



1,3-Dipolar Cycloaddition: Free Catalytic Synthesis and Esophageal Cancer Activity of New 1,2,3-Triazole-Oxydianiline-Maleimide Hybrids



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Abstract

A new series of 1,2,3-triazole-oxydianiline-maleimide hybrids **12-15** was synthesized by using 1,3-dipolar cycloaddition reaction of *N*-Arylmaleimides **6-9** with 4,4'-oxybis(azidobenzene) **11** under an efficient and free catalytic reaction. All the newly synthesized hybrids were characterized by their ¹H NMR, F-TIR, Mass spectral data and melting points. The cytotoxic activities (*in vitro*) of selected hybrids against esophageal cancer of human cell line (SKG) were evaluated by MTT assay. Among them, hybrid **13** exhibited a potent inhibition activity with the IC₅₀ value of 1.61±0.01 μM against esophageal cancer cell (SKG). Cellular mechanism investigations in esophageal carcinoma cells (SKG) elucidated that hybrid **13** inhibited cell growths *in vitro* and arrested cell cycle at an environmental phase. These results revealed that hybrid **13** holds a promising anticancer agent with the enhancement of further clinical applications in drug discovery field.

Keywords: Esophageal cancer; 1,3-dipolar cycloaddition; free catalytic synthesis; 1,2,3-triazole hybrids.

1. Introduction

Cancer is an uninhibited growth of cells, considered as one of the threatening diseases which causes fatal dangers to human lives in the worldwide [1-3]. Esophageal cancer is being ranked as the sixth deadly cancer type in the worldwide [4]. Esophageal cancer is a malignant tumor which occurs in the inner layers of the mucosa (lining) of the esophagus cell [5]. The esophageal cancer cells possess the ability to spread out into other organs of the human body [6]. The esophageal cancer's progression is a multistep process which starts with an accumulation of genetic and epigenetic alterations which leads to the activation of oncogenes [7]. By looking at the reported incidence of esophageal cancer it can be concluded that esophageal cancer is the most common cancer type among men than women. Although the real numbers of incidences of esophageal cancer remains moderate approximately 15,500 cases in year, it is increasingly growing cancer in the United States [8]. There are two types of esophageal cancer, including adenocarcinoma and squamous cell carcinoma. Squamous cell

carcinoma is often combined with several factors involving achalasia, advanced age, alcohol abuse, tobacco use and high-starch diets [9, 10]. Esophageal cancer's treatment normally includes healing strategies such as surgery, radiotherapy and chemotherapy. Chemotherapy is an effective strategy for suppressing cancer growth and eradication of tumors [11, 12]. The developed resistance of cancer cells toward the chemotherapeutic agents and association with side effects are a major obstacle toward an efficient cure of cancer [13]. Therefore, the development of novel anti-esophageal cancer agents with merits like a significant cytotoxicity, better efficacy and reduction of side effects is urgently needed [14, 15]. The creation of anti-esophageal cancer compounds is the top target to overcome these obstacles and leads to effective clinical therapies [16].

The hybridization of pharmacological molecules is a powerful strategy to drug discovery and applied to target various diseases. The hybridization of two or more drug pharmacophores into a single molecule supply a prospect of best drugs for the cure of a number of diseases, particularly for cancer [17, 18]. The synthesis of effective anticancer hybrids has recently emerged as an efficient protocol for

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esophageal squamous cell carcinoma [19, 20]. Moreover, the synthesis of hybrid organometallics has been systematically investigated as it can offer potent drugs, for example, "Hybrid anticancer drugs" reported by Saha *et al* [21].

On the other hand, 1,2,3-triazole ring has attracted a paramount attention of the medicinal and organic chemists due to this moiety which offers a broad spectrum of biological activities [22]. The 1,2,3-triazole derivatives are well known as privileged pharmacophores because of their efficient biological activities [23]. Literatures have reported several methodologies for the synthesis of 1,2,3-triazole derivatives, but thermal 1,3-dipolar cycloaddition (Huisgen reaction) of terminal alkynes with azides is the best traditional methodology for the synthesis of these derivatives [24].

