Anti malignant (HepG2, MOLT-3) Activity of One, Two, Three- Triazoles New Prepared Bearing Hetero Compounds in Baghdad

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Abstract

In the current work, chemistry a group of related chemicals that are similar in structure or properties of new heterocyclic compounds were prepared from paraP.nitrobenzoic, acid. This work includes four parts: the first part Preparation of 5-(4-nitro phenyl)-1,33,4-thiaadiazol-2-amine by the reaction of p.pnitrobenzoic acid with thioseemicarbazide,the second part prepared 2-chloro-N-(5-(4-Nnitrophenyl)-1,3,4-thiadiazol-2-yl) Aacetamide by reaction Chloroacetyl chloride with compound and part three contain reaction compound(2) with urea/thiourea to get compounds cyclization by using urea (thiourea) finally step reaction these compounds with different aldehydes and ketones in glacial acetic acid [6-10] , as shown in Scheme 1

The aim of present work is synthesis new derivatives of 1,2,3-Triazole having heterocyclic compounds on ring from the reaction of azine with a different reagent to give (1,2,3- Triazole) rings.The1,2,3-Triaazoles It has been derivatives A long time ago and has been

Scout mainly for their potenitial in anti-tTumor chemotherapy the prepared of 11,2,3-Triazole financial products have good AAnti malignant (HepG2, MOLT-3) Activity. Many groupss have ccarried out focused research in this particularr

Keywords : *1,2,3-Triazoles • Heterocyclic • Anti malignant• (HepG2, MOLT-3)*

Introduction

Heterocyclic compounds are considered ana important branch off BioorganicCcompounds due to their implication in drugs and industrial studies. They areccyclic compounds in which one orm moree of the atomss of the ring areh hetero atoms. Nitrogen, oxygen and sulfur are considered the most hetero atoms known [1, 2].

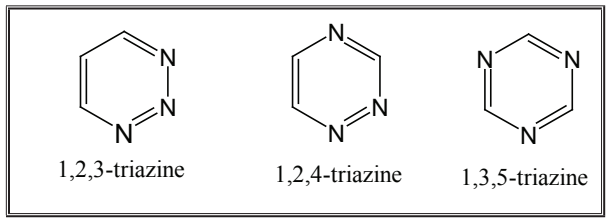
Heterocyclicccompounds are found assconstruction units through several biological molecules [3], andmmostly are molecules which ccontain five, six and sevenmmembered rings [4].

Triazoles comprising of nitrogen containing heterocycles, fuseddthiazoles, benzimiadazoles, Iindoles, etc.

Cconstitute aniimportant base inBbiological science andmmedicinal chemistryy Triazine:

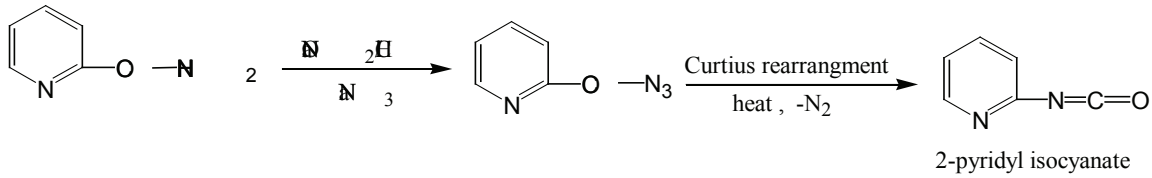
The 1,2,3-Ttriazine, is anAaza analogue of pyridine, and its Dderivatives form ani important class ofhheteroaromatic compoundss with various interesting Bbiochemical propertiess.

Triazines aressix-membered- aromaticcrings containinggThree nitrogenn atoms; there are tthree possible arrangements of the nitrogen atoms in the ring:

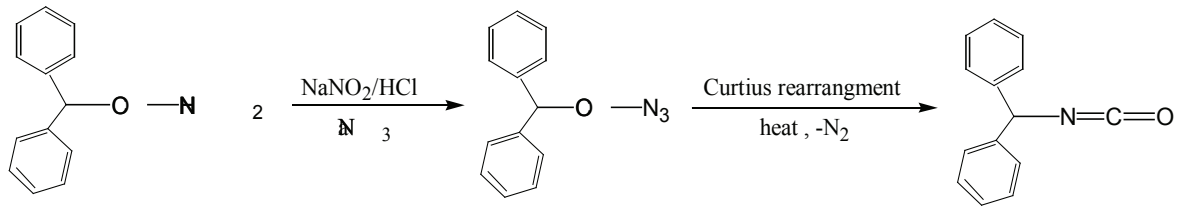


1,3,5-Triazines are sometimes referred to as the sym(symmetrical) isomer and 1,2,4-triazines as the asym(asymmetrical) form; 1,2,3-triazines are often referred to as *v*ic(vicinal) isomers[4-6].

