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New Oxadiazole Derivatives with Ag NPs :Synthesis, Characterization and Antimicrobial Screening

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ABSTRACT

The new novel Oxadiazole derivatives linked to Indole moiety were prepared, and biological screened for the anti-microbial activities. These compounds (3) and (4) were obtained from many series reactions. Four steps reaction procedure was utilized that start with the first step included simple method of synthesis 2-(2-chloroacetyl) hydrazinecarbothioamide (1) from refluxing equal moles from thiosemicarbazide and chloroacetylchloride. Compound (1) was used as the starting substance for preparing new 2-(2-(1*H*-indol-3-yl)acetyl)hydrazinecarbo thioamide (2) via a refluxing with Indole by using anhydrous Na_2CO_3 in Ethanol as a solvent. On the other hand, new Oxadiazole derivative (3) was prepared via a cyclization method of compound [2] in H_2SO_4. The new synthetic schiff base (4) was synthesized via condensation reaction of compound (3) with substituted aromatic aldehyde in ethanol. Finally, the new nanocomposites based Indole moiety and oxadiazole ring coated silver nanoparticles (AgNPs) were synthesized by using silver nitrate with the final oxadiazole derivative(4). All prepared compounds and chemical structure were proved by FTIR, ^{1}HNMR spectroscopy and colloidal (Ag NPs) it has been confirmed by XRD,SEM ,UV-Vis. Also the antimicrobial screening of the synthesized compounds against two resistant pathogenic bacteria (*G+*) *Staphylococcus aureus* , *E. coli*(*G-*) and *P. aeruginosa*(*G-*) was examined *in vitro* comparable with ampicillin and cefaxim as standard antibiotic, and they exhibited positive result.

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INTRODUCTION

The Oxadiazoles are very enormous diversity of useful heterocyclic compounds containing biological effects that are attributed to Oxygen and 2 Nitrogen atoms which forms the five membered rings [1]. The Oxadiazoles most used route by reaction between acid hydrazine hydrate and acids chlorides cyclization occurs via dehydrating agents such as ($POCl_3$, $SOCl_2$)[2]. Many researchers reported that both (*G+*) and (*G-*) bacteria are affected by oxadiazoles derivatives[3,4]. The gram negative has multi-layered cell walls and the gram positive has one layer cell wall so that why there is different in the sensitivity against antimicrobial agents [5]. The oxadiazole ring has many bio properties such as hypoglycemic [6], antifungal [7], antineoplastic [8] and antiviral activities [9]. Oxadiazole classified as therapeutic molecules has attracted many researchers to develop more active selective molecule screened

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higher pharmacological efficiency [10, 11]. Recently, Ag NPs have extremely interesting biological characteristics, from the wide spectrum antibacterial actions to the anti-cancer and antiviral activities, due to the fact that they prevent the bacterial growth and inhibit their activities[12]. Therefore , this study attempted to synthesis Nanocomposities through heterocyclic compound based oxadiazole ring with Silver (Ag NPs) to increase antibacterial activity.

MATERIALS AND METHODS

All raw chemical materials were supplied from ROMIL chemical Co. and used as received. FT-IR measurement was carried out by (Bruker) FTIR spectrophoto -meter. ^{1}HNMR spectra were recorded with Bruker spectrophotometer model ultra-shield at (400 MHz) using DMSO-d_6 as a solvent in university of Shiraz, Iran. Electronic spectra were determined using UV-1800 Shimadzo. The sliver nanoparticles also were confirmed by using SEM microscopy (Nova NanoSem 450), FEI FESEM and XRD analysis type (Xpert MPD).

The reaction series progressing to the forming a new Ag Nanocomposite is summarized in Fig. 1.