Hybridization of known pharmacophores with 1,2,3-triazole ring to enhance their physicochemical properties and anticancer activity has become a challenging scope in drug discovery [25]. Triazole moiety which conjugates with indoline (compound **A**) showed a significant role to inhibit growth of cancer cells and induce apoptosis [26]. Compound **B**, a 1, 2, 3-triazol-dithiocarbamate-urea hybrid exhibited a potency with IC_{50} values of 1.86 and 1.62 μM against cell lines MCF-7 and MGC-803, respectively [27]. In addition, 1,2,3-triazol-picolinamide hybrid (compound **C**) was found to be potent and better activity against breast cancer cell Line MCF-7 ($IC_{50} = 0.046 \pm 0.022 \mu M$) and lymphoma cell Line U937 ($IC_{50} = 0.58 \pm 0.42 \mu M$) [28].

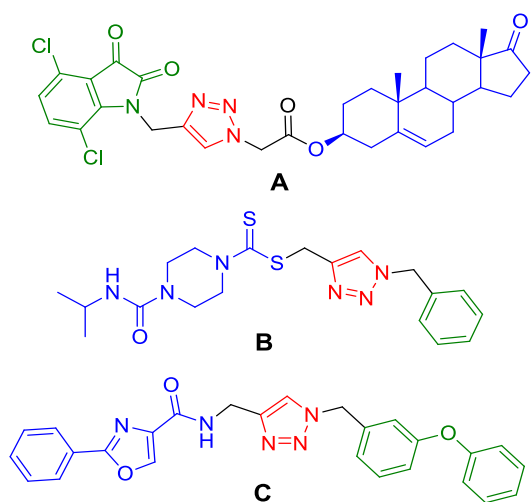


Fig. 1. Some anticancer active 1,2,3-triazole hybrids.

Several molecular hybrids were efficiently synthesized using a 1,3-dipolar cycloaddition reaction

to afford versatile 1,2,3-triazole hybrid systems [29, 30]. The study of new hybrid system in that 1,2,3-triazole, oxydianiline and maleimide are combined considered an unexplored field of organic chemistry. These findings have encouraged us to study the potential anticancer effect of 1,2,3-triazole, oxydianiline and maleimide hybrids. Thus, as a part of our interest with 1,3-dipolar cycloaddition reaction and in order to examine new 1,2,3-triazole-oxydianiline-maleimide hybrids with a good anti-esophageal cancer activity, herein we report the design, synthesis and anti-esophageal cancer of human cell line (SKG) evaluation of a new series of 1,2,3-triazole-oxydianiline-maleimide-hybrids **12-15**.

2. Materials and Methods

All chemicals and solvents were ordered from Sigma-Aldrich. All chemicals were at least of ACS grade, and solvents were obtained in analytical grade. Trypsin/EDTA was purchased from Capricorn (USA), RPMI 1640 and Fetal bovine serum from Gibco (USA), MTT stain from Sigma (USA), Cell culture plates from Thermo Fisher Scientific (USA), CO_2 incubator from Cypress Diagnostics (Belgium). Analytical properties of TLC were performed by using plates precoated with a silica gel 60 UV 254 (Merck). The dot spots of all synthesized compounds were visualized by UV light at 254 nm. The final purification of the synthesized compounds was performed with purity >95%. Melting points were obtained from a Gallenkamp melting point apparatus in capillary tubes. 1H NMR spectra were recorded on a Bruker inovo AV-400 spectrometer (Iran) at room temperature in $DMSO-d_6$ as solvent with a signal peak of 1H spectra at δ 2.50 ppm. Chemical shifts were given in ppm (δ scale) and the coupling constant values (J) are given in Hz. The splitting pattern was abbreviated as follows: (s, singlet), (d, doublet), (t for triplet) and (m, multiplet). Fourier transform infrared (FTIR) spectra were run on Shimadzu FTIR-8300 spectrophotometer (Iraq) using KBr (1%) discs and the absorbance was reordered between 4000-600 cm^{-1} . Accurate mass was performed by using a Micro Mass LCT operating in Electrospray mode (ES-MS) (Iran).