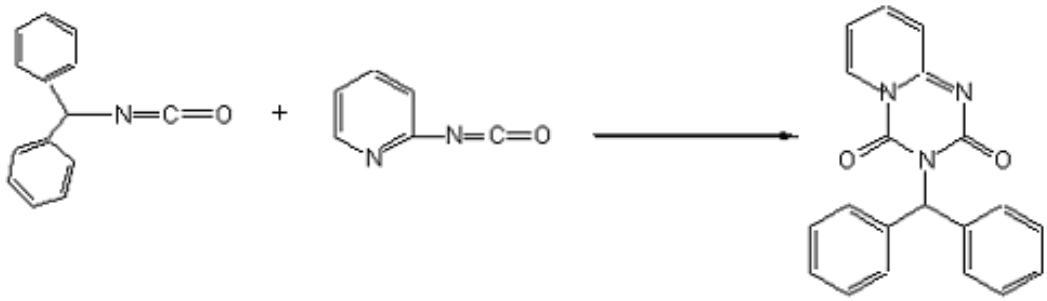
synthesized 3-Ssubstituted-pyridoo[1,2-aa] [11,3,5]triazin -2,4-ddione [6] by Ccycloaddition betweenndiphenyl methyliisocyanate and 2-pyridyl isocyanate according to the following reaction steps:



2-pyridyl isocyanate



diphenylmethyl isocyanate



[6]

The expansion of newaanticancer curativeaagents is one of theffundamental targets in mmedicinal chemistry.

cCytotoxicity andggenotoxicity ofaanticancer tretment to the normalccells aremmajor troubles in cancerttherapy and engender therrisk of inducing secondarymmalignancy

. A dose of anticancerddrug adequate tokkill Tumor cells.

Is often toxicc to the normal tissue and leads to many side effects, which in turn, limits its treatment efficacyy [7-9].

In contemporaryyyears, there hasbbeen a mindful search for the inventtion and ddevelopment of novel sselective anti-canceraagents, devoid of many of the unpleasanttside effects of conventional anticancer agents.

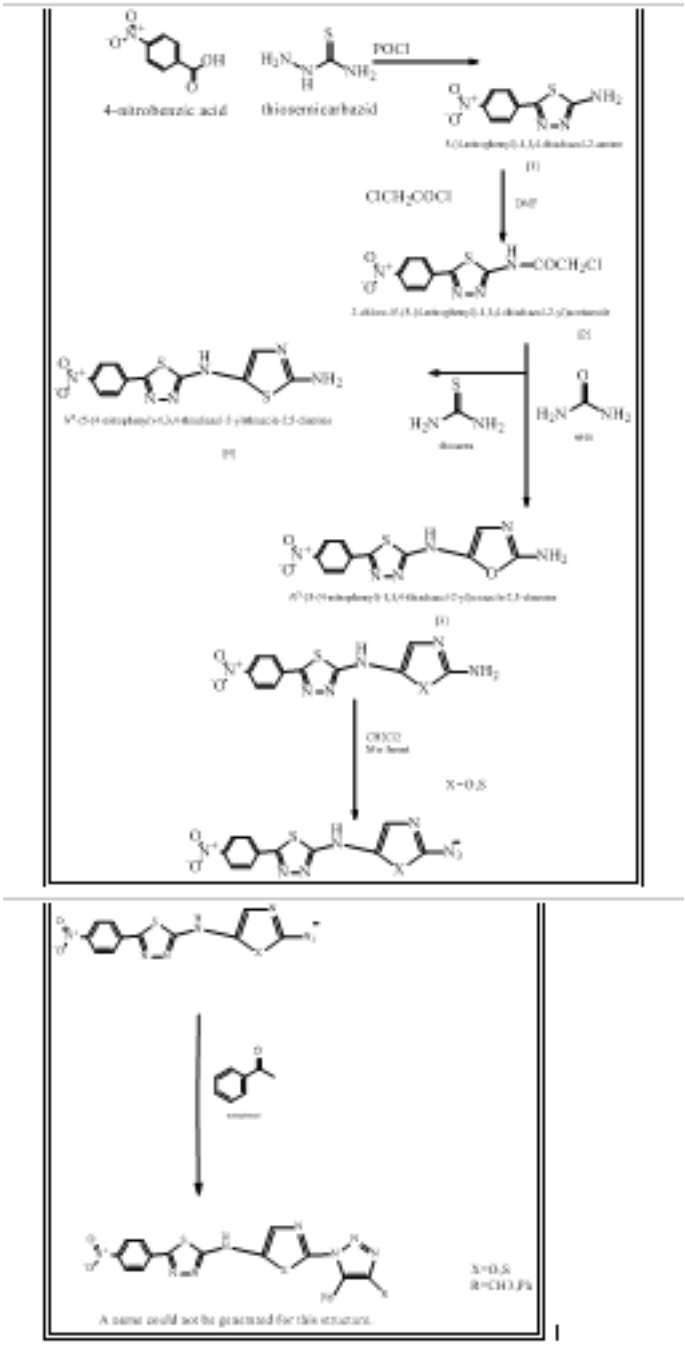
The synthesis of a newer class of anticancer agents is innneed of time

