شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
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HANAA ALY

كلية العلوم – قسم الكيمياء

Design and Synthesis of Some New Thiazole, Pyridine and Pyrimidine Derivatives for Biological Evaluation

Thesis Submitted by

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B.Sc.(Chemistry) ١٩٩٢

M.Sc. (Chemistry) ١٩٩٦

For the requirement of Ph.D. Degree of Science in Chemistry

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كلية العلوم – قسم الكيمياء

Title of thesis

Design and Synthesis of Some New Thiazol, pyridine and pyrimidine Derivatives for Biological Evaluation.

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ABSTRACT

Name: Manar ELsaied AbdElsatar Elasasy

Title: Design and Synthesis of Some New Thiazole, Pyridine and Pyrimidine Derivatives for Biological Evaluation

Degree: Philosophy of Doctor (Ph.D.)

Thiazoles, pyridine and pyrimidines, are few of the very important classes of heterocyclic compounds having great medicinal and pharmacological importance. In the present study, new series of biologically active compounds containing thiazole, pyridine and pyrimidine units have been synthesized and screened *in vitro* for their anticancer activities

The structures of all the new synthesized compounds were characterized by spectroscopic techniques such as, IR, NMR (^{١}H and ^{١٣}C), Mass spectroscopy and elemental analysis.

Keywords:

Thiosemicarbazone, thiazole, pyridine, pyrimidine, Nicotinamide, thienopyridine, and anticancer activity.

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Synthesis and Antiproliferative Activity of Novel Hydrazono Thiazolidene and Thiazole Derivatives Bearing Rhodanine Moiety

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Abstract—Some new fluoro-heterocyclic compounds containing thiazole and pyridine moities have been synthesized and studied for their antiproliferative activity. Thiazole derivatives have been synthesized by the reaction of alpha-halo carbonyl compounds with thiosemicarbazones. Some pyridine derivatives have been synthesized by the reaction of chalcone with cyanothioacetamide and/or malononitrile. Spectroscopic methods have been used for elucidating molecular structures of the products. Cytotoxic activity of several derivatives has been tested against human breast cancer (MCF-7), human colon cancer (HCT-116) and human liver cancer (Hep-G2) by the SRB method. Most of compounds exhibit mild effect on the tested cell lines. One of thiazolidin-4-one derivatives has been characterized by moderate to strong effect on MCF-7 cell line.

Keywords: thiosemicarbazone, thiazole, pyridine, antitumor activity

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INTRODUCTION

Rhodanines and their bioisostere thiazole derivatives [1–5] are considered as promising bioactive compounds (Fig. 1).

Molecules containing fluorine atoms exhibit a wide range of biological activities including anticancer activity [6, 7].

Thiosemicarbazides are widely used in medicinal chemistry as efficient intermediates in synthesis of biologically active compounds including antiviral [8], anticancer [9], antitumor [10], and some more. Thiosemicarbazone is one of the precursors in construction of novel class of thiazole containing rhodanine moiety (Fig. 1) characterized as anticancer [11], antioxidant [12], anti-inflammatory [13], antimicrobial [14], and anti-apoptotic [15] agents. Based on the above and our prior experience in synthesis of new heterocyclic compounds [16–24], we have synthesized novel 2-{[1-(4-fluorophenyl)ethylidene]hydrazono}thiazole derivatives and tested their anti-proliferative activity.

RESULTS AND DISSCUSION

In the current study, 4-flouroacetophenone thiosemicarbazones **3a**–**3c** were synthesized by reacting 4-flouroacetophenone **1** with thiosemicarbazides **2a**–**2c** in acidic media (Scheme 1). Analytical data of compounds **3a**–**3c** were similar to those reported earlier [25, 26].

Thiosemicarbazone derivatives were used as building blocks in the following synthesis of new fused thiazole rings [27, 28]. Hydrazine carbothioamide derivatives (**3a**–**3c**) were reacted with α-halo acid or α-halo esters (bromoethanoic acid, ethyl 2-bromoethanoate and ethyl 2-bromopropanoate) in the presence of CH_3COONa, the

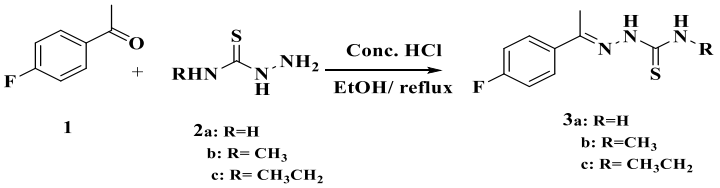
SUMMARY

Design and Synthesis of Some New Thiazole, Pyridine and Pyrimidine Derivatives for Biological Evaluation

