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Selective Cytotoxic Activity of a 5-BromoIndole Carbothioamide (BTIC) Against Human Cancer Cell Lines

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ABSTRACT

Objective: The goal of this study was to determine the cytotoxic and specific anticancer effects of a novel 5-bromo-indole-derived carbothioamide (BTIC) on several malignant and non-cancerous cell lines.

Methods: After a 48-hour treatment, BTIC's antiproliferative effectiveness against human breast cancer (MCF-7), lung cancer (A549), & normal endothelium (HUVEC) cell lines was evaluated using the MTT assay. Data shown as dose-response curves were subjected to nonlinear regression analysis to determine IC_{50} values. Preferential cytotoxicity was evaluated using the selectivity index (SI).

Results: In every cell line examined, BTIC had a cytotoxic impact; furthermore, this toxicity was concentration-dependent. This compound exhibited the most powerful activity against A549 cells (IC_{50} = 3.5 µg/mL), followed by MCF-7 cells IC_{50} (5.4 µg/mL), and significant cytotoxicity was recorded in HUVEC cells (IC_{50} = 10.4 µg/mL). A selective cytotoxicity on cancer cells was suggested by these reported SI values (2.97 and 1.93 for A549 and MCF-7, respectively).

Conclusions: BTIC was also a lead chemical with potent anticancer action against lung cancer cells in vitro, which exhibited high specificity. Therapeutic translation requires additional mechanistic and in vivo studies.

Keywords: ***A549 cells, Carbothioamide derivatives, Cytotoxicity, MCF-7 cells, MTT assay, HUVEC cells, Selective anticancer activity.***

INTRODUCTION

Despite improvements in chemotherapy and targeted therapies, cancer will continue to rank among the top three causes of morbidity and death worldwide, placing a heavy strain on global health systems [1,2].

One of the major drawbacks associated with conventional anticancer therapeutics is their low selectivity, which causes severe toxicity to normal tissues, affecting therapeutic efficacy [2,3].

Therefore, one of the main goals of modern oncology research is to develop novel anticancer medications with strong cytotoxic effect and exceptional selectivity for malignant cells [4].

Indole derivatives are naturally occurring and advantageous chemicals that have demonstrated various biological actions over a wide range of structural changes among the group of heterocyclic scaffolds [5,6].

A common characteristic of many synthetic and natural anticancer drugs is the favored pharmacophore indole nucleus. Cell cycle arrest, apoptosis induction, inhibition of key enzymes, including topoisomerases [3,7], and alteration of carcinogenic signaling pathways are only a few of the biological impacts of these compounds. Shanghai 15:1. Chemical modifications on the indole scaffold have been documented with carbothioamide moieties significantly increasing selectivity for and potency at malignant cells to serve as viable next-generation chemotherapeutics [7,8].

However, the evaluation of selectivity in both cancer and non-cancer cell models is an underused but critical component for identifying therapeutic indices and limiting off-target toxicity [1].

The compound that was studied in this work is a new carbothioamide (BTIC) derived from 5-bromo-indole, previously synthesized and structurally characterized [9].

Although CHM-25 is a dual-acting, strong cytotoxic and selective MEK0 inhibitor, nothing is known about its selectivity profile and probing cytotoxic efficacy. Before it becomes a lead for an anticancer medication, this gap must be filled. Therefore, the goal of this investigation was to assess the cytotoxic as well as specific anticancer effects of BTIC in vitro models of normal endothelial cells (HUVEC), lung cancer (A549), and human breast cancer (MCF-7).

This study quantifies the therapeutic potential of this compound by measuring IC_{50}, calculating selectivity indices, and laying the groundwork for future mechanistic studies and preclinical applications.

MATERIALS AND METHODS

Materials

Reagents and Chemicals

The analytical-grade chemicals and reagents for this study included PBS, amphotericin B, penicillin–streptomycin solution, DMSO (dimethyl sulfoxide), and MTT reagent [3-(4,5-dimethyltiazol-2-yl)-2,5-diphenyltetrazolium bromide (Moss Inc.)] from Sigma-Aldrich [Germany]. Gibco, USA: Dulbecco Modified Eagle Medium (DMEM), Endothelial cell growth medium (ECM), and Fetal bovine serum (FBS). The analytical grade reagents all arrived in a manner that was entirely unscathed.

