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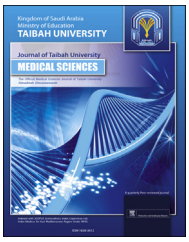

Original Article

Synthesis and screening of some new fluorinated quinazolinone–sulphonamide hybrids as anticancer agents

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الملخص

هدف البحث: يهدف هذا البحث إلى تحضير بعض مشتقات مركبات الكوينازولين المفلورة الجديدة المرتبطة بالسلفوناميد، وتقييم نشاطها السام ضد الخلايا في المختبر.

طرق البحث: تم تحضير ثمانية مركبات، وتقييم نشاطها المضاد للسرطان باستخدام ٣ مجموعات من الخلايا تتضمن خلايا سرطان الرئة من المعهد الوطني للسرطان، وخلايا سرطان الثدي من مؤسسة ميتشغان للسرطان، وخلايا طبيعية من كلى الجنين البشرية -٢٩٣.

النتائج: أظهر أحد المركبات نشاطا ذا أهمية مضادة للسرطان مع سمية منخفضة عند مقارنته مع ميثوتركسات كدواء مرجعي. كما أظهر الفحص البيولوجي نشاطا مضادا للسرطان جيدا إلى معتدل للمركبات في القائمة بالمقارنة بالأدوية المرجعية. المركبات الحديثة لها سمية أقل على الخلايا الطبيعية بالمقارنة بالميثوتركسات.

الاستنتاجات: يمكن أن توفر المركبات المحضرة حديثا قالبا ذا قيمة للتحضير الأمثل مستقبلا لإنتاج نظائر أكثر نشاطا من مضادات للسرطان.

الكلمات المفتاحية: كوينازولين؛ سلفوناميد؛ مضاد للسرطان؛ سميات الخلايا؛ تركيب

Abstract

Objectives: The aim of the present research was to synthesise several novel fluorinated quinazoline–sulphonamide derivatives and to evaluate their *in vitro* cytotoxic activity.

Methods: Eight compounds were synthesised. The compounds' anticancer activities were determined through the [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyltetrazolium bromide] (MTT) assay using a three-cell-line panel consisting of National Cancer Institute (NCI) lung cancer cells, Michigan Cancer Foundation-7 (MCF-7) breast cancer cells, and Human Embryonic Kidney-293 (HEK-293) normal kidney cell. The values of C log P correlations were determined to interpret the results.

Results: One compound exhibited significant anticancer activity with low toxicity compared with the methotrexate as the reference drug. The biological screening showed good to moderate anticancer activity for the title compounds compared with the reference drug. The reference drug exhibited an IC_{50} value of 2.4 μM, whereas compound 9, which was identified as the most active compound, exhibited an IC_{50} value of 2.51 μM on the NCI cell line. The other compounds showed IC_{50} values that ranged from 2.89 to 46.34 μM on the three cell lines. The newly synthesized compounds had lower toxicity on the normal cell line than did methotrexate.

Conclusions: The newly synthesized compounds may provide a valuable template for future design and

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optimization to produce analogues that act as more active anticancer agents.