Synthesis of 2-(2-chloroacetyl) hydrazinecarbothioamide (1).[13]

Thiosemicarbazide (2.0 g 0.0128 mol) Et_3N (1.6 mL 0.0130) were cooled to $0C^0$ under stirring then added drop by drop of chloroacetylchloride (1.2mL). The combination was kept string for 2hrs at room temp. After that the temperature of heating was up gradually to (80-90)^{0}C for 4hrs. The

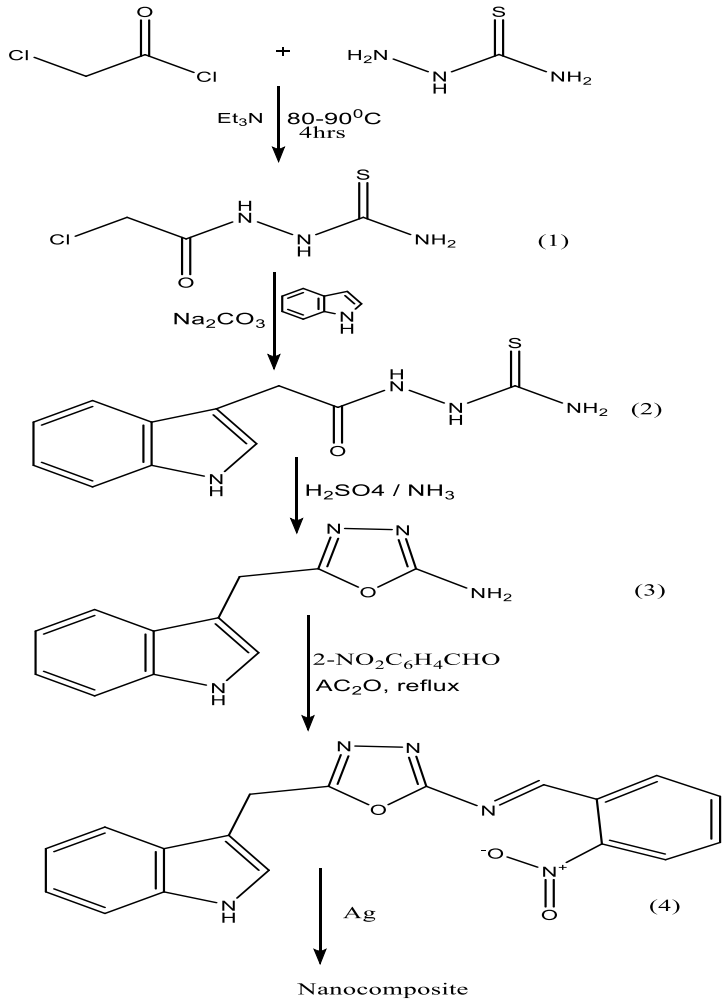


Fig. 1. Synthesis of target compounds

complete mixture was dripped into ice water and the obtained crystal filtered and recrystallized from EtOH. Physical properties of comp. (1) and yield are listed in the table (1). IR(cm^{-1}, KBr):3400-3427, 3290(NH, NH_2), 2875-2955(C-H alph),1630(C=O amide),742(C-Cl).

Synthesis of 2-(2-(1H-indol-3-yl)acetyl) hydrazinecarbothioamide (2)[14].

Indole (1.17 g, 0.01 mol) with 2-(2-chloroacetyl) hydrazinecarbothioamide (1) **(**2.18 g, 0.01 mol**)** in EtOH (35 m L) and anhydrous Na_2CO_3 (9.01 g). The mixture were refluxed heating in steam bath for 9hrs at (70 -80) C^0, the mass left to cooled of then filtered under reduced pressure. The P.P.T thus collected were recrystallized from absolute ethanol, the analytical data given in Table 1 IR (cm^{-1}, KBr): 3130(NH of Indole) ,3290-3300(NH,NH_2), 3041(C-Harom.), 2837(CH_2) ,1722(C=O amide). ^{1}HNMR (DMSO-d_6) ppm: δ =10.00 (s,1H ,NH Indole), 8.50 (s,4H,NHNHCSNH_2), 7.20-6.70(m,5H,Ar-H), 4.22(s,2H,CH_2).