The test substance, 2-(5-bromo-1H-indole-2-carbonyl)-N-(p-tolyl)hydrazine-1-carbothioamide (BTIC), was created by the Department of Pharmaceutical Chemistry at the College of Pharmacy/University of Baghdad. Previously, this molecule was produced and semi-purified [9]. Complete culture media was used to dilute a stock of BTIC (in DMSO) to the chosen working concentrations. In order to rule out any possible solvent-released cytotoxicity, the final DMSO doses employed in all treatments did not exceed 0.1% (v/v).

Cell Culture

The American Type Culture Collection, USA, provided human umbilical vein endothelial cells (HUVEC), human lung cancer (A549), and human breast adenocarcinoma (MCF-7). MCF-7 & A549 cells were kept in DMEM with 1% penicillin-streptomycin and 10% fetal bovine serum. The company states that HUVEC cells were grown in endothelial cell growth medium (ECM) that was enhanced with a variety of growth agents. They were subcultured and incubated at 37°C in a humidified environment with 5% CO2 after they reached a confluence of 70–80%. Every experiment employed cells that were in the exponential growth phase [10].

Cell Viability Assay (MTT Assay)

The MTT test was used to evaluate cell viability. To put it briefly, 1×10^3 cells were added to each well of the 96-well plates, and the cells were allowed to adhere overnight. For 48 hours, cells were exposed to progressively higher BTIC concentrations (3.125–100 µg/mL). Control wells received culture medium that contained 0.1% DMSO. Each well received 20 µL of MTT solution (5 mg/mL in PBS) following treatment. After that, the mixture was incubated for four hours at 37°C. The formazan crystals were dissolved in 100 µL of DMSO following the careful removal of the media [11,12]. A microplate reader was used to measure the absorbance at 570 nm. The following formula was used to determine cell viability:

$$Cell\ inhibition\ (\%) = 1 - \{(A0/A) \times 100\}$$

(A0 = Absorbance of sample and A = Absorbance of control)

Dose–Response Analysis and IC_{50} Determination

Analyzed data with a four-parameter logistic (4PL) model in GraphPad Prism (version 7.0): nonlinear regression analysis (log[inhibitor] vs. response was used to generate the dose response curves. Concentration to fully decrease the cell viability was used to calculate IC_{50} values.

Selectivity Index (SI)

Selection index (SI), defined as the ratio of the IC_{50} in normal vs cancer cells, is a critical metric for determining the therapeutic selectivity of anticancer drugs [13,14]. They computed it using the following formula:

$$SI = IC_{50}\ (normal\ cells) / IC_{50}\ (cancer\ cells)$$

The selective antitumor activity of BTIC was evaluated against the normal cell lines based on this metric.

Statistical Analysis

All tests were performed independently of each other, minimum three times and twice. They show the mean ± SD. Statistical evaluations. Statistical analysis was performed using one-way analysis of variance (ANOVA),

and for multiple comparisons, Tukey's post hoc test. Statistical significance was defined as differences with $p < 0.05$. Statistical analysis and graphical representation were performed using GraphPad Prism (version 7.0).

RESULTS AND DISCUSSION

Cytotoxic Effect of BTIC on Cancer and Normal Cell Lines:

After 48 hours of treatment, the MTT test was used to assess the cytotoxic activity of BTIC in both normal endothelial cells (HUVEC) and human cancer cell lines (MCF-7 & A549). Figure 1 depicts the chemical structure of BTIC.

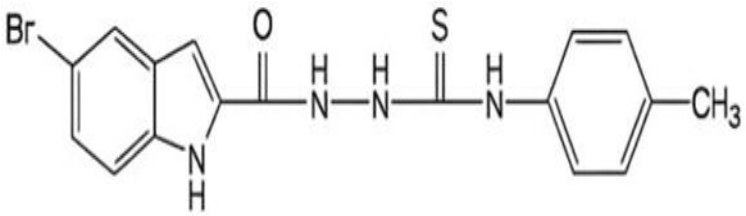

Figure 1: BTIC's chemical structure (2-(5-bromo-1H-indole-2-carbonyl)-N-(p-tolyl)hydrazine-1-carbothioamide).

