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ORIGINAL ARTICLE

Design, synthesis and cytotoxic evaluation of novel imidazolone fused quinazolinone derivatives

Deepak Kumar [a], G. Mariappan [a,*], Asif Husain [b], J. Monga [c], S. Kumar [d]

[a] *Department of Pharmaceutical Chemistry, Himalayan Pharmacy Institute, Sikkim Central University, Majitar, Sikkim 737136, India*
[b] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard University, New Delhi 110062, India*
[c] *L.R. Institute of Pharmacy, Solan 173212, Himachal Pradesh, India*
[d] *Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, PR China*

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Abstract A congeneric series of novel imidazolone fused quinazolinone derivatives were synthesized and characterized by IR, NMR, mass spectra and elemental analyses. All the compounds were evaluated for their in vitro cytotoxic activity against cervical cancer (HeLa), breast cancer (MCF-7), leukemia cells (HL-60) and hepatocellular carcinoma (HepG2) cell lines. The derivative **4e** which bears a methoxy group at *para* position in phenyl ring of imidazolone displayed three fold potent activity against MCF-7 than that of the standard drug Cisplatin. The IC_{50} value of **4e** against HepG2 is twofold lesser than Cisplatin whereas the IC_{50} value against HeLa and HL-60 was equivalent to Cisplatin. The result concludes that these derivatives can be further utilized as a promising anticancer agent.

1. Introduction

Cancer is a leading cause of death worldwide that is accounted for 7.6 million deaths in 2008. More than 70% of all cancer deaths occurred in low and middle income countries. Deaths from cancer worldwide are projected to rise over 11 million in 2030 as per WHO Cancer Fact sheet No 297 February 2011. Chemotherapy constitutes one of the modalities of cancer treatment, either *per se* or in conjunction with other treatment regimens. However, despite much progress in the chemotherapy of cancerous diseases, anticancer drugs in current clinical use generally do not address issues of excessive organ toxicity, lack of cell specificity, short circulation half-life, angiogenesis, metastasis and a pronounced tendency to induce resistance in the target cells. Hence it is imperative to develop a safe and effective drug candidate to save the lives of million people worldwide.

Quinazolinone and its derivatives have drawn much attention because of their pharmacological activities particularly a wide range of antitumor activities (Khalil et al., 2003). Anilinoquinazolines in particular are potent inhibitors of growth

* Corresponding author. Mobile: +91 9474530205; fax: +91 3592246462.
E-mail address: gmariappanhpi@yahoo.co.in (G. Mariappan).
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factor receptor tyrosine kinase (GFRTK) and have found clinical applications in epidermal and vascular endothelial GFR targets (Grunwald and Hidalgo, 2003). Quinazolinone heterocycles possess diverse pharmacological activities including antimycobacterial (Karel et al., 2001) antifungal (Sawhney et al., 1980) antimalarial (Martin et al., 1964), antihypertensive (Dienei et al.,1973), antihistaminic (Alagarsamy et al., 2005, 2006), local anesthetic (Chandrasekhar et al.,1986) anti-Parkinson (Naithani et al., 1989), antiviral (Alagarsamy et al.,2004), and thymidylate synthase inhibitory activities (Hennequin et al.,1996). The simple and condensed quinazolinones are also known to exhibit analgesic (Alagarsamy and Murugesan, 2007), anti-inflammatory (Ravishankar et al., 1984) and anticonvulsant activities (Hori et al.,1990). Interest in quinazolinones as anticancer agents has further increased since the discovery of Raltitrexed and Thymitaq (Fig. 1) and their activity as Thymidylate enzyme inhibitors (Bavetsias et al., 1997). The compounds containing imidazolone chromophore are known to have a wide range of biological activities like anti-cancer, anti-inflammatory, cardioactivity and angiotensin II receptor antagonistic activity (Siamaki et al., 2008). A trisubstituted imidazolone induces a high degree of apoptosis in human leukemia cells and also has prominent cytotoxicity (Fang et al., 2007; Lai et al., 2002). Inspired by these findings; we attempted to synthesize novel quinazolinone derivatives fused with imidazolone and to evaluate anticancer activities against cervical cancer, breast cancer, leukemia and hepatocellular carcinoma cell lines.