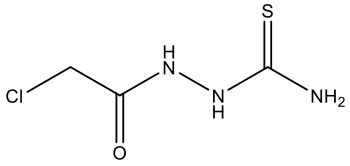
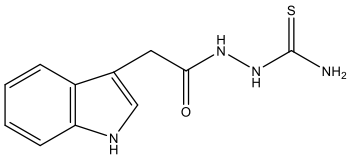
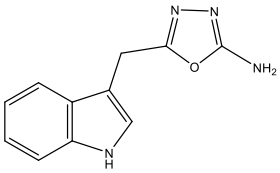
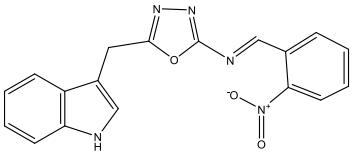
Synthesis of 5-((1H-indol-3-yl) methyl)-1,3,4-oxadiazol-2- amine (3) [15].

2 - (2 - (1 *H* - i n d o l - 3 - y l) a c e t y l) hydrazinecarbothioamide(2) (5.80 g, 0.01 mol) and H_2SO_4 concentrated (18mL) were sttired for 14 hrs at room temperature then cooled off to (5^0C) and treated with NH_3 solution . The mixture kept under stirring for half hour. The solid mass which is formed was dehydrated and recrystallized from methanol. the analytical data given in Table 1. IR(cm^{-1},KBr) 3120(NH of Indole), 3400(NH_2), 3066(C-Harom), 2985(CH_2),1690(C=N), 1080(C-O-C). ^{1}HNMR (DMSO-d_6), ppm: δ = 10.12 (s, 1H, NH Indole); 8.41 (s, 2H,NH2); 7.81-7.00(m,5H,Ar-H);4.15(s,2H,CH_2).

Synthesis of 5-((1H-indol-3-yl) methyl)-N-(2-nitrobenzylidene)-1,3,4-oxadiazol-2-amine(4) [16,17].

5-((1*H*-indol-3-yl)methyl)-1,3,4-oxadiazol-

Table 1. Physical and analytical data of compounds (1-4)

	physical characters			
No.	Structure	M.P °C	colour	Yield%
1		185-187	Pale yellow	65
2		190-192	Off white	70
3		197-199	Brown	80
4		178-180	Dark yellow	81

2-amine(3)(5.4g,0.01mol) dissolved in ethanol 70mL, glacial acetic acid 0.5ml, (0.01 mol ,2.0 g) 2-nitro benzaldehyde was added . Combination was refluxed for 10 h (80-90 °C). The solid achieved was filtered off, and washed with mix of distilled water and ether petroleum (1:1), recrystallized from absolute ethanol. The physical properties of compound (4) and yield are listed in the table (1). IR (cm^{-1},KBr): 3200(NH of Indole), 3030(CH aroma), 2835(CH_2),1624(C=N) 1599, (C=C arom ring),1050(C-O-C).

Silver nanoparticle synthesis

Colloidal silver nanoparticles (Ag NPs) were synthesized by take (11mL,1.2 M) of silver nitrate solution and added drop by drop into a (25mL, 2.5 M) sodium borohydride solution in a cold bath and kept vigorous stirring at 4 C^0 degrees. Using extra amount of sodium borohydride to keep the BH_4^- surrounding the (Ag NPs) in solution moiety reaction continuous stirring till the color changed to pale yellow first and dark yellow [18]. The organic nanomaterial was prepared as follow.