The purpose of this work is to synthesize novel biologically active compounds as drugs analogues through the following two parts:

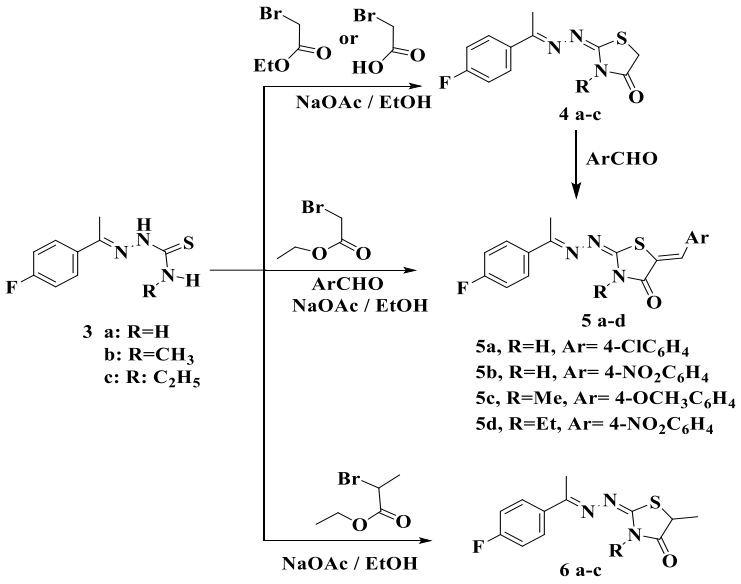
Part ١: Synthesis, characterization and investigation of antiproliferative activity of novel thiazole, pyridine and pyrimidine derivatives using Fluoroacetophenone

In this part of study, ٤- fluoroacetophenonethiosemicabazones **٣a-c** were synthesized by reacting ٤-flouroacetophenone **١** with the thiosemicarbazides **٢a-c** in the presence of few drops of conc. HCl , in refluxing ethanol (**Scheme ١**).



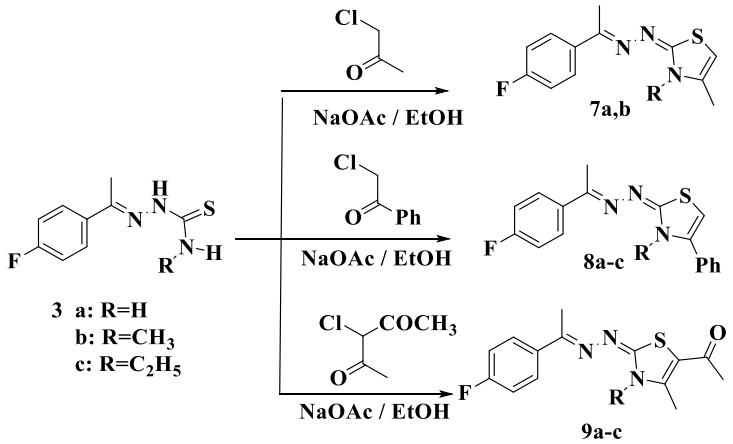
Scheme ١: Synthesis of hydrazine carbothioamide derivatives ٣a-c

The thiosemicarbazones **(٣a-c)** were reacted with *α*-haloacid and/or *α*-haloesters namely; ٢-bromoacetic acid, ethyl ٢-bromoacetate and ethyl ٢-bromopropanoate, in the presence of anhydrous sodium acetate, the substituted thiazolidinones **٤a-c, ٥a-d** and **٦a-c** were obtained respectively (**Scheme ٢**).



Scheme ٢: Synthesis of new thiazolidine-٤-one derivatives

Different α-halo substituted ketons namely, ١-chloropropane-٢-one, ٢-chloro-١-phenylethane-١-one and ٣-chloropentane-٢,٤-dione were reacted with thiosmicarbazone derivatives (**٣a-c**) under refluxing condition to afford the thiazole derivatives **٧a,b, ٨a-c** and **٩a-c** respectively (**Scheme ٣**).



Scheme ٣: Synthesis of new thiazole derivatives

Treatment of the thiosemicarbazones **٣a-c** with ٢-oxo-*N*-arylpropanehydrazonoyl chloride **١٠a-c** in the presence of a catalytic