2.1. Synthesis of *N*-arylmaleimides (**6-9**) [31]

To a solution of maleic anhydride **5** (20 mmol) in diethyl ether (25 mL), an equivalent of various anilines **1-4** (20 mmol) dissolved in diethyl ether (5 mL) was added. The suspension mixture was subjected to stirring at room temperature for an hour and the resulting mixture was monitored by TLC until the starting materials were consumed. The resulting *N*-substituted maleamic acids were filtered, dried, and

delivered to a flask (50 mL) containing an anhydrous solution of sodium acetate (8 mmol) in acetic anhydride (6.7 mL). The mixture was additionally stirred for 30 min over a steam bath, cooled to room temperature and transferred into an iced water (100 mL). The resulting precipitate was filtered and washed thoroughly with cold water (30 mL). The pure *N*-arylmaleimides **6-9** were obtained through recrystallization from EtOH: H₂O (1:1) as follows: *N*-(4-Methylphenyl)maleimide **6** as yellow solid: Yield 84%, m.p 158-160 °C. 4-Maleimidobenzoic acid **7** as colorless solid: Yield 85%, m.p 232-234 °C. *N*-(2-Methoxyphenyl) maleimide **8** as brown solid: Yield 70%, m.p 158-160 °C and *N*-(2-Methylphenyl)maleimide **9** as yellow solid: Yield 85%, m.p 147-148 °C.

2.2. Synthesis of 4,4'-oxybis(azido benzene) (**11**) [32]

To a solution of 4,4'-oxydianiline **10** (2.0 mmol), conc. HCl (0.7 mL) and water (10 mL), sodium nitrite (2.0 mmol) dissolved in water (5 mL) was added drop wise at 0 °C. The mixture was stirred at 0 °C for 15 min and water (10 mL) was added. To above mixture, sodium azide (2.0 mmol) dissolved in water (5 mL) was gradually added and the resulting mixture was stirred at 0 °C till a beige solid would precipitate. The collected precipitate was filtered, dried and re-crystallized from chloroform: hexane (1: 1) to give 4,4'-oxybis(azidobenzene) **11** as a beige solid: Yield 90%, m.p 311-312 °C.

2.3. General method for the synthesis of 1,2,3-triazole-oxydianiline-maleimide hybrids (**12-15**) [33]

To a solution of appropriate *N*-arylmaleimides **6-9** (2.0 mmol) in EtOH: H₂O (1:1, 10 mL), 4,4'-oxybis(azido benzene) **11** (1.0 mmol) was slowly added. The reaction mixture was refluxed for an appropriate time as shown in Table 1. The resulting mixture was checked by TLC until the starting materials were consumed. The resulting reaction was cooled to precipitate crude products. The crude products were separated, washed with cooled ethanol, re-crystallized from THF: hexane (1:1) and dried under vacuum desiccators to afford the pure hybrids **12-15** in yield 55-75%. The purification of synthesized hybrids **12-15** was performed with purity >95%. The structures of these hybrids were confirmed by their ¹H NMR, FTIR and Mass spectral data (see supplementary materials).

1,1'-(Oxybis(4,1-phenylene))bis(5-(*p*-tolyl)-3a,6a-dihydropyrrolo[3,4-d][1,2,3]triazole-4,6 (1H, 5H)-dione) (**12**)

Hybrid **12** was obtained as a white solid, yield 65%. mp 154-155 °C. FTIR spectrum (KBr, cm⁻¹):

2982 (C-H), 1724 (C=O), 1502 (C=C, Ar), 1381 (N=N). ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm): 7.13-7.64 (m, 16H, CH of phenyl ring), 5.98 (d, 2H, *J* = 10.1 Hz, 2CH), 5.30 (d, 2H, *J* = 10 Hz, 2CH), 1.82 (s, 6H, 2CH₃). Mass (EI⁺) (M⁺) calculated for C₃₄H₂₆N₈O₅: 626.2026 found: 625.2016.