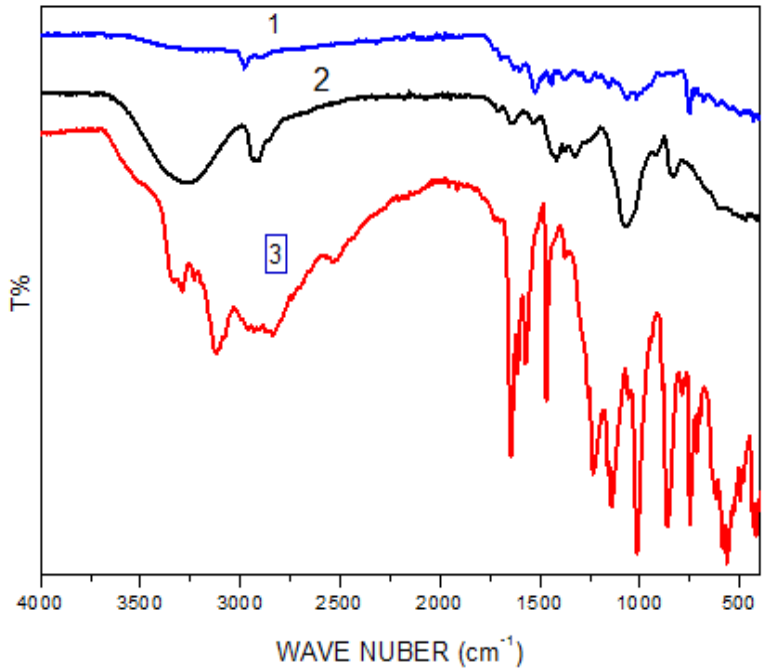


Fig. 2. FTIR-spectral data for compunds (1-2-3)

Table 2. The zone of inhibition in (mm) for Ag Nanocomposite

Comp.	Inhibition zones (mm)			
	Compound Concentration (μg/mL)	*E.coli*	*P. aeruginosa*	*S. aureus*
Ag Nanocomposite	50	17	--	10
	100	22	12	11
	200	22	12	11
	Minimum inhibitory conc. M.I.C (μg/mL)			
	E.coli	*P. aeruginosa*		*S. aureus*
	40	90		40
control	--	--		--
cefaxim	40	300		300
Amoxicillin	13	150		200

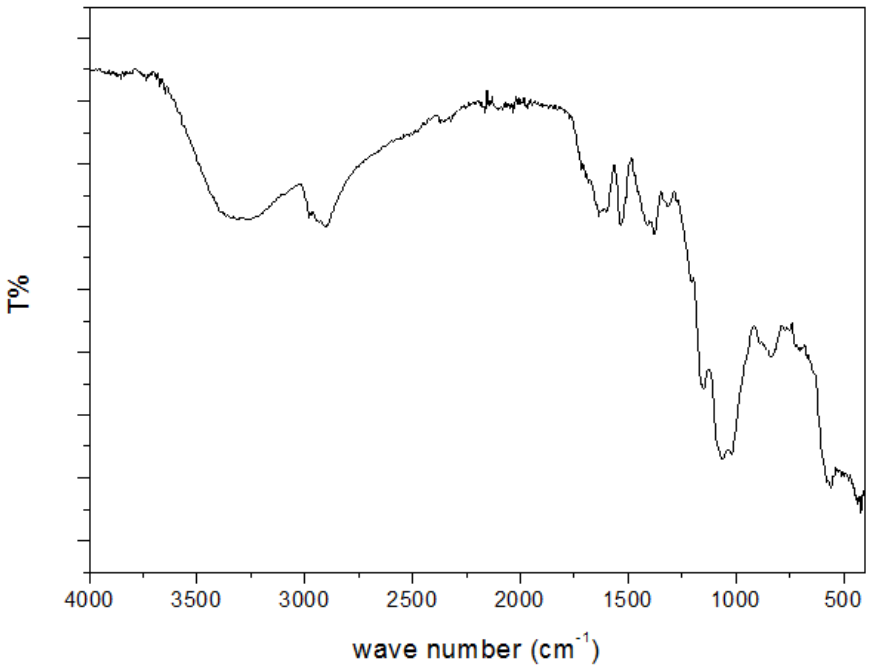


Fig. 3. FTIR-spectral data for compound (4)

