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Design, synthesis and biological evaluation of some novel substituted quinazolines as antitumor agents

Amer M. Alanazi [a], Alaa A.-M. Abdel-Aziz [a,b], Ibrahim A. Al-Suwaidan [a], Sami G. Abdel-Hamide [c], Taghreed Z. Shawer [d], Adel S. El-Azab [a,e,*]

[a] Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia
[b] Department of Medicinal Chemistry, Faculty of Pharmacy, University of Mansoura, Mansoura 35516, Egypt
[c] Department of Pharmaceutical Chemistry, College of Pharmacy, Salman Bin Abdulaziz University, Alkharj, Saudi Arabia
[d] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Al-Azhar University, Cairo 11884, Egypt
[e] Department of Organic Chemistry, Faculty of Pharmacy, Al-Azhar University, Cairo 11884, Egypt

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ABSTRACT

A novel series of 6-chloro-2-*p*-tolylquinazolinone and substituted-(4-methylbenzamido)benzamide (**1**–**20**) were designed, synthesized and evaluated for their *in-vitro* antitumor activity. Compounds **3, 14** and **16** possessed remarkable broad-spectrum antitumor activity. Compound **16** was found to be a particularly active growth inhibitor of the renal cancer (GI_{50} = 4.07 μM), CNS cancer (GI_{50} = 7.41 μM), ovarian cancer (GI_{50} = 7.41 μM) and non-small cell lung cancer (GI_{50} = 7.94 μM). Compound **16** ranks as nearly 1.5-fold more potent (mean GI_{50} = 15.8 μM) compared to 5-FU (mean GI_{50} = 22.6 μM).

1. Introduction

Cancer is a disease characterized by a shift in the controlled mechanisms that govern cell proliferation and differentiation [1]. Malignancy is caused by abnormalities in cells, which might be due to inherited genes or caused by outside exposure of the body to chemicals, radiation, or even infectious agents [2,3]. The development of new anti-cancer therapeutic tools has advanced greatly in the past decade; thus approaches for the treatment of cancer have moved towards targeting the specific molecular alterations that occur in tumor cells. This approach has been concentrated on the development of ideal anticancer drugs that eradicate cancer cells without harming normal tissues [4,5]. Unfortunately, no currently available agents meet this criterion and clinical use of drugs involves a weighing of benefits against toxicity in a search of favorable therapeutic index [6].

Many of chemotherapeutics currently used in cancer therapy are agents which inhibit tumor growth by inhibiting the replication and transcription of DNA. The practice of chemotherapy of cancer suffers from various drawbacks viz. the participation of a number of enzymes like ribonucleotides reductase (RNR), topoisomerase I (Topo I) and topoisomerase II (Topo II) at different stages of development of cancer [7], survival of cancer cells even under anaerobic conditions [8], and ultimately the problem of multidrug resistance [9–11] developed in the cancerous cells towards chemotherapeutic agents.

As an important pharmacophore, quinazoline has a variety of biological activities [12–29].

FDA has approved several quinazoline derivatives as anticancer drugs, such as Gefitinib, Erlotinib, Lapatinib and Vandetanib. Based on the good performances of quinazoline derivatives in anticancer application, development of novel quinazoline derivatives as anticancer drugs is a promising field.

In the present study, we have designed a number of new quinazoline and diamide derivatives (**1**–**20**) containing various substituent with different electronic environment which would affect the lipophilicity, and hence the activity of the target molecules and biologically evaluated there *in-vitro* antitumor activities. The

* Corresponding author. (Adel S. El-Azab), Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia.
E-mail addresses: adelazaba@yahoo.com, adelazaba@hotmail.com (A.S. El-Azab).

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objective of forming these hybrids is an attempt to attain an active antitumor agent with potentiated activity and selectivity toward cancerous cells.

2. Results and discussion

2.1. Chemistry

6-Chloro-2-*p*-tolyl-4*H*-benzo[d][1,3]oxazin-4-one (**1**) was prepared by the reaction of 5-chloroanthranilic acid with 4-methylbenzoyl chloride in pyridine followed by boiling with acetic anhydride [27]. Treatment of **1** with formamide furnished 6-chloro-2-*p*-tolylquinazolin-4(3*H*)-one (**2**) in 73% yields. Boiling of compound **1** with various amines in anhydrous pyridine afforded 5-chloro-2-(4-methylbenzamido)-*N*-substituted benzamide (**3**–**5**) in 90–94% yields.

Additionally, reaction of 6-chloro-2-ptolyl-4*H*-benzo[d][1,3] oxazin-4-one (**1**) with ethyl 2-aminoacetate hydrochloride in boiling pyridine gave a mixture of ethyl 2-(5-chloro-2-(4-methylbenzamido)benzamido)acetate (**6**) and ethyl 2-(6-chloro-4-oxo-2-*p*-tolylquinazolin-3(4*H*)-yl)acetate (**7**) in 34% and 60% yields, respectively.

Moreover, 2-(6-chloro-4-oxo-2-*p*-tolylquinazolin-3(4*H*)-yl)acetohydrazide (**8**) and 5-chloro-*N*-(2-hydrazinyl-2-oxoethyl)-2-(4-methylbenzamido)benzamide (**9**) were obtained in a good yield (80% and 86%, respectively) via the reaction of compound **6** or **7** with hydrazine hydrate in boiling ethanol (Scheme 1).

IR spectra of compounds **3**–**5** showed absorption bands at 3173–3182 cm^{-1} and 1668–1670 cm^{-1} due to stretching vibration of the (CONH) group, moreover, ^{1}H NMR spectra showed the appearance of two (CONH) as a singlet signal at δ (12.46, 9.57 ppm), (11.57, 10.64 ppm) and (11.39, 11.14 ppm) respectively. The presence of a band at 1720–1716 cm^{-1} due to the (CO) group of the ester moiety as well as ^{1}H NMR spectra showed the appearance of two signals at δ 4.14–4.11 and 1.20–1.13 ppm of the ester function confirmed compounds **6**–**7**.