4,4'-((Oxybis(4,1-phenylene))bis(4,6-dioxo-3a, 4,6,6a-tetrahydropyrrolo[3,4-d][1,2,3] triazole-1,5 (1H)-diyl))dibenzoic acid (**13**)

Hybrid **13** was obtained as a white solid, yield 75%. mp 173-175 °C. FTIR spectrum (KBr, cm⁻¹): 3053 (C-H, Ar), 1726 (C=O), 1500 (C=C, Ar), 1377 (N=N). ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm): 7.12-7.65 (m, 16H, CH of phenyl ring), 5.96 (d, 2H, *J* = 10 Hz, 2CH), 5.28 (d, 2H, *J* = 10 Hz, 2CH). Mass (EI⁺) (M⁺) calculated for C₃₄H₂₂N₈O₉: 686.1509 found: 685.1500.

1,1'-(Oxybis(4,1-phenylene))bis(5-(2-methoxy phenyl)-3a,6a-dihydropyrrolo[3,4-d] [1,2,3] triazole-4,6(1H,5H)-dione) (**14**)

Hybrid **14** was obtained as a white solid, yield 55%. mp 148-150 °C. FTIR spectrum (KBr, cm⁻¹): 3061 (C-H, Ar), 2976 (C-H) 1728 (C=O), 1500 (C=C, Ar), 1377 (N=N). ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm): 7.11-7.64 (m, 16H, CH of phenyl ring), 5.94 (d, 2H, *J* = 9.2 Hz, 2CH), 5.26 (d, 2H, *J* = 9.2 Hz, 2CH), 2.34 (s, 6H, 2OCH₃). Mass (EI⁺) (M⁺) calculated for C₃₄H₂₆N₈O₇: 658.1924 found: 657.1918.

1,1'-(Oxybis(4,1-phenylene))bis(5-(*o*-tolyl)-3a, 6a-dihydropyrrolo[3,4-d][1,2,3]triazole-4,6 (1H, 5H) -dione) (**15**)

Hybrid **15** was obtained as a white solid, yield 60%. mp 160-162 °C. FTIR spectrum (KBr, cm⁻¹): 3060 (C-H, Ar), 2970 (C-H) 1728 (C=O), 1500 (C=C, Ar), 1386 (N=N). ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm): 7.12-8.06 (m, 16H, CH of phenyl ring), 5.99 (d, 2H, *J* = 6.2 Hz, 2CH), 5.30 (d, 2H, *J* = 6.1 Hz, 2CH), 2.08 (s, 6H, 2CH₃). Mass (EI⁺) (M⁺) calculated for C₃₄H₂₆N₈O₅: 626.2026 found: 625.2019.

2.4. Cell culture

Human SKG cancer cell line was obtained from the IRAQ Biotech Cell Bank Unit in Basrah, maintained in in plate (10 cm) containing RPMI-1640 and supplemented with 10% Fetal bovine, 100 units/mL penicillin, and 100 µg/mL streptomycin. Cells were conducted through Trypsin-EDTA, reseeded at 50% confluence twice a week and incubated with a humid atmosphere (CO₂, 5%) at 37 °C.

2.5. Cytotoxicity assays and dose response

To determine the cytotoxic effect, the MTT assay of cell viability was carried out on 96-well plates for 48 h. SKG cells were seeded at 1 × 10⁴ cells/well. After 24 h, a confluent monolayer was performed

and cells were treated with the screened compounds with final concentration (1000 $\mu\text{g/mL}$). After treatment for 72 h, the cell viability was measured by removing the medium, adding 28 μL of solution (2 mg/mL, MTT) and incubating at 37 $^{\circ}\text{C}$ for 2 h. After the MTT solution was removed, the remaining crystals in the wells were solubilized by an addition of DMSO (100 μL) and followed by shaking at 37 $^{\circ}\text{C}$ for 15 min. The absorbance of cell viability was determined on a micro-plate reader (Thermo Fisher Scientific) at 620 nm (tested wavelength) and all experiments were repeated in triplicate. The inhibition rate of cell growth (the percentage of cytotoxicity) was calculated by using the following Equation 1 [34].

$$\text{Proliferation Rate (PR)} = \text{B/A} * 100 \dots \dots \dots \text{Eq (1)}$$

Where, A = an optical density of untreated wells.