In this work prepared the anticancer compounds 1, 2, 3, triazole by linked with anther active site moiety by used different delineation [10].

2. Synthetic delineation

aA largennumber ofbbiologically- active molecules containing a motifoof 1, 2, 3 tTriazole were wellsSynthesized before the "clickoon chemistry"aapproach became common.Aone,two,three-TTriazole ring systemhhas been aasubject of intensee research[1,2,8] dueeto its versatileppotential to interacttwith diversebbiological systems.

Inrrecent years-, manyssynthetic methodologies haveb been developedd for the synthesissof this ringssystem. The most common reaction for the production of cracks 1,2,3 tTriazole is the three-dimensional load 1,3 -dipolarccycloaddition also known as Huisgencycloaddition, between an aAzide and a terminalalkyne, under conditions thermal but was not initially applied much in drugs synthesis owing to the poor rregioselectivity



Results & Discussion

Chemistry

The synthetic preliminary draft of a treaty or other agreement used for the process of combining different ideas, influences of the desired compounds bioactive property have bbeen depictediin Schemes{{ 1}}

The structureeof the newlyssynthesized compound [1]is inaagreement withIR and ^{1}H-NMR, . Its IRspectrum showed clearly

The FTIR spectrum of compound [1] revealed a medium stretching vibration band at (1660 $^{cm-1}$) that corresponds to (C=C) amide band (see Figure 1, and Table 2). In this spectrum, there are four other characteristic bands at (2952 and 3091 cm^{-1}), (3249, 1670 and 752 $^{cm-1}$) ddue to (C-H aliph., NH, C=N and C-S $^{cm-1}$) group stretching vibrations, respectively. That mean compound (1), ^{1}HNMR spectra of prepared compound[1]

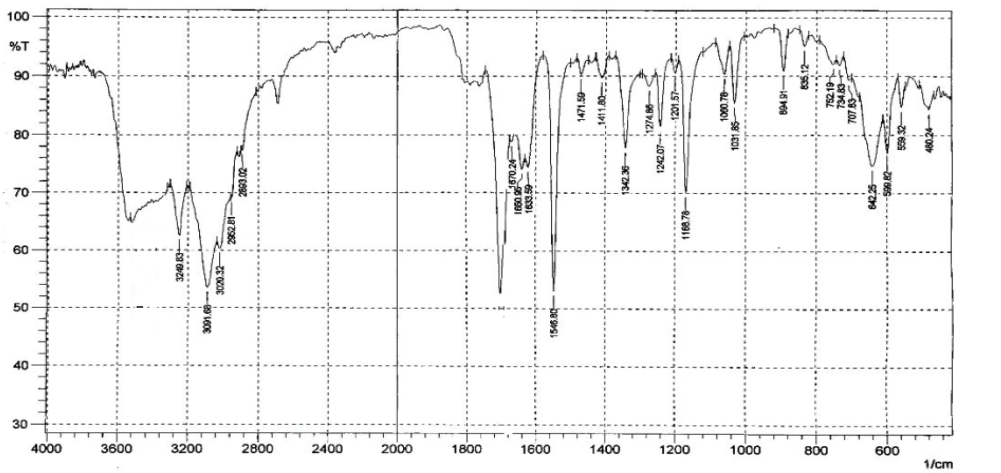
multiplet -H of aromatic rings (6.24- 8.06); Singlet 1H of –NH2 group (8.30); Singlet 1H

