بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

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جامعة عين شمس ـ كليه العلوم – قسم الكيمياء

Utility of Aroyl isothiocyanate in Construction of Novel Heterocyclic Compounds with Anticipated Biological Activity

Thesis Submitted by

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ARTICLE

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Nano nickel [1,2,4]-triazole-3-thiones complex: Design, sonochemical synthesis, and antimicrobial evaluation

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Abstract

A series of new 1,2,4-triazole-3-thiones were synthesized by calm, benign, no risk, eco-friendly, and energy efficient sequential reaction methodology like grinding and ultrasonic (US). In addition, 1,2,4-triazoles were prepared under conventional method and comparative study was done. The synthesized 1,2,4-triazoles were complexed with Ni(II) to produce nanoparticles complexes (NPC's) with average particle size vary from 55 to 100 nm (using scanning electron microscope technique) with good yields via both US and conventional techniques. X-ray diffraction technique and spectra analysis techniques were used to confirm the square planer geometry of the synthesized NPC's. Antimicrobial activity of the prepared 1,2,4-triazoles and their nickel complexes were studied which evaluated a high activity with complexes instead their triazoles.

1 | INTRODUCTION

Multicomponent reactions have achieved substantial influence as a tool for the syntheses of varieties of significant compounds in pharmaceuticals applications. Improvement of fewer hazardous synthetic methodologies for organic reactions is one of the preponderances required after the troubles in existing research. Therefore, green chemistry[1–3] is planned to be a native aim in the synthesis of heterocyclic compounds. The convenient and rapid synthetic procedure that is energy efficient and atom economy (AE) is highly required.[4–7] To be of practical value, such a procedure should be proper for large-scale operation also. As reported in the literatures, the one-pot stepwise[8–10] synthesis of 1,2,4-triazole-3-thiones, using as starting for many compounds. An alternate approach is that of solid-state grinding, wherein solids are milled together with a mortar and pestle or in a mixer mill to persuade co-crystal formation. In addition to its "green" nature, in that way it avoids excessive using of crystallization solvent, also solid-state grinding offers a means of acquisition nearly quantitative yields with a collective particle size. The technique of co-crystal formation through solid-state grinding has been recognized for a few times.[11,12] A significant development to solid-state grinding was illustrated recently, the co-crystallization kinetics can be significant enhanced by the addition of a few drops of solvent. Nowadays, we perceive that the "solvent-drop grinding" methodology may afford a fruitful means of controlling the polymorphic outcome of a co-crystallization.[13,14]

1,2,4-Triazoles chemistry are fascinating heterocycles and their derivatives specially they belong to isothiocyanates (ITCs)[15–21] class. Also, they possess significant pharmacological activities such as antitumor,[22] antifungal,[23] antiviral,[24] stimulants sedatives,[25–26] anti-inflammatory,[27] and antimycotic agents,[28] for example, **1** fluconazole, **2** voriconazole, **3** Fluconazole, **4** itraconazole, **5** Triazolam, **6** Alprazolam, and **7** Etizolam (Figure 1).

Metal complexes play act a very important role in many fields of physics, chemistry and other matters of science. Extensively, they are consumed in the designing of healthcare products. The approach of nanotechnology is coming into view, a goal to make nanoarrays or nano structures with exclusive properties for individuals of bulk or single particle types.[29] The interaction of nickel as a heavy transition metal with N,S-donor atoms have

ABSTRACT

Abstract

Part I:

VEGFR-2 inhibitors have been becoming one of the most therapeutic strategy for treatment of cancer diseases because of their critical role in preventing cancer growth and metastasis. Herein, new series of novel *N*-(1,3,4-thiadiazol-2-yl)furan-2-carboxamide derivatives were designed and synthesized based on the same essential pharmacophoric features of the reported VEGFR-2 inhibitors by adopting a hybridization of bioisosteric strategy. Antiproliferative activities were biologically evaluated against three human cancer cell lines (MCF-7, HCT-116 and PC-3) using MTT assay technique and doxorubicin was used as a positive control. Compounds, **6**, **7, 11** and **14** were found to be significantly more potent than doxorubicin against all tested cell lines. Moreover, compounds, **6** and **11** proved to be the most active compounds with IC_{50} values of 6.58, 4.19, and 7.76 µM, and 6.41, 5.01, and 8.47 µM, respectively. The most active cytotoxic agents were further evaluated *in vitro* for their VEGFR-2 inhibitory activities. Among them, compounds, **11**, **7** and **15** exhibited excellent inhibition against VEGFR-2 with IC_{50} values of 7.6±0.4, 9.4±0.8 and 8.2±0.4 µM, respectively, compared with pazopanib as control drug with IC_{50} value of 9.7±0.4 µM. Furthermore, structure-activity relationship (SAR) studies indicated the active methylene linker substituted with

heteroaromatic ring enhances the antiproliferative activity. Besides, molecular docking studies were also performed and attributed the promising activity of this series to their hydrogen bonding interactions with the key amino acid residues, Glu885, Cys919 and Asp1026 and hydrophobic interactions with the VEGFR-2 binding site.

Part II:

A series of new 1,2,4-triazole-3-thiones were synthesized by calm, benign, no risk, eco-friendly, and energy efficient sequential reaction methodology like grinding and ultrasonic (US). In addition, 1,2,4-triazoles were prepared under conventional method and comparative study was done. The synthesized 1,2,4-triazoles were complexed with Ni(II) to produce nanoparticles complexes (NPC's) with average particle size vary from 55 to 100 nm (using scanning electron microscope technique) with good yields via both US and conventional techniques. X-ray diffraction technique and spectra analysis techniques were used to confirm the square planer geometry of the synthesized NPC's. Antimicrobial activity of the prepared 1,2,4-triazoles and their nickel complexes were studied which evaluated a high activity with complexes instead their triazoles.

Keywords: Isothiocyanate, Anticancer, VEGFR-2 inhibitors, 1,3,4-thiadiazole derivatives, Molecular docking, 1,2,4-triazole derivatives, green chemistry Nanoparticles, Organometallic, XRD.

List of Abbreviation

List of Abbreviations

AcOH	Acetic acid
Aq.	Aqueous
Ar	Aromatic
b.p.	Boiling point
br.	Broad
cm	Centimeter
d	Deuterated
d	Doublet
dd	Doublet of doublet
DMF	*N*,*N*-dimethyl formamide
DMSO	Dimethyl Sulfoxide
Et	Ethyl
EtOH	Ethanol
Fig.	Figure
h	Hour
hυ	Light
Hz	Hertz
I.R.	Infrared
J	Coupling Constant
m	multiple or medium
M.p.	Melting Point
M.W.	Microwave

min.	Minutes
mmol	milli mole
mol	mole
N.M.R.	Nuclear Magnetic Resonance
OAc	Acetate
p-	Para-position
Ph	Phenyl
PhH	Benzene
Pip.	Pipredine
ppm	parts per million
quin	Quintet
r. t.	Room temperature
s	singlet/ strong/ second
Stirr.	stirring
t	triplet
T	Temperature
TLC	Thin Layer Chromatography
US	Ultrasonic
UV	Ultra-Violet
W	Watt
Δ	heat/ reflux
δ	Chemical shift
υ	Absorption