2. Experimental

In the present study, fourteen novel congeneric series of quinazolinone derivatives were synthesized as illustrated in Scheme 1. The starting compound 3,5-dibromo anthranilic acid (**1**) was synthesized according to the reported literature procedure (Bogert, 1903) .Compound (**1**) was reacted with acetic anhydride under anhydrous condition for 4 h. The intermediate **(2)** 6,8-dibromo-2-methyl-3,1-benzoxazin-4-one obtained as a solid mass was used immediately for the next step (Misra et al., 1995). Compound (**2**) was subjected to reflux conditions with hydrazine hydrate in the presence of pyridine for 3 h to get the building block 3-amino-6,8-dibromo-2-methyl-quinazolin-4(3*H*)one (**3**) (Raghvendra et al., 2007). Differently substituted oxazolone derivatives were prepared according to the reported literature (Cantello et al., 1994). Compound (**3**) was subjected to reflux with various substituted oxazolone derivatives in pyridine to yield the target compounds (Radadia et al., 2006; Patel et al., 2003).

2.1. Materials

All the chemicals were of synthetic grade and commercially procured from S.D. Fine Chem. Ltd., Mumbai, India. Melting points were recorded on a Buchan capillary melting point apparatus and are uncorrected. IR spectra were recorded on a FT-IR8400S, Fourier Transform (Shimadzu) Infrared spectrophotometer using the KBr disk method. ^{1}H NMR spectra were recorded on a Perkin Elmer NMR Spectrophotometer-300 MHz in DMSO-δ_6 using TMS as an internal standard. Mass spectra were recorded on a Micro mass Q-TOF and Shimadzu LCMS 2010A Mass spectrometer. Elemental analysis was performed using a Perkin Elmer Auto system XL Analyzer.

2.1.1. Synthesis of 6,8-dibromo-2-methyl-3,1-benzoxazin-4-one, 2

A mixture of 3,5-dibromo anthranilic acid **1** (0.05 mol) and acetic anhydride (0.1 mol) was subjected to reflux under anhy-

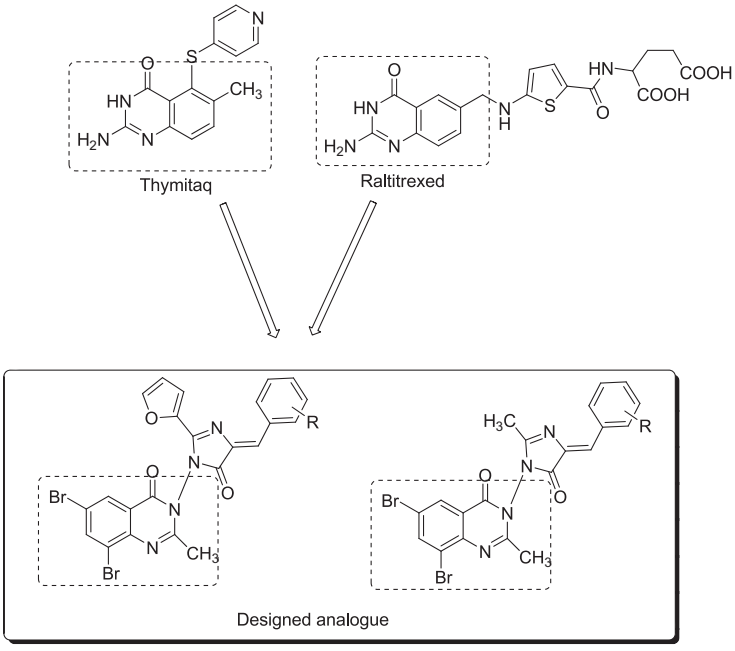

Figure 1 Structural resemblance of Raltitrexed and Thymitaq with designed analogs.