B = an optical density of treated wells.

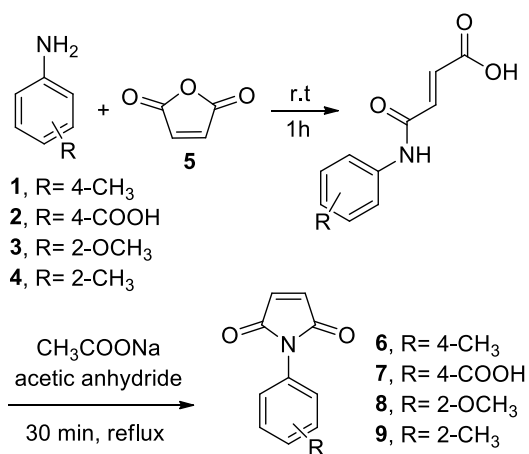
2.6. Statics analysis

Results and data were expressed as mean \pm SEM, GraphPad Prism 8.1 and the values of $*p < 0.05$ were taken as a statistical significant.

3. Results and Discussion

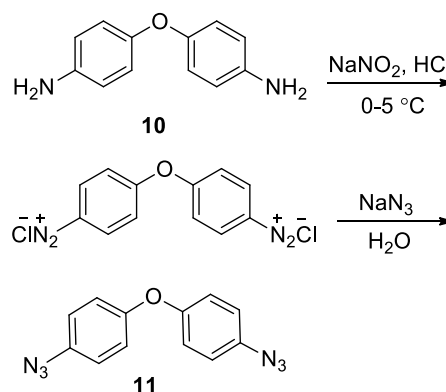
3.1. Chemistry

N-Arylmaleimides **6-9** were synthesized from various anilines **1-4** and malic anhydride **5** by stirring the mixture in diethyl ether at temperature room for an hour. Then, the resulting mixtures were treated with sodium acetate and acetic anhydride under refluxing for 30 min over a steam path. The formation of *N*-arylmaleimides **6-9** was indicated by TLC (petroleum ether/ethyl acetate, 6:4) as an eluent for the crude reaction mixture (Scheme 1).



Scheme 1. Synthetic route of *N*-arylmaleimides **6-9**.

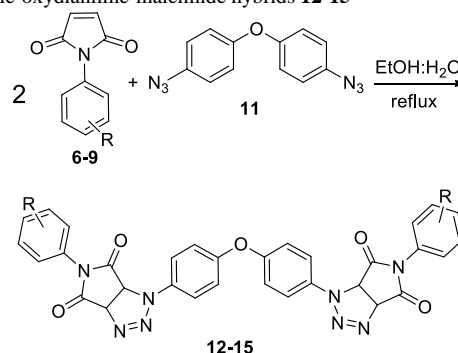
Next, the 4,4'-oxydianiline **10** treated with con. HCl and NaNO₂ at 0-5 $^{\circ}\text{C}$ offered the solution of diazonium salt which was immediately used for the next step without purification. Thus, an addition of an aqueous solution of NaN₃ to diazonium salt solution led to produce 4,4'-oxybis(azido benzene) **11** (Scheme 2).



Scheme 2. Synthetic route of 4,4'-oxybis(azido benzene) **11**.

The final step includes synthesis of new 1,2,3-triazole-oxydianiline-maleimide hybrids **12-15** through a 1,3-dipolar cycloaddition reaction. Free catalytic reaction was applied for the synthesis of new 1,2,3-triazole-oxydianiline-maleimide hybrids **12-15**. Initially, the model reaction was carried out by refluxing *N*-arylmaleimides **6** and 4,4'-oxybis(azido benzene) **11** for an appropriate time as shown in the table 1. As result, EtOH: H₂O (1:1) was chosen as the best appropriate solvent for the 1,3-dipolar cycloaddition synthesis of new 1,2,3-triazole-oxydianiline-maleimide hybrids **12-15** (Table 1).