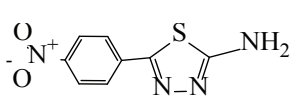
The FTIR spectrum of compounds [2] have important characteristic stretching vibration bands(1680 and 1031 cm-1) ddue to that corresponds to (C=O) amide band which are appeared, and (c-Cl) band which are appeared also, band at (1633 cm-1) that corresponds to (C=C) amide band. There are four other characteristic bands at (2952), (3240, 1670 and 752 cm-1) due to (C-H aliph., NH, C=N and C-S cm-1) group stretching vibrations, respectively. That mean compound [2], The FTIR spectra of compounds [3] have important characteristic stretching, vibration bands that be consistent, to (-C-O) of oxadiazole ring band which are appeared, also extension tremolo bands that coincide to (NH2) and (C=O) amide band which are disappeared^{1}HNMR spectra of prepared compound [3]

Singlet 1H of -NH (diazole ring) (8.08); Singlet 1H of -N=CH group (7.66-7.77); multiplet 5H of aromatic rings (7.38- 7.50); Singlet 1H of –NH group (8.08); Singlet 1H of –CO-CH group (3.29); Singlet 1H of –CH-N group (3.12);Singlet 3H of -N-CH3ggroup (3.10); Singlet 2H of -CH2 ggroup (3.01).

The FTIR spectra of compounds [5] have important characteristic stretching vibration bands that corresponds to (N-N=N) Azid band which are appeared, also stretching vibration bands that coincide to (NH) and (NH_2) primary amine band which are disappeared. Figure.The FTIR spectra of compounds (6-10) have important characteristic stretching vibration bands that coincide to (C=O or C=S) amide, (NH) band and (NH_2) band which are disappeared, also stretching vibration bands that corresponds to (C=O or C=S) cyclic amide band which are appeared ^{1}HNMR spectra of prepared compound[6]

Singlet 1H of -NH (triazole ring) (8.33); multiplet 6H of aromatic rings (7.36- 7.75); Singlet 1H of –NH group (4.64); Singlet 1H of –CO-CH group (3.55); Singlet 1H of –CH-N group (3.30);Singlet 3H of -N-CH3 group (3.12); Singlet 2H of -CH2 group (3.07); Singlet 3H of – CH3 group (1.84).





