decrease in the synthesis of thyroid hormones. To ascertain its antithyroid characteristics, it was manufactured.



26h

Figure 3: Compound 26h/CDC

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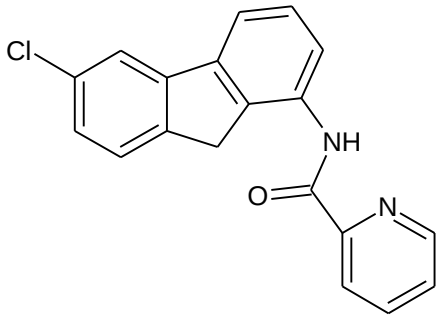
The results of our inquiry reveal an exceptionally effective (yield of 75.6%) method for synthesizing N-[(1R)-6-chloro2,3,4,9-tetrahydro-1H-carbazol-1-yl]. The compound is designated as 2-pyridine carboxamide. The manufacturing of this drug involves a vital step called asymmetric reductive amination, which is guided by chiral (phenyl)-ethylamines. This level demonstrates a disastereo facial selectivity of 96% according to Bogg's et al. (2007). Compound 14h displayed a notable binding affinity of -10.6 kcal/mol on 1XZX during the molecular docking simulation, surpassing that of the ligand. Consequently, it was assessed for its capacity to impede the synthesis of thyroid hormones.



14h

Figure 4: Compound 14 h/CTCP

In this study, we evaluated the antithyroid effects of three drugs, namely prop, compound 26h, and compound 14h, using the MTT assay on anaplastic thyroid cancer cell lines (ARO and FRO) and a papillary thyroid cancer cell line (TCP1 and BHP 7-12). In vitro experiments using Figure 5 and 6 and Table 1 indicated that the chemicals CDC/26h and CTCP/14h inhibited the growth of anaplastic thyroid cancer cell lines (ARO and FRO) as well as a papillary thyroid cancer cell line (TCP1 and BHP 7-12). Living cells have mitochondrial dehydrogenase. It degrades the tetrazolium ring structure of the MTT dye, which has a light-yellow color, and produces dark purple crystals known as formazan. Due to their inability to traverse cell membranes, these crystals accumulate within the cells. The synthesized compounds exhibited enhanced inhibitory effects on the proliferation of the cell line in

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comparison to the standard drug propylthiouracil. Table 1 displays the IC50 values (in µg/ml) for both the synthesized compounds and the pure medicine. The findings demonstrated that 26h displayed potent antithyroid action, as evidenced by IC50 values of 10.1 µg/ml, 5.8 µg/ml, 6.2 µg/ml, and 11.43 µg/ml against TPC1, BHP 7-12, ARO, and FRO cell lines, respectively. The activity of this compound was more significant compared to pure propylthiouracil. The IC50 values for pure propylthiouracil against the same cell lines were 44.89 µg/ml, 35.21 µg/ml, 28.77 µg/ml, and 30.41 µg/ml, respectively.

