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Furo[2,3-*d*]pyrimidine based derivatives as kinase inhibitors and anticancer agents

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ABSTRACT

Furopyrimidines are fused heterocyclic ring systems. Structurally, they are bioisoteres to purines and exerting pharmacological actions in various aspects. They are known to play an important role in different disease conditions. Furo[2,3-*d*]pyrimidines derivatives have been explored for their inhibitory activity against different protein kinase enzymes. The present review, to the best of our knowledge, is the first compilation on synthesis, anticancer activity, via inhibition of various protein kinase enzymes, and structure–activity relationships of furo[2,3-*d*]pyrimidines derivatives reported to date.

1. Introduction

Furopyrimidine heterocyclic ring systems are structural analogues of purines which were subjected to biological investigations to assess their potential therapeutic usefulness [1]. Furopyrimidines attract considerable attention because of their great practical significance through exerting various pharmacological potential as antiviral [2–4], antimicrobial [5,6] and antitumor agents [7,8].

The present review highlights synthetic strategies, the anticancer therapeutic effect of furo[2,3-*d*]pyrimidine derivatives via inhibition of particular kinase enzymes, in addition to their structure activity relationships (SAR) that was covered since the year 2004 to present.

Protein kinases are enzymes that have the ability modify other proteins by phosphorylation through the transfer of a phosphate group from a nucleoside triphosphate (usually ATP) and attaching it covalently to specific amino acids bearing a free hydroxyl group [9,10]. Phosphorylation process usually causes a functional change of the target protein by changing hydrophilicity, cellular location, enzyme activity, or association with other proteins [11].

The human genome contains about 518 genes coded for protein kinase. They make up about 2% of all human genes. About 30% of all human protein are regulated by kinase activity, and kinase enzymes are specifically regulate the cellular pathways, especially those involved in signal transduction [12].

Based upon their catalytic specificity, the protein kinase classes can be subdivided into three categories:

1. Tyrosine kinases (TK): act on tyrosine amino acid. 90 kinases belong to the group of tyrosine kinases [13,14].
2. Serine/Threonine kinases: act on serine and threonine amino acids. Six other groups have been identified to phosphorylate serine and threonine residues [15,16].
3. Dual-specificity kinases: phosphorylate all three amino acids, tyrosine, serine and threonine amino acids [17,18].
4. Histidine kinases: phosphorylate the nitrogen atom of histidine residues [19,20].

Protein kinases play a dual role as surface transmembrane receptors, as well as enzymes having kinase activity. The structure of the kinase receptor consists of a multi-domain extracellular receptor for conveying ligand specificity that recognizes an external messenger (growth hormones, growth factors) [21]. Then, a single transmembrane hydrophobic helix, followed by a cytoplasmic portion, which contain the kinase domain that is activated upon binding of the messenger. This causes a subsequent dimerization of receptor, triggering a signaling cascade that eventually controls the transcription of specific genes that regulate cellular proliferation and differentiation [22,23].

Crystal structure of protein kinases, bound to ATP had been studied and revealed that ATP fits quite loosely to the binding

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site [24]. There is also significant difference in the amino acids present in the ATP binding site from one kinase to another, thus enabling the design of various selective inhibitors [25].

The development of different protein kinase inhibitors dates back 25 years beginning with the fundamental studies of natural products that inhibit some protein kinases in biochemical assays [26]. Small-molecule kinase inhibitors are currently being pursued intensively as novel anticancer therapeutic agents through targeting ATP binding site within the kinase [27–29].

Furopyrimidine ring is one of the most recently explored scaffolds to have potential anticancer activity through inhibition of various protein kinases.

