شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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جامعة عين شمس

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قسم

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Synthesis and Reactions of Some Heterocyclic and Poly Heterocyclic Nitrogen Compounds with Expected Biological Activities

A thesis submitted for the degree of Ph.D. of science in chemistry

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Synthesis and Reactions of Some Heterocyclic and Poly Heterocyclic Nitrogen Compounds with Expected Biological Activities

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ABSTRACT

The aim of this work is the synthesis of new biologically active compounds through three parts.

Part 1: Synthesis of new pyrazole and pyridine derivatives as tricyclic fused ring system via reaction of some 2-aryl-1,3-indandione derivatives with different nitrogen nucleophiles e.g. hydrazine derivatives, ethyl cyanoacetate, and malononitrile. Molecular docking, antiproliferative activities and kinase inhibition screening of some new derivatives were described against breast, leukemia, lung, melanoma and prostate carcinoma cell lines.

Part 2: Synthesis of 2-thiopyrimdine, thiazolopyrimidine and triazolopyrimidine derivatives as tri-, tetra- and pentacyclic fused ring system. Thiopyrimidine derivatives were obtained by reaction of arylindandione derivatives with either thiourea, or 2-aminothiouracil. Thiazolopyrimidine and triazolopyrimidine derivatives were prepared from the reaction of thiopyrimidine derivatives with chloroacetic acid, 2-propanoic acid, and 3-chloroacetyl acetone, hydrazine hydrate, or various hydrazonyl chloride derivatives. Many of the newly synthesized derivatives were screened as antiviral agents against HSV-1 including cytotoxicity, and mechanism of action of the most active compounds were also performed.

Part 3: Synthesis of macrocyclic Tröger's base analogue via the reaction of *p*-aminobenzylidine-1,3-indenedione with paraformaldehyde and trifluoroacetic acid. Treatment of the Tröger's base with dimethyl sulfate, acetic anhydride, benzoyl chloride, or trifluoracetic anhydride can afford the corresponding *N*,*N*′-disubstituted phenhomazines. Complexation of the Tröger's base with ferric nitrate trihydrate or nickel chloride hexahydrate has resulted in the corresponding complexes. All the newly synthesized Tröger's base and the derived *N*,*N*′-disubstituted phenhomazines were tested for anticancer activity against Hep-G2, HCT-116 and MCF-7 cancer cell lines.

The structure of the newly synthesized compounds of the three parts were confirmed by elemental analyses and spectral data.

Keywords: 2-Aryl-1,3-indandione, pyrazole, pyridine, 2-thiopyrimidine, Thiazolopyrimidine, Triazolopyrimidine, Tröger's base derivatives, Anticancer, Antiviral.

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Synthesis and Anti-Proliferative Activity of Novel Tricyclic Compounds Derived from 2-Substituted 1,3-Indandione

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Abstract—A new series of fused 1,3-indandione derivatives has been synthesized and evaluated for anti-proliferative activity. 2-Alkene-1,3-indandione derivatives have been used as the precursors of a number of tricyclic compounds. The latter have been tested for anti-proliferative activity.

Keywords: 1,3-indandione, anti-proliferative, p38αMAPK and ERK1/2 protein kinases, molecular modeling

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INTRODUCTION

Indenone scaffold fused with different heterocycles has been identified as a promising anticancer molecular system. Indenopyrazoles, indenopyrimidines and indeno[1,2-*c*]isoquinoline have received much attention as anti-cancer agents due to their broad spectrum of kinase inhibition such as platelet-derived growth factor receptor inhibitors (PDGFR), CDK inhibitors and tubulin polymerization inhibitors [1–4].

In the current study the newly synthesized indenone derivatives were tested for their *in vitro* antiproliferative activities, kinase inhibition activity. Molecular modeling was carried out for their molecular structures.

RESULTS AND DISCUSSION

1,3-Indandione (**1**) reacted with aromatic aldehydes **2a**–**2d** at 50–60°C giving the corresponding 2-substituted derivatives **3a**–**3d**. One-pot reaction of 1,3-indandione **1** with ethylcyanoacetate and aromatic aldehydes **2a**, **2b** in the presence of anhydrous ammonium acetate proceeded via intermediates **A** and **B** affording 2-pyridinone derivatives **4a**, **4b** [5] (Scheme 1).

Reaction of arylidineindanedione **3a** and **3b** with hydrazine hydrate in ethanol [6] or in glacial acetic acid [7] gave indenopyrazole derivatives **5a**, **5b** and **6**. Also, compounds **3a**, **3b** reacted with 2,4-dinitrophenylhydrazine or phenyl hydrazine to give the corresponding arylindenopyrazole derivatives **7a**, **7b**. Reaction of compounds **3a**, **3b**, **3d** with semicarbazide or thiosemicarbazide [8] led to amide or thioamide derivatives **8a**–**8d**. The precursors **3a**–**3c** reacted with hydroxylamine hydrochloride to give the respective oxazole derivatives **9a**–**9c** (Scheme 2).

2-Substituted indene-1,3-diones **3a**, **3b** reacted with ethylcyanoacetate [7] to give indenocyanopyridone derivatives **10a**, **10b**, respectively. Reaction of the same precursors **3a**, **3b** with malononitrile [8–10] gave the corresponding derivatives **11a**–**11d**, **12a**, **12b** and **13a**, **13b** (Scheme 3).

Anti-proliferative activity. Anti-proliferative activity of compounds **4**–**13** was tested against breast, leukemia, lung, melanoma, and prostate carcinoma cell lines. Growth inhibitory activity of the screened compounds was evaluated using the MTT method [11] and sorafenib as a reference (Table 1). All compounds exhibited considerably potent anti-proliferative activity against breast (MCF-7 and T47D), leukemia (K-562), lung (A-549), melanoma (MDA-MB-435), and prostate carcinoma (PC-3) cell lines. The compounds **11a** and **11c** displayed the highest potency.