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SYNTHESIS OF CERTAIN 2-FURANONES AND DERIVED N-HETEROCYCLES AS POSSIBLE ANTINEOPLASTIC AND ANTI-HIV CANDIDATES

Thesis

Presented By

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CHAPTER

I

ABSTRACT

The wide spread of cancer and acquired immune deficiency syndrome in recent years obligated the continuous search for new therapeutic agents in this field.

As a part of an ongoing program aimed towards the development of new potential antitumor and anti-HIV, the synthesis of diverse furanones and their derived pyrazoles and quinoxalines was projected.

The deregulation mechanisms of cyclin-dependant kinases (CDKs) in some human tumor progression prompted the testing of some selected compounds as CDKs inhibitors in addition to other screening protocols.

The present thesis is subdivided into the following parts:

Introduction

It comprises a review of the literature concerning the cell cycle regulation and the unique role of CDKs inhibitors in interfering undesirable cell proliferations, in addition to a presentation of selected models of compounds having CDK inhibition activity and / or antitumor effect. The importance of 2-furanones, pyrazoles and quinoxalines in this area, is also reviewed.

Research objectives

This part deals with the chemical and biological bases on which the synthesized compounds were selected. It was also planned to screen some selected compounds for their anticancer and anti-HIV activity.

Discussion

In this part, the various methods applied for the synthesis of the intermediate and final compounds are discussed. Reinvestigation of some of the adopted processes have been detailed. The structures assigned to the prepared compounds were substantiated by elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR and Mass Spectral data. The discussion is subdivided into 3 parts.

Part I

It illustrates the synthesis of three series of compounds; the pyrazoline derivatives 1-[4-(substituted aminosulfonyl)phenyl]-4-(2-hydroxyethyl)-3-methyl-3-pyrazolin-5-ones **(5a-c)** and the derived spiro compound 5-(4-aminosulfonylphenyl)-7-methyl-5,6-diazaspiro[2.4]hept-6-en-4-one **(6)**; the furanone derivatives 3-[4-(substituted aminosulfonyl)phenylhydrazono]-4,5-dihydro-2(3H)-furanones **(7a-e)** and 3-(4-substituted phenylhydrazono)-4,5-dihydro-2(3H)-furanones **(11a-d)**; and the furoindolone derivatives 7-substituted-1,4-dihydrofuro[3,4-b]indol-3-ones **(12a-c)**.

Part II

It comprises a literature review concerning the reaction of 3-acetyl-4,5-dihydro-2(3H)-furanone (α-acetyl-γ-butyrolactone) **(1)** with some primary amines, hydroxylamine and hydrazines, followed by a reinvestigation of some selected compounds as 3-[1-(substituted amino)ethylidene]-4,5-dihydro-2(3H)-furanones **(38, 41, 44a-c)**. Compound 3-[1-(2-hydroxy-phenylamino)ethylidene]-4,5-dihydro-2(3H)-furanone **(44a)** could be cyclized with phosphorus oxychloride in different conditions to yield either 4-chloro-3-(2-chloroethyl)-8-hydroxy-2-methylquinoline **(48a)** or 2,3-dihydro-6-hydroxy-4-methylfuro[3,2-c] quinoline **(49)**. On the other hand, 3-[1-(2-aminophenylamino)ethylidene]-4,5-dihydro-2(3H)-furanone **(44b)** is either cyclized to 4-(2-hydroxyethyl)-3-methyl-2-pyrazolin-5-one **(47)** when reacted with hydrazine hydrate, or with 4-chlorobenzaldehyde to form the Schiff's base 3-{1-[2-(4-chlorobenzylideneimino)phenylamino]ethylidene}-4,5-dihydro-2(3H)-furanone **(52)**.

Additionally the reaction of α-acetyl-γ-butyrolactone **(1)** with hydroxylamine hydrochloride to yield the furanone 3-[1-(hydroxylamino)-ethylidene]-4,5-dihydro-2(3H)-furanone **(54)** is included.

Part III

It depicts the conversion of the key intermediate 4-chlorobenzyl-idenepyruvic acid **(66)** to either 3-(substituted phenylamino) or 3-benzyl-amino-5-(4-chlorophenyl)-2(5H)-furanones **(67a-c,69)**. Each of the three furanones **(67a-c)** is then reacted with 2-phenylenediamine to yield 3-(4-chlorostyryl)-2(1H)-quinoxalinone **(70)**. This quinoxalinone is by turn chlorinated to 2-chloro-3-(4-chlorostyryl)quinoxaline **(71)** which is reacted with either 4-fluoroaniline or with sodium azide giving either 3-(4-chloro-styryl)-2-(4-fluorophenylamino)quinoxaline **(72)** or 4-(4-chlorostyryl)tetra-zolo[1,5-a]quinoxaline **(73)**, respectively.

Experimental

In this part the experimental procedures applied throughout the present work are described. It also includes the physical characters, microanalyses and the spectral data that support the assigned structures. It is subdivided into 3 parts relevant to those of the discussion.

Biological studies

This part describes the biological testing of some selected compounds. This testing was directed to realize feasible biological activity in the following aspects:

1. Antitumor activity using cell line panel protocol.
2. Cyclin-dependent kinase inhibition screening.

References

The thesis is terminated with 56 references relevant to the present study.