Table 1. 1,3-Dipolar cycloaddition for the synthesis of new 1,2,3-triazole-oxydianiline-maleimide hybrids **12-15**



Com	R	Time (h)	M.p ($^{\circ}\text{C}$)	Yield (%)
12	4-CH ₃	8	154-155	65
13	4-CO ₂ H	19	173-175	75
14	2-OCH ₃	3	148-150	55
15	2-CH ₃	2	160-162	60

The success of synthesis of new 1,2,3-triazole-oxydianiline-maleimide hybrids **12-15** was clearly evidenced by their ^1H NMR analysis through the appearance of two distinct doublets at δ 5.24–6.01 ppm for fused 1,2,3-triazole-maleimide protons (CH groups) at the expected region. The ^1H NMR spectrum confirmed that the absence of CH protons (CH=CH groups) of *N*-arylmaleimides **6-9** was a good evidence of the success of 1,3-dipolar cycloaddition reaction. The other aromatic protons were displayed in the expected regions. The formation of hybrids **12-15** was also confirmed by the presence of absorption bands at the expected region in FTIR spectra. FTIR spectrum clearly showed the absence of an azido benzene group at 2121 cm^{-1} and the appearance of strong absorption bands at $1377\text{-}1386\text{ cm}^{-1}$ attributed to the azo group (N=N) of 1,2,3-triazole moiety. Furthermore, mass spectra data of all 1,2,3-triazole-oxydianiline-maleimide hybrids **12-15** were in consistent with the expected structures. (See experimental section).

3.2. Cytotoxicity on esophageal cancer cells

The favorable properties of 1,2,3-triazole ring involve a hydrogen bonding capability, moderate dipole character and stability under *in vivo* conditions [34]. 1,2,3-Triazole moiety can actively participate in dipole-dipole interactions, stable for oxidative and not be protonated by physiological pH due to its low basicity [35]. These properties are potentially responsible for its enhancement of biological activities. The action of new 1,2,3-triazole hybrids **12-15** against esophageal cancer cell line (SKG) was evaluated via a cytotoxic screening and estimation of IC_{50} . When cell viability test (a cytotoxic assay) was used for new hybrids screening, it was observed that a significant role of these hybrids for reducing the living cells growth of human esophageal cancer cells (SKG). After 72 h of treatment with $1000\text{ }\mu\text{g/mL}$ for each hybrid, it was noted that hybrid **13** showed the best action against cancer cell line (SKG). GraphPad Prism 8.1 was used to calculate the IC_{50} values for new hybrids **12-15**. In particular, hybrid **13** displayed a significant cytotoxic activity with IC_{50} value of $1.61\pm 0.01\text{ }\mu\text{M}$, meanwhile, hybrids **12**, **14** and **15** exhibited low cytotoxic activity against human esophageal cancer cells (SKG). It is clear from **Figs. 2** and **3**, the triazole residue hybrid with *N*-arylmaleimides **7** compound enhance the effect of cytotoxicity of hybrid **13** on human esophageal cancer cell line (SKG), while the nature of the combination of the triazole moiety with *N*-arylmaleimides **6**, **8** and **9** (hybrids **12**, **14** and **15**) does not influence the relevant cytotoxicity. This can be described to its disparity in either binding properties of protein or bioavailability. The IC_{50} value of hybrid **13** confirms that hybrid **13** is

being considered as a promising anti-esophageal cancer agent.