BTIC clearly reduced cell viability across all examined cell lines in a concentration-dependent manner, as seen in Figures 2-4. As the compound's concentration increased, a steady decline in viability was seen, suggesting an unusual dose-response relationship.

A549 cells exhibited the highest sensitivity to BTIC treatment (Figure 2), followed by MCF-7 cells (Figure 3), whereas HUVEC cells showed relatively lower sensitivity (Figure 4).

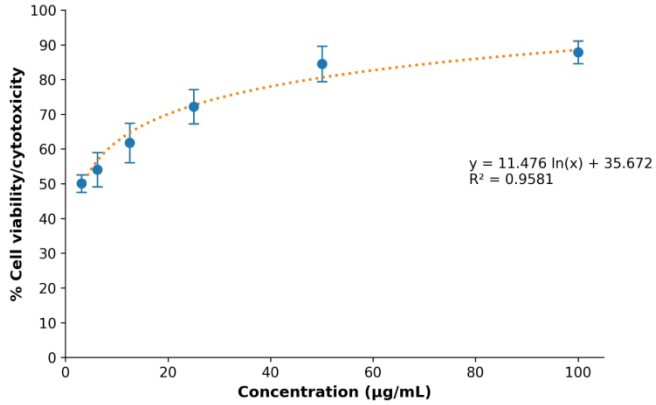

Figure 2: BTIC dose-response curve in A549 cells following treatment for 48 hours. The MTT test was used to measure cell viability, and the results were expressed as mean ± SD (n = 3).

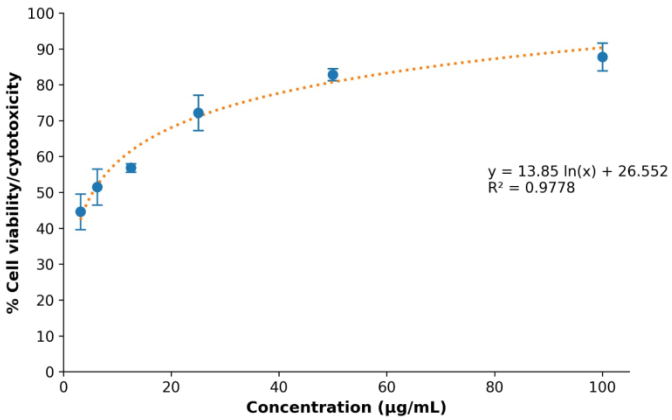

Figure 3: BTIC dose-response curve in MCF-7 cells following a 48-hour treatment. The data show the mean ± SD (n = 3).

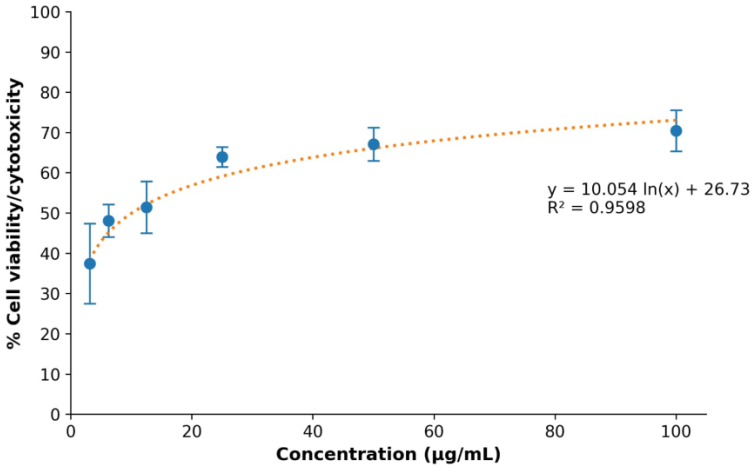

Figure 4: HUVEC cells' BTIC dose-response curve following a 48-hour course of therapy. The values are displayed as mean ± SD (n = 3).

BTIC had the most cytotoxic impact against A549 cells, with an IC_{50} value of 3.5 µg/mL, followed by MCF-7 cells, with an IC_{50} value of 5.4 µg/mL, according to nonlinear regression analysis of the dose–response curves. HUVEC cells, on the other hand, showed much less cytotoxicity, with an IC_{50} value of 10.4 µg/mL. Table 1 provides a summary of these data.