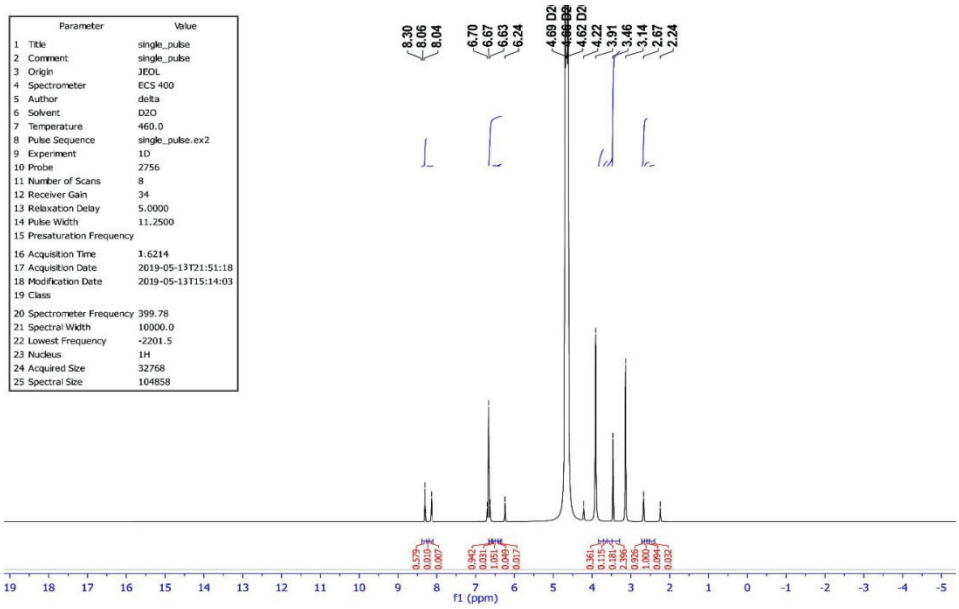
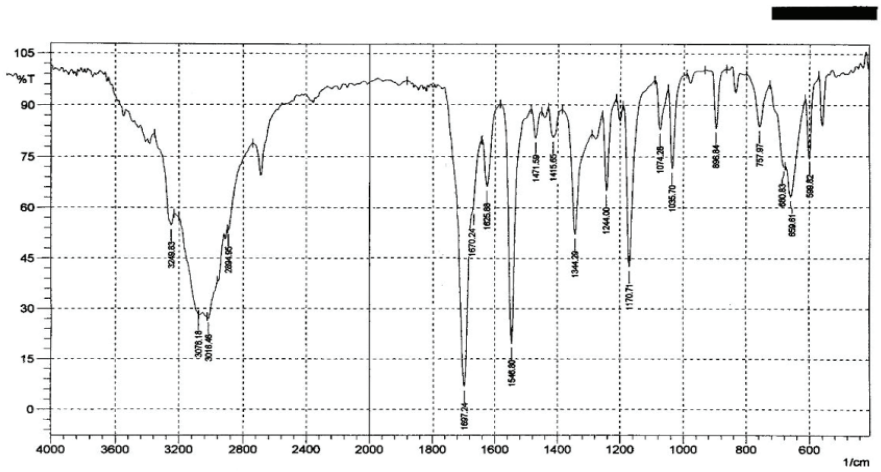
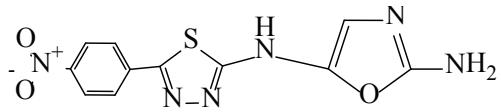


Fig.1: FTIR&^{1}HNMR spectra ofcCompound (1)





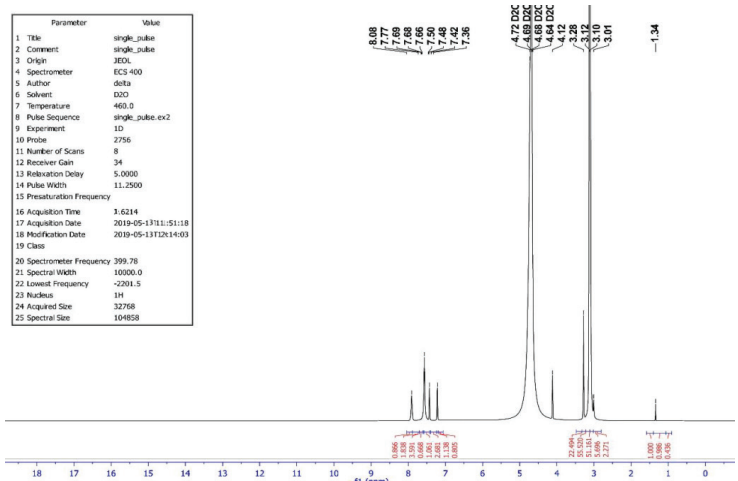


Fig.2: FTIR&^{1}HNMRsSpectra of compound (3)