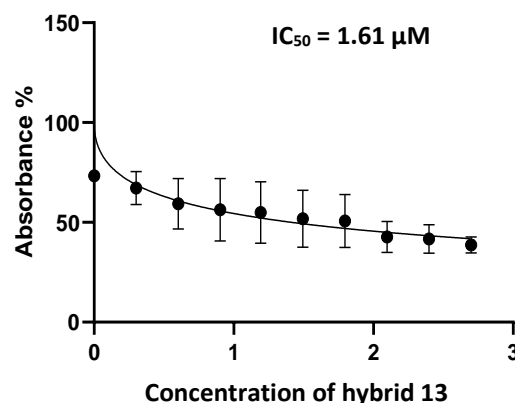


Fig. 2. GraphPad Prism 8.1 for estimation of IC_{50} value of hybrid **13**.

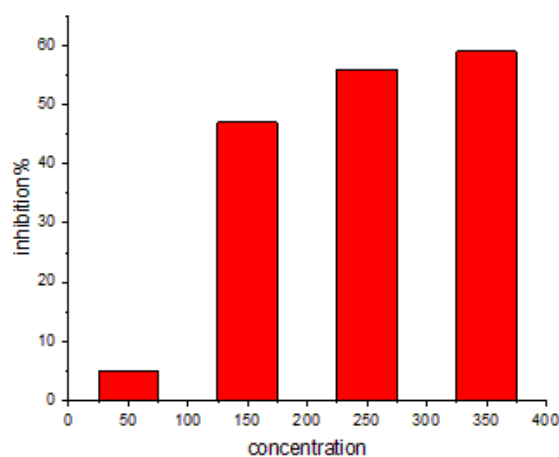


Fig. 3. Rate of inhibition for four concentrations of hybrid **13**.

4. Conclusions

A new series of 1,2,3-triazole-oxydianiline-maleimide hybrids was synthesized through a simple, efficient and free catalytic 1,3-dipolar cycloaddition reaction. As the discovery of new anticancer agents is the top target for medicinal chemistry, the new 1,2,3-triazole-oxydianiline-maleimide hybrids have been evaluated *in vitro* against esophageal cancer. The results exhibited that one hybrid molecule showed a significant activity as a novel potential anti-esophageal cancer agent. Particularly, hybrid **13** showed an excellent growth inhibition against esophageal cancer cell (SKG) with IC_{50} value of $1.61\pm 0.01\text{ }\mu\text{M}$ and less toxic to normal cells *in vitro* cytotoxicity. It is expected to be a promising anti-esophageal cancer agent. In addition, a further investigation to evaluate its mechanistic study and action is in progress.

Conflicts of interest

There are no conflicts to declare.

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تحضير مشتقات جديدة لماليميد اوكسي دايانالين ترايزول وتوصيفها وتقييم فعاليتها البايولوجية كمضادات لسرطان المريء

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استخدم تفاعل 1,3- للاضافة الحلقية في تحضير اربعة مركبات هجينة جديدة لماليميد اوكسي دايانالين ترايزول من تفاعل مشتقات الماليميد لاريلا مختلفة مع ثنائي اوكسي ازيد بنزين بوجود مزيج من الماء والايثانول كمذيب مناسب وبدعم وجود اي محفز كما تم توصيف واثبات تراكيب المركبات المحضرة باستخدام وساءل التحليل المختلفة مثل التحليل الطيفي بالاشعة تحت الحمراء (FT-IR), الرنين النووي المغناطيسي (¹H NMR), طيف الكتلة ودرجات الانصهار.

تم دراسة وتقييم سمية المركبات الجديدة المحضرة باستخدام , كما تمت دراسة وتقييم النشاط MTT assay نظام الصبغة المضاد لسرطان لهذه المركبات الهجينة المحضرة في اختبارات الفحص الخاصة بالخلايا السرطانية البشرية والمتضمنة سرطان Esophageal Carcinoma Cell line المريء من نوع , حيث اظهرت النتائج ان المركب الهجيني 13 له تأثيرا (SKG) عاليا تجاه هذا النوع من الخلايا السرطانية لذلك اثبت ان هذا النوع من المشتقات هي عوامل تحضيرية مختبرية واعدة ضد ويخمن ان تساهم هذه المشتقات في امراض سرطان المريء تطوير بعض التطبيقات الطبية في مجال تخليق ادوية السرطان