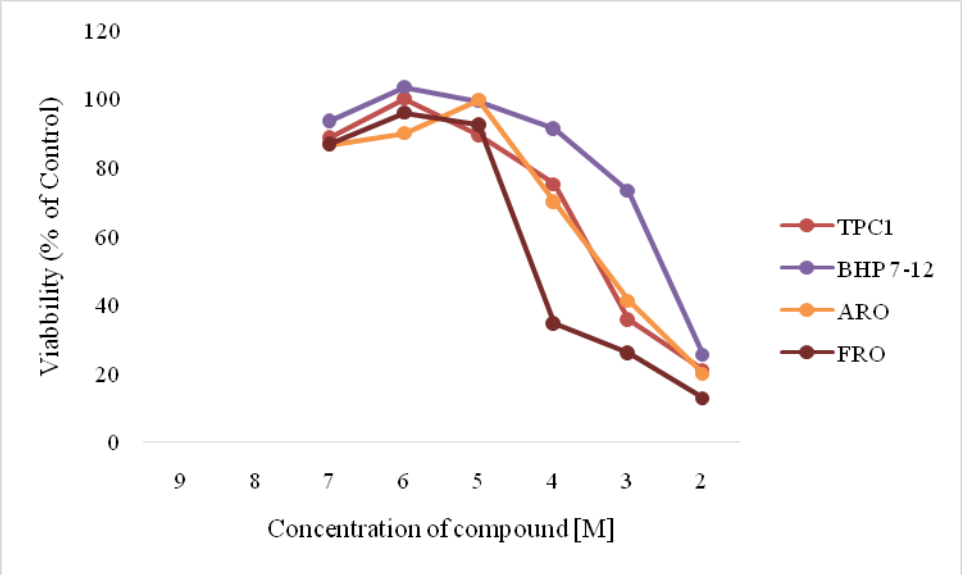

Figure 5: MTT Assay of compound 26h/CDC

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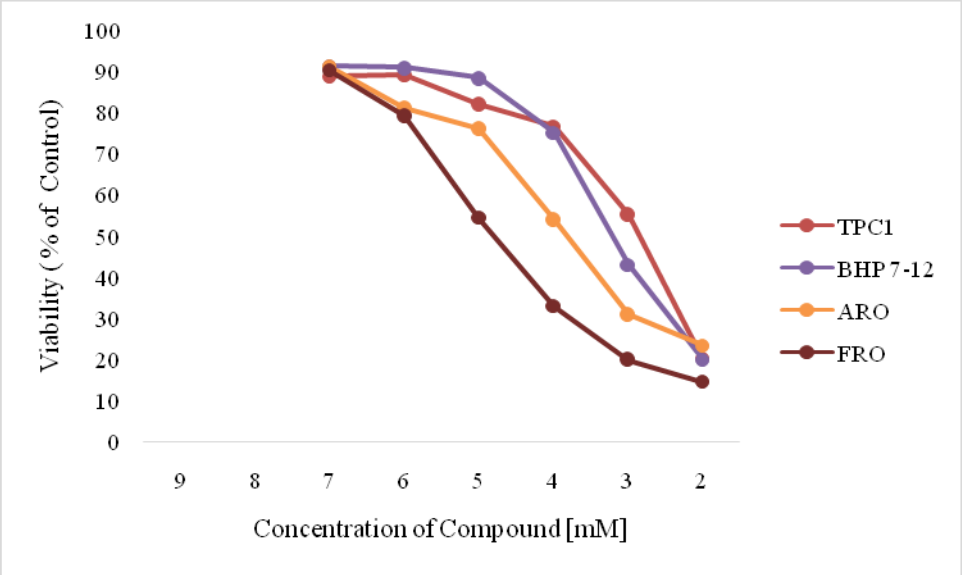

Figure 6: MTT Assay of compound 14h/CTCP

Table 1:The IC50 values (µg/ml) of compound 26h and 14h along with pure drug propylthiouracil

Sample	TPC1	BHP 7-12	ARO	FRO
	IC50	IC50	IC50	IC50
Propylthiouracil	44.89	35.21	28.77	30.41
26h/CDC	10.1	5.8	6.2	11.43
14h/CTCP	14.3	7.66	8.10	12.27

In 1999, Hirata et al. [29] produced a variety of N-alkyl-pyrido[4,3-c] carbazoles by synthesizing 2-hydroxy-9H-carbazole-3-carbaldehyde (mukonal), a chemical derived from Rutaceous plants. These chemicals possess a comparable chemical composition to the anticancer alkaloid Ellipticine and its artificially produced alternatives. They underwent testing to ascertain their efficacy as antiviral

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medications. In 2006, Gopalsamy et al. did a study on a collection of compounds that has the ability to hinder the activity of RNA polymerase. The compounds possess a framework composed of a 2,3,4,9-tetrahydro-1H-carbazole structure [31]. In 2009, Harvey et al. presented a comprehensive description of a unique antiviral compound called GSK983, which has the chemical formula N-[(1R)-6-chloro-2,3,4,9-tetrahydro-1H-carbazol-1-yl].The compound is identified as 2-pyridine carboxamide. This chemical demonstrated a unique and broad range of antiviral activity. GSK983 shown strong antiviral effectiveness in laboratory tests, successfully inhibiting the replication of several viruses. The documented EC50 values varied between 5 and 20 nM. The specified viruses consist of adenovirus Ad-5, polyomavirus SV-40, human papillomaviruses (HPV) with episomal maintenance, and Epstein-Barr virus (EBV). In 2018, Saturnino et al. did a study in which they chemically produced several chloro-1,4-dimethyl-9H-carbazoles. Subsequently, these compounds were assessed in TZM-bl cells that exhibited CD4, CXCR4, and CCR5. Several chemicals demonstrated a considerable degree of efficacy against viruses. Furthermore, Chaudhary and Chaudhary (2016) discovered that the newly created compounds, J-3 (1-(4-bromophenyl)-3-1(1,2,3,4-tetrahydro-9H-carbazole-9yl)propan-1-one) and J-4 (1-(4-nitrophenyl)-3-1(1,2,3,4-tetrahydro-9H-carbazole-9yl)propan-1-one),demonstrated significant anti-cancer properties when tested against the A-549 cell line at concentrations of 1000µg/ml, 500 µg/ml, and 250µg/ml [32]. Therefore, the carbazole nucleus is an essential feature found in a diverse array of very effective compounds that have shown strong inhibitory effects on multiple cancer cell lines through various mechanisms, such as arresting the cell cycle and inducing apoptosis[33].

Conclusion

Carbazole compounds are highly advantageous in the search for innovative and efficient anticancer therapies. Researchers have recently achieved the synthesis of a diverse array of carbazole hybrids to

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convert them into highly potent cancer-fighting medications. In the present investigation, we investigated the antithyroid activity of two carbazole derivatives, namely CDC and CTCP, using in vitro testing. According to the results of our research, compound CDC is an antithyroid agent that is quite effective, particularly in vitro trials, when compared to standard medication. To create the framework for the creation of successful therapeutic medications derived from this molecule, it will be necessary to conduct additional preclinical and clinical investigations.

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