Table 1: Dose-response curves were used to calculate the IC_{50} of BTIC in A549, MCF-7, and HUVEC cell lines. The data are displayed as mean ± SD (n = 3). The ratio of IC_{50} in HUVEC cells to that in cancer cell lines was used to compute the selectivity index (SI).

Cell line	IC_{50} (µg/mL) ±SD	Selectivity Index (SI)
A549	3.5±0.3	2.97
MCF-7	5.4±0.4	1.93
HUVEC	10.4±0.6	—

A one-way ANOVA with Tukey's post hoc test confirmed a substantial drop in cell viability at higher doses compared to control cells ($p < 0.05$). In both cancer cell lines, very statistically significant changes (p 25 µg/mL, but lower concentrations exhibited moderate to non-significant effects, dependent on the cell type tested. A549 cells were most sensitive to BTIC, based on these results followed by MCF-7, and HUVECs were least sensitive.

Selectivity of BTIC Toward Cancer Cells

The toxicity was induced from both HUVEC and surface functionalization of BTIC, then evaluated 10 days after infection in a cancer cell line model selected on the basis of BTIC. The Selectivity Index (SI) value found by dividing the IC_{50} values of A549 and MCF-7 in Table 1 individually was recorded as 2.97 and 1.93, respectively. Compared to the corresponding cancer cell lines, cytotoxicity against normal cells was significantly lower, as evidenced by a higher IC_{50} value in HUVEC (human umbilical vein endothelial cell). This discrepancy was statistically significant ($p<0.05$), further supporting the highly selective antiproliferative effects of BTIC. Certainly, BTIC had the highest selectivity index of any compound we tested in A549 cells over lung cancer vs. breast among the three cell lines presented here, which indicates that actually BTIC is actually only marginally less selective for lung as compared to breast cancer.

Dose–Response Relationship Analysis

These appear as dose – response curves (Figs. In all cases (2-4), responses were characteristic and sigmoidal with the appearance of a pharmacologically relevant response. The more linear the linearity of change from low to high inhibition suggests that nonlinear regression modeling can be used, which indicates that there are reliable experimental data. The shallow and then plateau slope at higher concentrations suggests that BTIC is moderately potent but with a maximal capacity for cytotoxic activity.

Discussion

BTIC is Dose-Dependent and Highly Cytotoxic to Human Cancer Cells: BTIC was shown to have a concentration-dependent nature, which confers powerful cytotoxicity on many human cancer cells (Fig. 2-4). The activity of the compound was higher against A549 (Fig. The 2 $FC_{52}C$ IC50 was calculated as 3.5 µg/mL (Fig 4). Compared to MCF-7 cells: IC50 for cytotoxicity analysis in ATDB cells was higher, with a value of 94.89 µg/mL (range, 18.03–235 $FC_{52}C$; P =0.0032) and much lower than the corresponding value >100 VAB0075 (>100 HUVEC cells: IC50=10.4 µg/mL). The summarized values (Table 1) support a cancer-selective cytotoxicity that is an advantageous feature in anticancer drug design.

Structural Features and Their Impact on Cytotoxic Activity

BTIC structure, as illustrated in Fig., has an indole nucleus connected to a carbothioamide unit as well as bromine substituents that serve as a structural basis for the biological action of this molecule. The indole nucleus has been widely known as a privileged pharmacophore with broad anticancer activity by targeting multiple oncogenic pathways essential for tumor progression [15,16]. The biological activity is greatly increased by the indole ring with the 5-position bromine atom. A method for improving lipophilicity, enhancing membrane permeability, and establishing ligand–target contacts through halogen bonding effects that lead to increased pharmacological activity has been discovered as halogenation [17]. These effects may account for the strong cytotoxic activity to BTIC, particularly in A549 cells (Fig. 2).

Role of Carbothioamide Moiety

The carbothioamide functional group itself is one of the characteristics and is crucial to BTIC's biological action. Antiproliferative and cytotoxic activity of carbothioamide analogue derivatives in different cancer cell models has been demonstrated [18,19]. It can form hydrogen bonds and coordinate interactions with biomolecular targets to improve binding affinity and biological activity [20]. Furthermore, derivatives that provide carbothioamides interfere with essential cell tests, including DNA replication, protein synthesis, and redox balance [21,22]. The observed cytotoxic effects of BTIC across all the treated cell lines (Fig. 2-4).