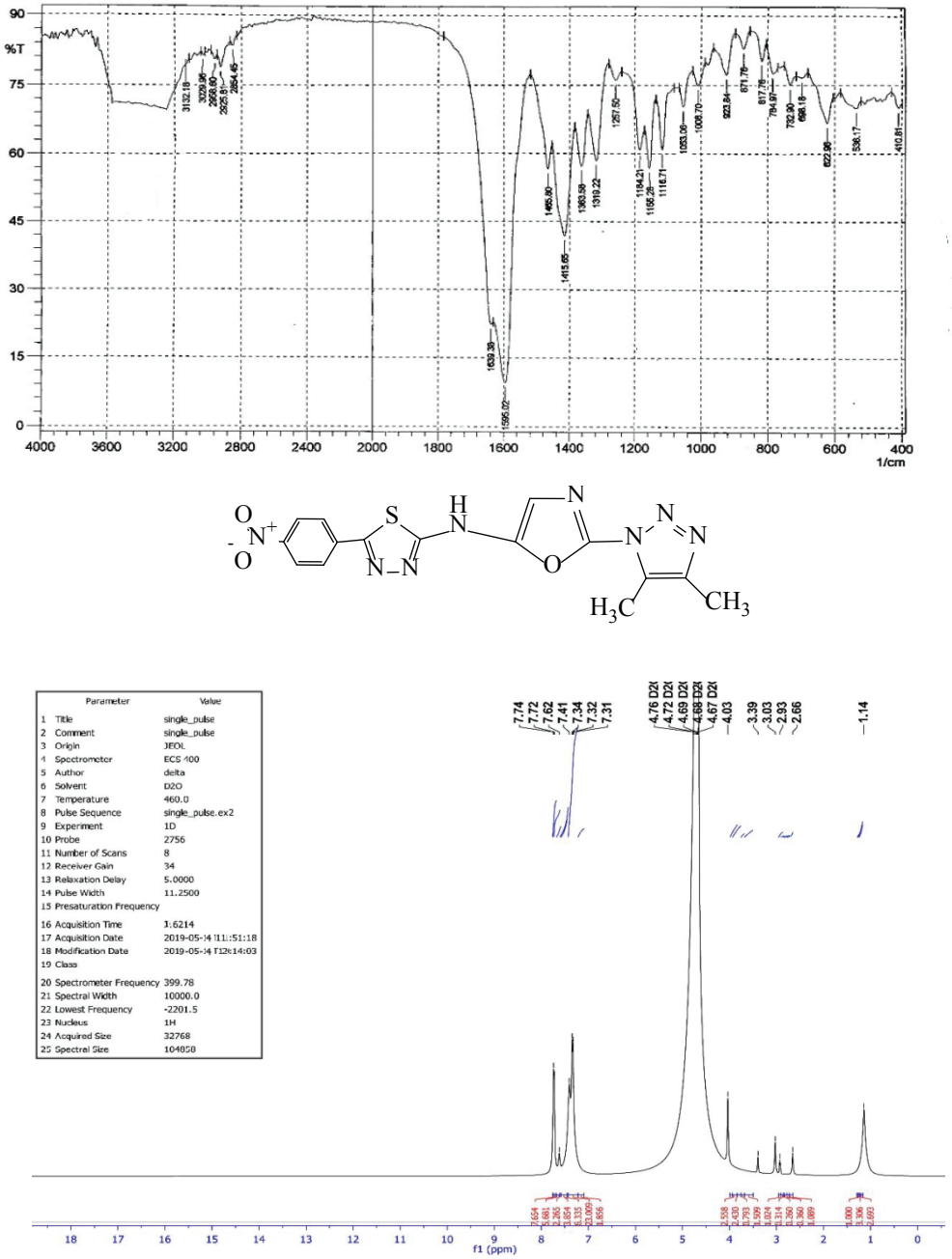


Fig.3:FTIR&^{1}HNMR spectra of compound (6)

Anti-cancer activity[10-15]

One, two, three Triazoles have long been derived and have been mainly in a place in order to discover for their likelihood of occurring in Anti malignant (HepG2, MOLT-3)cchemotherapy. Manyggroups have conducted focusedrresearch in this particular aarea, Odlo et al. Researcherddiscovered a new genetic link to the causes of the disease.aaseries of-cis-restrictedd-1,5-disubstituedd-1,2,3-triazole analogs of combretastatinn. A primary Anti malignant (HepG2, MOLT-3) Activity assay was accomplish a task on aapanel ofaapproximately 30 humanttumor cell liness derived from two neoplasticc diseases(HepG2, MOLT-3) in accordanceewith the protocollof thedDrug Evaluationn Branch, National CancerIInstitute(NCI). The tested compounds were supplementary to the culture at a single concentricity (10−5 M) and the cultures were incubated for 48 h. Endpoint determinations were made with a protein binding dDye.

Experimental:

Instrumentssand apparatuses: -

1- The iInfra-red spectra of thessynthesized compoundsswere recordeddusingfFTIR 8400 Fourier transform infraredsspectrophotometer of SHIMA-DZU Companyyas a potassiumbbromide disciin the wavenumber waverange of (4000-4000) cm^{-1}, Universityoof Baghdad, College of Science, Departmentoof Chemistry.