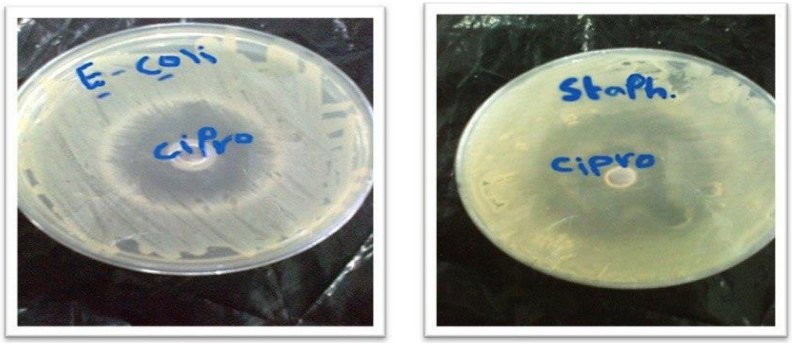


Fig. 4. The effect of Ag Nanocomposite against bacteria

The oxadiazole derivative from step one dissolved in 1.5 DMF mixed with different amount of (Ag NPs) 1\5 in (25mL) round flask on hot path at 85^{0}C under magnetic stirring for one hour to ensure the mixing complete between the content of mixture. Then the homogenous mixture transfer to a glass dish and dried in an oven at 75^{o}C to remove the resident solvent from the prepared nanoparticle composite and the result confirmed by X-RAY diffraction.

Biological screening

The antimicrobial potency was screened by using the usual method of cup plate The microorganisms which used (*E.coli, P. aeruginosa , S. aureus*). Nutrient agar media were prepared in Petri-dish as culture media [19,20] . By bunching the agar media with a sterile probe to make pore (6mm) the solution of different concentration made from the target compound Ag Nanocomposite by DMF taken as blank and Cefixime, Amoxicillin were taken as positive control[21,22]. The plates were incubated for 24 hrs at 37^{0}C. The inhibition zones data for antibacterial Ag Nanocomposite compound are listed in Table 2. The zones of the microbial increase were measured in millimeters.

RESULTS AND DISCUSSION

This study procedure is to perform the synthesis of 5-membered cyclic ring oxadiazole (3-4) based on Indole. The compounds were exploited to made new oxadiazole derivatives represented by final compounds which consist four steps Fig. 1. Stretching band of (NH) belonged to Indole appeared in (2939-3200) cm^{-1},(CH_2) at 2835 cm^{-1} (C-H) aromatic at (3030) cm^{-1}, (C=C) aromatic ring at (1599) cm^{-1} . Compounds (1-4) have been totally characterized and correlated with their spectroscopic analysis (Figs. 2and 3) and their physical properties are explains in (Table 1) [23,24].

The antibacterial potency of the synthesized Ag Nanocomposite was achieved by agar cup plate method [18] the mean radius of zone inhibition (mm) and MIC (μg/mL) were tested in comparison with cefixime, amoxicillin antibiotics. The inhibition of Ag Nanocomposite shows that the oxadiazole derivatives with phenyl ring made the biological activity at the high level of affection against the significant type of bacteria , this could