Proposed Mechanisms of Cytotoxic Action

The specific mechanism was not studied in the present work, but the cytotoxicity indicated that (Fig. Mechanisms for these effects of indole-based compounds (2-4) are discussed based on previously reported mechanisms. It has been suggested that causing mitochondrial malfunction and activating a caspase-dependent pathway is how indole derivatives undergo apoptosis [21]. Inhibiting topoisomerases and interfering with DNA replication is an alternative mechanism that results in cell cycle arrest and stops cell proliferation [23]. Additionally, carbothioamide-containing compounds have been correlated with disruption of important cellular processes, including protein metabolism as well as redox homeostasis [24]. Recently, investigations targeting a few novel derivatives, namely 4-chloro phenyl carbothioamide indole, have proved to show potent antiangiogenic activity acting towards the inhibition of tumor blood vessel formation [19]. The dose-dependent cytotoxic activity reported in this article may be explained by these mechanisms taken together.

Differential Sensitivity Between Cancer and Normal Cells

The dose-response curves (Fig. 2–4) and IC_{50} values (Table 1) amply demonstrate this differential sensitivity of cancer and normal cells. In contrast, normal cells like HUVEC have more effective regulatory machinery, such as improved DNA repair mechanisms and antioxidant defenses, which allow them to withstand these cytotoxic injuries [19,24]. This is one of the reasons why cancer and other rapidly proliferating cells usually have higher rates of proliferation, metabolic activity, and basal oxidative stress, which makes them more susceptible to cytotoxic insults that impair mitochondrial antioxidants. This discrepancy likely accounts for the higher IC_{50} value obtained in HUVEC cells (Fig. 4, Table1).

Rationale for Selection of Cell Lines

This will allow characterization of BTIC belonging to various malignant disorders, where the same physiologically disparate tumor types can be assessed, as shown by their matching response profiles utilizing the cell lines MCF-7 and A549. These are examples of systems that fulfill these parameters (Fig. 2 and Fig. 3). These cell lines differ in their genetic background, receptor regulation, and pathway metabolism; therefore, together with complementary anticancer activity assessment are used [24, 25]. The inclusion of HUVEC cells(Fig. 4) is a non-cancer cell model for defining selective-cell death that will separate the overall cytotoxic activity from the anticancer-selective action.

Selectivity and Therapeutic Implications

As shown by their pairwise matching response profiles across the cell lines MCF-7 and A549, this will enable characterization of BTIC associated with a range of malignant disorders in which tumor types are physiologically

disparate but where cell type effects can be rationally evaluated. Representative systems that satisfy these requirements are shown in Fig. 2 and Fig. 3). These cell lines have different genetic backgrounds and also differ in terms of receptor regulation and pathway metabolism; therefore used along with complementary anticancer activity assessment [24, 25]. The inclusion of HUVEC cells(Fig. 4) is a model of the non-cancer cell, defining selective-cell death, separating the total cytotoxic activity from anticancer-selective action.

Study Limitations

However, a number of restrictions should temper the above-mentioned findings. The study has several drawbacks. First, it was performed only in vitro and may not represent the complexity of biological systems in vivo. Second, there was no experimental validation or exploration of BTIC cytotoxicity molecular mechanisms. The relatively small number of cell lines and the inherent heterogeneity of cancers are additional problems. This will need to be complemented by mechanistic studies in a different cancer model.

Significance and Future Perspectives

In this work, we have performed detailed comparisons of BTIC activity between malignant and non-cancerous cell lines with respect to its cytotoxic and selective anti-cancer potential. The results highlight that, through structural modification (halogenation and carbothioamide introduction), biological activity may be significantly increased while maintaining high selectivity. In summary, additional experiments to elucidate the mechanisms of action on BTIC, validate in vivo and pharmacophore studies, will define better its clinical applicability.