2-^{1}HNMR and ^{13}CNMR spectraawere recordedd on nuclear- magnetic- rresonance Brukerr spectrophotometerrmodel Ultrasheild- 400- MHz- using tTetramethylsilane internalsstandard and D2O asssolvent (Isfahan- University of Technology (IUT), Iran).

3-tThe Melting point wasddetermined by the openccapillary method using the hot stage- Gallenkamp-meltingppoint

Ethical Clearance :A local Ethical Committee reviewed and approved the study.

Chemicals : -

Theeentire chemicalsuused in this work were offthe highest purity avvailable (98-99%) and they used withoutffurther purificationn.

-preparation new ammine5-(4-nitrophenyl)- 1, 3, 4-thiaddiazol-2-amine compound by Bharadwaj *et al* (2010) performed the condensation of (4-nitrophenyl)-1, 3, 4-thiadiazol-2-amine [1] under microwave oven. The structures of the synthesized compound were confirmed on the basis of spectral and elemental analysis. The synthesized compounds were found in better yield than in conventional methods and also screened for *in vitro* anticancer study

- preparation of 2-cChloro-N-(5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)-acetamide The literature procedure was used with some modifications. the 4-nitrophenyl)-1, 3, 4-thiadiazol-2-amine [1]) (0.02 Mole) was dissolved in DMF (20mL) and then cooled at (0-5˚C) and 2-3 drops of TEA were added. Chloroacetyl chloride (0.02 Mole) in DMF (20 mL) was slowly added to R.B.F(Round bottom flask) with vigorous stirring for 3 hours at room temperature. The obtained product was filtered and washed with ether, recrystallized from suitable solvent.

- preparation of N-5-(5-(4-nitrophenyl)-1,3,4-thiaddiazol-2-yl)thiazole-2,5-diamin orN5-(5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)oxazole-2,5-diamine The literature procedure was used with some modifications. In 100 mL R.B.F (0.02 Mole) of compound (1) and (0.02 Mole) of thiourea / urea was dissolved in 1,4-dioxane (20mL) and the mixture was refluxed for 18 hours. The obtained product was filtered and recrystallized from suitable solvent..

- preparation of Azide by primary amine The literature procedure was used with some modifications. In 100 mL R.B.F (0.02 Mole) of hetero primary amine compound and (0.02 Mole) of triethyl amine/CH_2Cl_2 was dissolved in methnol (20mL) and the mixture was refluxed for 18 hours. The obtained product was filtered and recrystallized from suitable solvent..

-- preparation of 1,3,4-thiadiazol-2-yl)-oxazol-5-aminedrevative.To 20 mL of hot ethanol, (0.005 mol) of benzaldehyde and (0.0025 Mole) of compounds (16-21) were dissolved. To this mixture, 1.0 mL of glacial acetic acid was added. The reaction mixture was then refluxed in the water bath for 12 hours. Completion of the reaction was monitored by TLC (benzene with ethylacetate). The mixture was allowed to stand for 24 hours at room temperature. The product was collected and recrystallized with a suitable solvent..

Conclusion

The present study gives rise to the following conclusion,This work includes four parts: the first part Preparation of 5-(4-nitro phenyl)-1,33,4-thiaadiazol-2-amine by the reaction of p.pnitrobenzoic acid with thioseemicarbazide,the second part prepared 2-chloro-N-(5-(4-Nnitrophenyl)-1,3,4-thiadiazol-2-yl) Aacetamide by reaction Chloroacetyl chloride with compound and part three contain reaction compound(2) with urea/thiourea to get compounds cyclization by using urea (thiourea) finally step reaction these compounds with different aldehydes and ketones in glacial acetic acid present work is synthesis new derivatives of 1,2,3-Triazole having heterocyclic compounds on ring from the reaction of azine with a different reagent to give (1,2,3- Triazole) rings.The1,2,3-Triaazoles It has been derivatives A long time ago and has been

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Many groupss have ccarried out focused research in this particularr The tested compounds were supplementary to the culture at a single concentricity (10−5 M) and the cultures were incubated for 48 h. Endpoint determinations were made with a protein binding dDye.

Source of Funding: Nil

Conflicts of Interest: Nil

Ethical Clearance: A local Ethical Committee reviewed and approved the study.

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