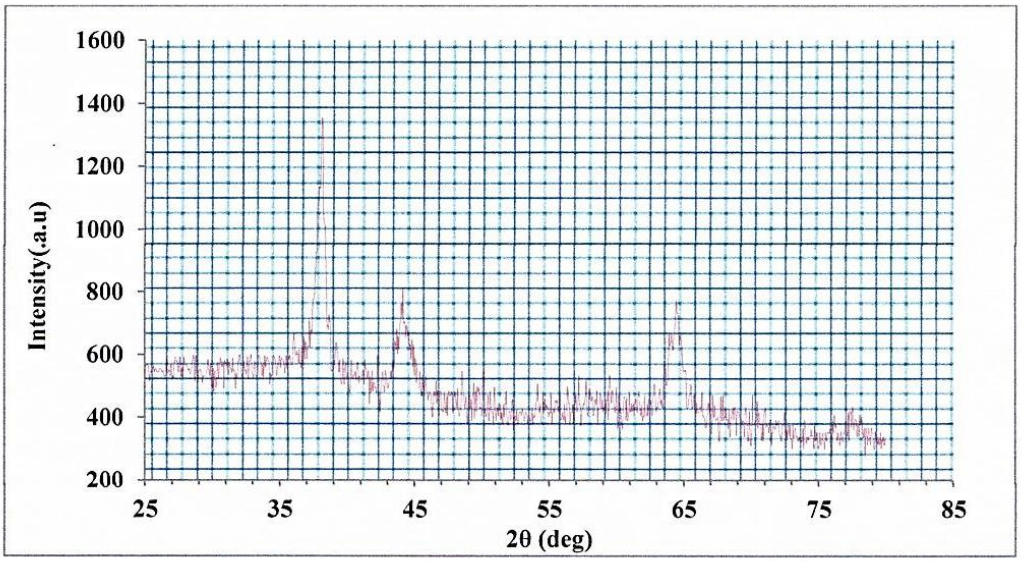


Fig. 5. XRD patterns of synthetic AgNPs

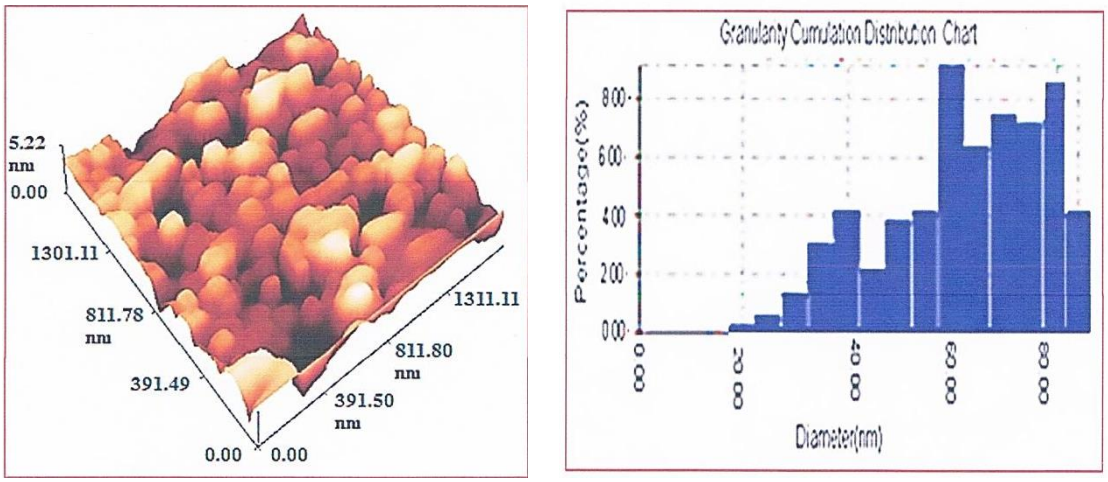


Fig. 6. AFM 3-D photo and the granola size

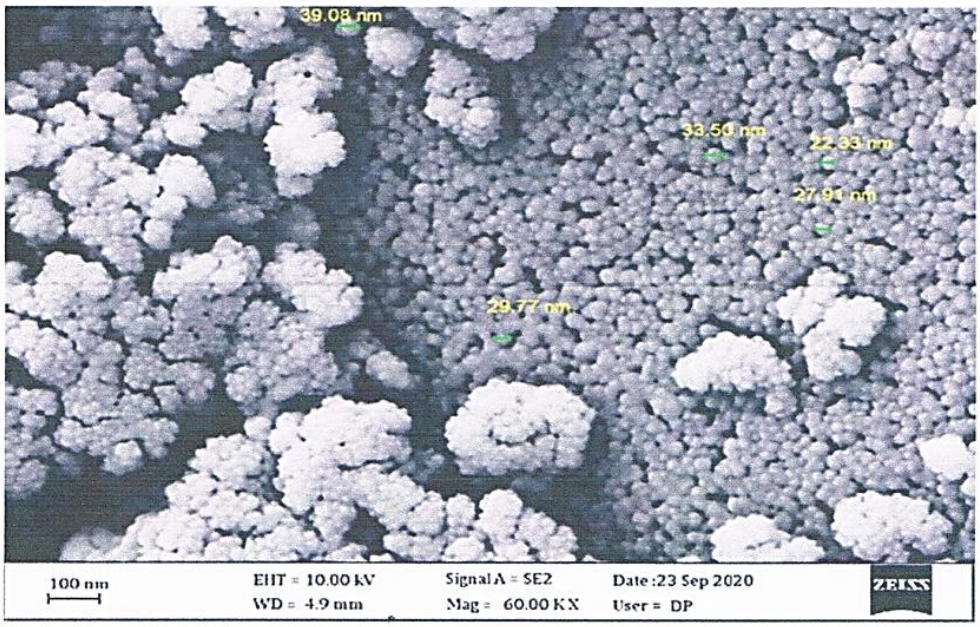