Keywords: Anticancer; Cytotoxic; Quinazolinone; Sulphonamides; Synthesis

Introduction

Quinazolinones have various biological activities, including anticonvulsant,[1,2] antihistaminic,[3] anti-inflammatory, antibacterial,[4] antidiabetic,[5] antifungal,[6] anticancer,[7] anthelmintics[8] and antiviral activities.[9] Quinazolinone derivatives produce their anticancer activity through potent inhibition of various enzymes, such as epidermal growth factor receptor tyrosine kinase, dihydrofolate reductase, folate thymidylate synthase, tyrosine kinase, aldose reductase, cyclic GMP phosphodiesterase and DNA repairing enzymes.[7] Quinazolinone derivatives have therefore been widely used in the production of anticancer drugs.[7] In contrast, sulphonamides have various biological activities, and some of them are widely used in therapy as substantial anticancer agents.[10,11] Sulphonamides act as anticancer agents through a variety of mechanisms, such as cell cycle perturbation in the G1 phase, disruption of microtubule assembly, functional suppression of the transcriptional activator NF-Y[12,13] and inhibition of the carbonic anhydrase (CA) enzyme.[14] In our previous studies,[15] we reported that some derivatives of 6,8-diiodo-2-phenyl-3-substituted-quinazolin-4(3H)-ones, such as compound (A), exhibit good cytotoxic activity (Figure 1). These derivatives are hybrid molecules that included 6,8-diiodo quinazolinone as a fixed moiety with different L-amino acids. Iodine atoms at positions 6 and 8 of the quinazolinone moiety have larger atomic size, atomic radius, atomic covalent bond and van der Waals radius than other halogens, such as fluorine.[18] The large size of iodine atoms may negatively affect the drug receptor binding process by changing the desolvation energy, which plays an important role in ligand−receptor interactions.[19,20] Furthermore, fluorine improved the lipophilicity, absorption and bioavailability of many well-established anticancer drugs[16] such as lapatinib, gefitinib and caneratinib.[17,21] We therefore decided to synthesise some novel fluorinated quinazolinones with the same structure as our previously reported compounds but with an iodine atom instead of a fluorine atom at position 6 of the quinazolinone moiety. Figure 1 shows the structural similarities between the previously reported anticancer quinazolinones (A, B), Thymitaq and the newly synthesized derivatives.[22,23] The present study is thus a continuation of our attempt to identify novel, safe and effective anticancer agents.

Materials and Methods

Synthesis

The strategy used to synthesise the compounds is shown in Scheme 1. It comprises two simple reactions, namely acetylation followed by ring closure of 2-amino-5-flurobenzoic acid (1). This compound was refluxed with acetic anhydride for 1 h to afford a quantitative yield of 6-fluoro-2-methyl-4H-benzo[d][1,3]oxazin-4-one (2). The second reaction is the nucleophilic displacement of the oxygen of benzoxazinone with the nitrogen of the amino group upon treatment with sulphonamides, which was achieved by refluxing compound (2) with the appropriate sulphonamide under dry conditions for 6 h and gave sulphonamide derivatives of 6-fluoro-2-methyl-quinazolinone (4−11) in variable yields ranging from 60 to 79%.

Chemistry

The compounds were analysed at the Analytical Centre, College of Science, Cairo University, Egypt. The melting points were measured using a Griffin melting point apparatus (Griffin) and are uncorrected. The Infrared spectra were recorded as KBr discs on a Nicolet IR 200 (Thermo Fisher Scientific). The ^{1}HNMR spectra were run using TMS as the internal standard (Sigma−Aldrich) on a Varian Mercury VXr-300 NMR instrument (Varian). The mass spectra were measured on a JEOL-SX-102 instrument through electron impact ionization. Elemental analyses (C, H, and N) were performed using a Perkin-Elmer 240C analyser (Perkin-Elmer). All of the values were within ±0.4% of the theoretical values. All of the chemicals were purchased from Sigma−Aldrich.

Experimental

6-Fluoro-2-methyl-4H-benzo[d][1,3]oxazin-4-one (2)

Compound 2 was prepared by refluxing 2-amino-5-fluorobenzoic acid (1, 1.55 g, 0.01 mol) with an appropriate amount of acetic anhydride for 1 h. The residue obtained was evaporated to complete dryness, allowed to cool, washed several times with petroleum ether, collected, filtered and dried without moisture.

Yield 79%, mp: 87−89 °C; ^{1}H NMR (DMSO-d_6): δ 1.41 (s, 3H, CH_3), 7.31−8.24 (m, 3H, Ar−H). ^{13}C NMR (DMSO-d_6): δ 24.23, 82, 90.5, 118.5, 138.2, 149.6, 150, 154.1, 158. Anal. Calcd. For $C_9H_6FNO_2$ (179.04): C, 60.34; H, 3.38; N, 7.82. Found C, 60.12; H, 3.61; N, 7.64. MS (EI) m/z 180.04 [M + 1].

General method for preparation of test compounds (4−11)

Compounds 4−11 were prepared by mixing 1.79 g (0.01 mol) of compound (2) with 0.01 mol of sulphonamide derivatives in 100 ml of dry pyridine, refluxing for 6 h, cooling, treating with a small amount of 10% hydrochloric acid and pouring onto crushed ice. The crystals obtained were collected by filtration and re-crystallised from ethanol or glacial acetic acid.