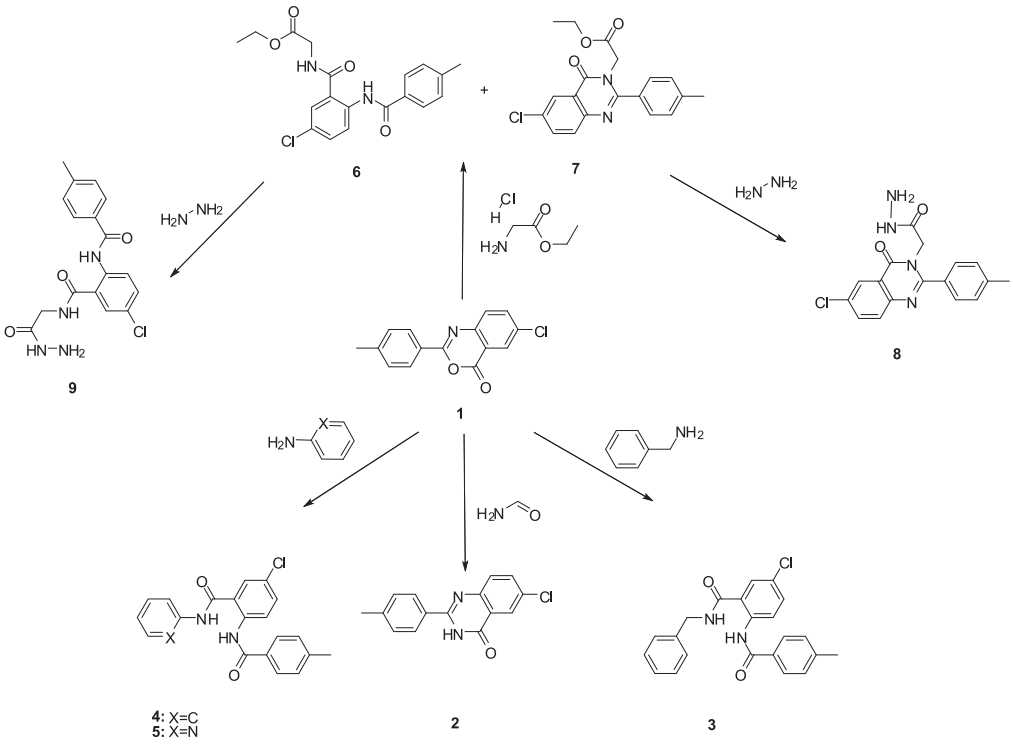
Furthermore, when compound **1** was reacted with hydrazine hydrate in ethanol at room temperature and/or boiling ethanol gave *N*-(4-chloro-2-(hydrazinecarbonyl)phenyl)-4-methylbenzamide (**10**) and/or 3-amino-6-chloro-2-*p*-tolylquinazolin-4(3*H*)-one (**11**) in 90% and 88% yield, respectively.

As well, the reaction of compound **11** with chloroacetylchloride and/or benzaldehyde provided 2-chloro-*N*-(6-chloro-4-oxo-2-*p*-tolylquinazolin-3(4*H*)-yl)acetamide (**12**) and 3-(benzylideneamino)-6-chloro-2-*p*-tolylquinazolin-4(3*H*)-one (**16**) in 89% and 92% yield, respectively. 2-Amino-*N*-(6-chloro-4-oxo-2-*p*-tolylquinazolin-3(4*H*)-yl)acetamide (**13**) and *N*-(6-chloro-4-oxo-2-*p*-tolylquinazolin-3(4*H*)-yl)-2-hydrazinylacetamide (**14**) were obtained by stirring of compound **12** with concentrated ammonia solution and/or hydrazine hydrate at room temperature in relatively good yield.

In addition, 11-chloro-7-*p*-tolyl-2,3-dihydro-[1,2,4,5]tetrazepino[2,3-c]quinazolin-4(5*H*)-one (**15**) was achieved via boiling of compound **14** with acetic acid in the presence of fused sodium acetate in 46% yield (Scheme 2).

Compound **10** showed a characteristic (CO) band of diamide moiety at 1671, 1668 cm^{-1} and (NH) absorption band at 3277, 3172, 3168 cm^{-1} as well as ^{1}H NMR showed a singlet signal at 11.20 and doublet signal at 8.11 ppm corresponding to (CONH) group. Additionally compound **11** revealed (NH_2) and (CO) groups at 3266, 3121 and 1680 cm^{-1} respectively, in addition to singlet signal at 5.70 ppm due to the presence of (NH_2) group in ^{1}H NMR spectrum. ^{1}H NMR spectra of compounds **12** and **16** were characterized by the disappearance of (NH_2) singlet signal at 5.70 ppm of compound **11** with appearance of new singlet signal at 9.01 ppm and 11.67 ppm for (HNCO) and (HC=N) moieties respectively, as well as the presence of additional aliphatic carbon at 40.4 ppm for compound **12** in ^{13}C NMR spectrum.

IR of compounds **13** showed absorption bands of (NH_2) at 3269, 3175 cm^{-1} and 1704, 1670 cm^{-1} due to stretching vibration of (CO) groups with the presence of (NH_2) signal at 7.27 ppm in ^{1}H NMR. Compound **15** showed characteristic (CO) band at 1702 cm^{-1} and (NH) absorption band at 3167 cm^{-1} due to the amide moiety as well



Scheme 1. Reactions of 6-chloro-2-*p*-tolyl-4H-benzo[d][1,3]oxazin-4-one.