Fig. 7. SEM of nanoparticle composite (AgNPs)

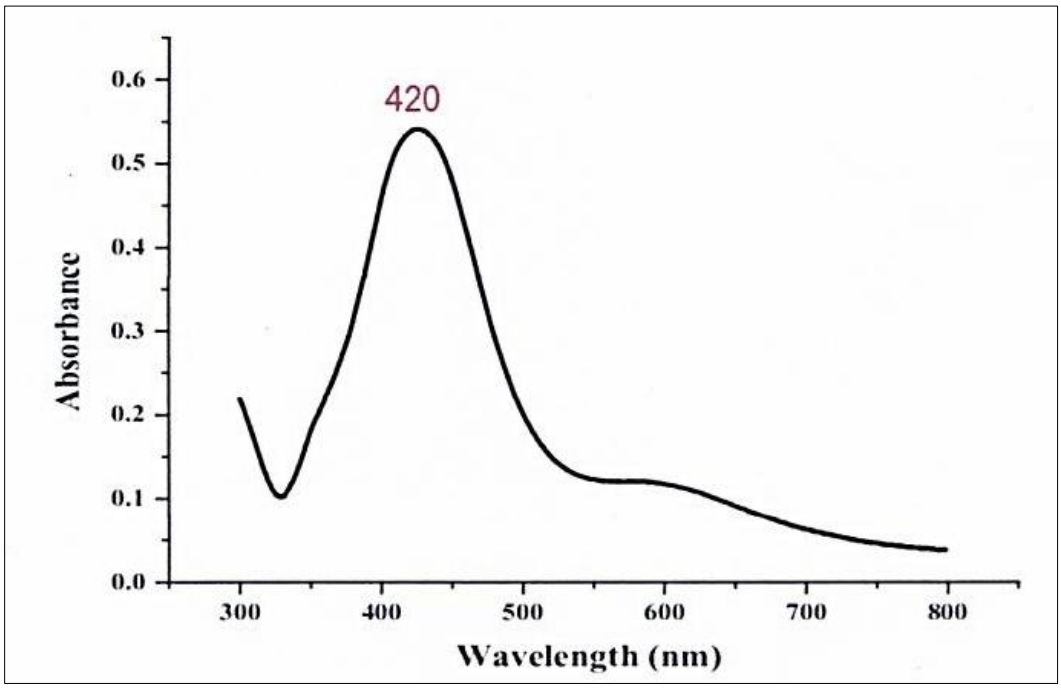


Fig. 8. UV-Vis of AgNPs

be due to the presence of the oxadiazole ring and NO_2 group[25,26], as displayed in Fig. 4, Table 2.