2. Synthetic strategy

Numerous synthetic strategies were outlined for the synthesis of furo[2,3-*d*]pyrimidine scaffold **(1)** incorporated in different kinase inhibitors (Fig. 1). Compound **(I)** was successfully condensed with Formamide/DMF/formic acid 4:2:1 to afford **1** (route a) [30]. Substituted 5-Amino-4-cyanofuran **(II)** has been used in number of reactions to attain the synthesis of the desired compound **(1)** through different routes. Se Young Kim et al. [31] reported the treatment of **II** with acetic anhydride in formamide (route b) or with acetic anhydride in formic acid (route c) to afford **(1).** Meanwhile, refluxing compound **(II)** with neat formic acid for 4 h afforded **(1)** (route d) [5]. Treatment of the furan **(II)** with

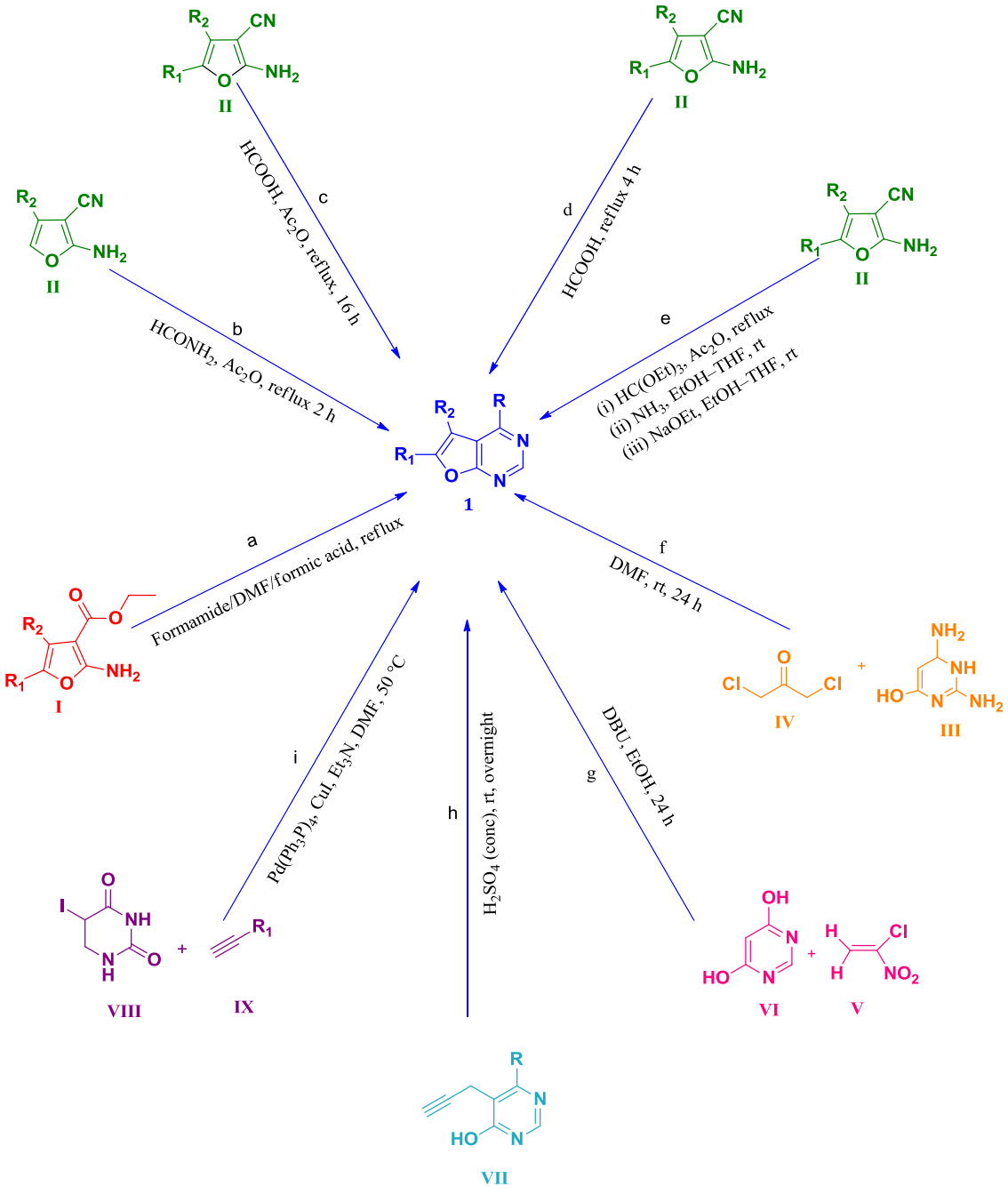

Fig. 1. Synthetic approaches for furo[2,3-*d*]pyrimidines.