CONCLUSION

Overall, this study demonstrates that BTIC exhibits powerful and concentration-dependent antiproliferative activity in human cancer cell lines. However, it was less toxic for the MCF-7 breast cancer cell line but more cytotoxic against A549 lung cells than it was against normal human umbilical vein endothelial cells (HUVECs) in the MTT assay. Here, the differential response provides a highly beneficial selectivity profile for anticancer drug development. We speculate that the biological activity noted may in part be the consequence of structural moieties affiliated with the indole skeleton present in the binder, and functional groups (e.g., bromine substitution; carbothioamide moiety), which modulate pharmacodynamic interactions and likely cellular absorption. Like other lead compounds, the likely activity of BTIC as an anticancer agent is also very well supported by calculated selectivity indices. However, in vivo benefits, if any, and the mechanism (or mechanisms) of action require further examination. This study provides a solid groundwork for subsequent studies on BTIC as a pharmacological candidate.

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CONFLICTS OF INTEREST

We have no conflict of interest to declare.

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ETHICS STATEMENTS

The institution's reviewing board at Al-Nahrain University's College of Medicine surveyed the comprehensive research and licensed the latest instalment. The study was conducted following the ethical principles outlined in the Declaration of Helsinki. A local ethical board reviewed the research protocol, topic data, and consent paperwork and gave its stamp of approval on 9/10/2023, according to document 20230789.

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السام الانتقائي لمركب 5-بروموإندول كاربوثيوأميد (BTIC) ضد خطوط الخلايا السرطانية البشرية

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[1]قسم الادوية، كلية الطب، جامعة النهرين، بغداد، العراق.

الخلاصة

تُعد السمية المنخفضة الانتقائية للعوامل الكيميائية التقليدية من أبرز التحديات في علاج السرطان، إذ تؤدي إلى تأثيرات سامة شديدة على الأنسجة الطبيعية غير السرطانية. وقد حظيت المركبات المعتمدة على هيكل الإندول باهتمام متزايد بوصفها مرشحات واعدة مضادة للسرطان، إلا أن تحقيق السمية الانتقائية تجاه الخلايا السرطانية ما يزال هدفًا أساسيًا في تطوير العلاجات الحديثة. هدفت هذه الدراسة إلى تقييم الفعالية السمية الخلوية والنشاط المضاد للسرطان لمركب جديد مشتق من الإندول يُعرف بـ 5-(BTIC) bromo-indole-derived carbothioamide ضد عدد من الخطوط الخلوية السرطانية وغير السرطانية. تم تقييم التأثير المضاد للتكاثر الخلوي للمركب باستخدام اختبار MTT بعد تعريض خلايا سرطان الثدي البشري (MCF-7)، وسرطان الرئة (A549)، والخلايا البطانية الطبيعية (HUVEC) للمركب لمدة 48 ساعة. كما تم تحليل منحنيات الاستجابة للجرعة باستخدام تحليل الانحدار غير الخطي لحساب قيم IC_{50}، بالإضافة إلى تقييم السمية الانتقائية باستخدام مؤشر الانتقائية (SI). أظهرت النتائج أن المركب BTIC يمتلك تأثيرًا سميًا خلويًا معتمدًا على التركيز في جميع الخطوط الخلوية المدروسة. وقد سجل المركب أعلى فعالية ضد خلايا سرطان الرئة A549 بقيمة IC_{50} بلغت 3.5 µg/mL، تلتها خلايا سرطان الثدي MCF-7 بقيمة IC_{50} بلغت 5.4 µg/mL، في حين سُجلت سمية خلوية ملحوظة تجاه خلايا HUVEC بقيمة IC_{50} بلغت 10.4 µg/mL. كما أظهرت قيم مؤشر الانتقائية (2.97 و1.93 لخلايا A549 وMCF-7 على التوالي) وجود سمية انتقائية تجاه الخلايا السرطانية مقارنة بالخلايا الطبيعية. تشير هذه النتائج إلى أن المركب BTIC يُعد مركبًا واعدًا يمتلك فعالية قوية ومحددة ضد خلايا سرطان الرئة في المختبر، إلا أن تأكيد إمكانياته العلاجية يتطلب المزيد من الدراسات الآلية والدراسات الحية المستقبلية .

الكلمات المفتاحية: خلايا (A549)، مشتقات الكاربوتيواميد، السمية الخلوية، خلايا (MCF-7)، مقايسة (إم تي تي)، خلايا (HUVEC)، النشاط الانتقائي المضاد للسرطان.