The XRD of silver nanoparticle shown in Fig. 5 the pattern of XRD it contain three peak (37.5–

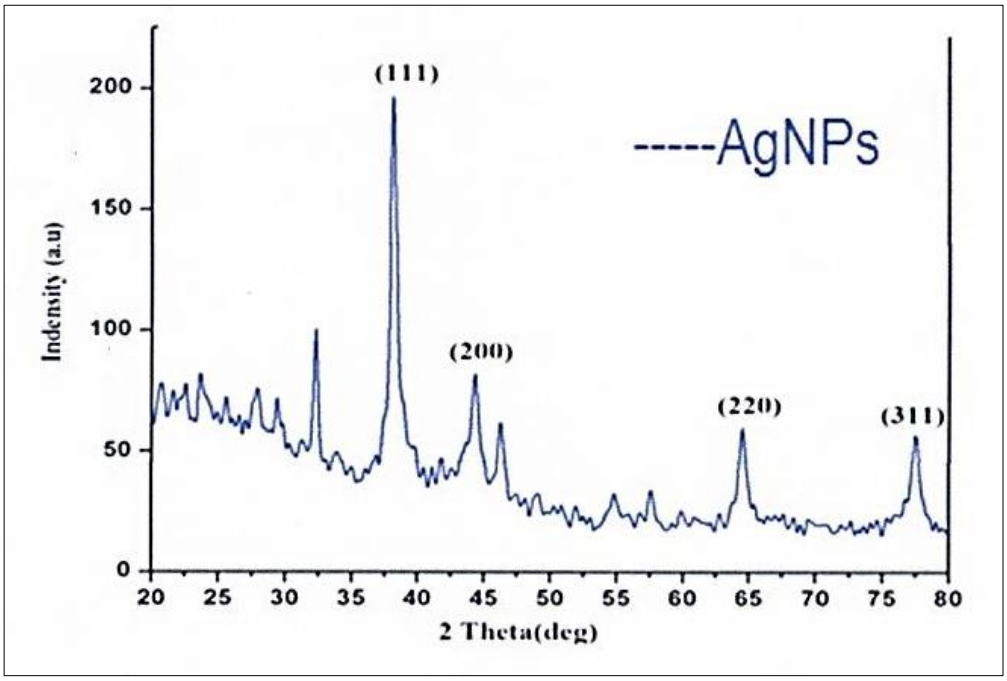


Fig. 9. The diffraction angles of AgNPs

44–65) and diffraction angles was (111), (200) and (220). Fig. 6 reveals AFM chart of silver NPs – texture. However, SEM micrograph for presence of AuNPs has been noticed the grain size as result of examination showed in Fig. 7 also, the particles in nanoparticle composite (Ag NPs) were found with almost spherical morphology and the size range from 21 to 38 nm[27].

The sliver nanoparticles also confirmed by (UV-Vis) spectrum in 10^{-3} M, Fig. 8 exhibited intense absorption peaks of Ag NPs at 420 nm affiliated to (n → π*) electronic, it's calculated during the color change to pale yellow. Fig. 9 showed diffraction angles of Ag NPs. The anti-microbial effect of silver depends on Ag+, as it bonds closely to electron donor groups in microbial cell walls like S, N, or O elements. However, the effect of silver nanoparticles on this cells through, the efficiency of silver nanoparticles to bind and log into the cell wall, and create the free radicals by Ag NPs, which may damage the cell membrane and puncture it[26].

CONCLUSION

The target of the study was to produce a new oxadiazole derivatives linked to Indole moiety with Silver (Ag NPs) to increase antimicrobial activities. The Ag nanocomposities synthezied by a series of reactions that began by the formation oxadiazole derivatives. The anti-macrobial activity of Ag nanocompositie synthesized compounds was tested *in vitro* and exhibited very good antimicrobial activities comparable with cefixime, amoxicillin as standard antibiotic, however, more studies are also needed.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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