Synthesis, Characterization and Antibacterial Activity of New Chalcones Derived from New Aldehyde; 4-[5-(4`-tolyl)-1,3,4-thiadiazole-2-yl] benzaldehyde

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Abstract

New chalcones of 3-{4-[5-(4`-tolyl)-1,3,4-thiadiazole-2-yl] phenyl}-2-propene-1-one-3‴- or 4‴- substituted phenyl have been prepared from condensation of a new of 4-[5-(4`-tolyl)-1,3,4-thiadiazole-2-yl] benzaldehyde (which is synthesized by the reaction of 2- amino-5-(4`-tolyl) -1,3,4-thiadiazole and benzaldehyde) with 3- or 4- substituted acetophenones in alkaline medium. The physical, CHNS analysis and spectral data of the synthesized compounds were determined. The biological activity evaluated of new compounds showed that many of these compounds possess antibacterial activity.

Key words: 1,3,4-thiadiazole; chalcones; aldehyde; antibacterial activity

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Introduction

In drugs and biological field, 1,3,4-thiadiazoles have occupied an important place [1-4]. Furthermore, some of these 1,3,4-thiadiazoles are interested in photography and as potential anticancer agents [5,6]. Claisen-Schmidt condensation includes synthesis chalcones from proper aldehydes and ketones in base catalyzed or acid catalyzed followed by dehydration. Which have been possessed anti-oxidant [7], anti-fungal [8,9], anti-cancer [10], anti-inflamatory [11], antibacterial activity[12-15] and anthelmintic activity [16]. The reactive and unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity [17]. Additionally, some of chalcone derivatives have been found to inhibit several enzymes in cellular[18]. Many workers synthesized new chalcones containing heterocyclic moiety which have a good biological activities [19,20]. From our knowledge that, the synthesis of chalcones containing 1,3,4-thiadiazole unit have not been reported in literature. Thus, we decided to synthesize, identify and have antibacterial activity of new chalcones containing 1,3,4-thiadiazole ring.

Experimental

Chemicals: All chemicals were supplied by fluka, GCC, merek and Aldrich chemicals Co.

Techniques: : FTIR spectra were recorded (by KBr discs) on a Shimadzo (Ir prestige -21) ^{1}HNMR spectra were examined by: Bruker , model: ultra shield 300 MHz , origin : Switzerland and are reported (in DMSO as a solvent), ppm(δ), uses TMS as an internal standard were made in Al-al Bayt University, Jordan . Hot-Stage, Gallen Kamp melting point apparatus was used for determined (uncorrected) melting points. UV spectra of solutions were performed on CECL 7200 England Spectrophotometer using $CHCl_3$ as a solvent. Elemental analysis (C.H.N.S) were carried out by a Perkin-Elmer model 2400 instrument. The purity of the synthesized compounds was determined using thin layer chromatography (the spots were observed using employing iodine chamber).

General procedures

The compounds [I] , [II] and [III]$_{a-f}$ were synthesized via Scheme 1.

preparation of 2- amino-5- (4`-tolyl) -1,3,4-thiadiazole[I]

Thiosemicarbazide (0.01mol) was a mixed with tuloic acid (0.01mol) in $POCl_3$ (5mL) , the mixture was refluxed for 6 hrs. After cooling, the reaction mixture was poured onto ice water (50mL) with stirring. The yellow precipitate was separated by filtered, washed (with water), dried and re-crystallized from ethanol [21]. Thin layer Chromatography was used toconfirmed the purity of this compound. Yield 77%, mp 219-222 ^{o}C. IR(KBr, υ, cm^{-1}): 3160,3257(NH_2) , 2965-2945 (CH aliph.) ,1627(C=N).

4-[5-(4`-tolyl)-1,3,4-thiadiazole-2-yl]benzaldehyde[II]:

Was synthesized following the procedure described by D. Bhoot et al. [22].
pale brown , yield (70%) , m.p 226-228°C; IR (KBr, υ, cm^{-1}): 2700,2790 (C-H ,aldehdic), 1692 (C=O) , 1627 (C=N);Anal. Calcd. (%) for $C_{16}H_{12}N_2OS$: C= 68.57 ; H=4.28 ; N=10 ; S=11.42. found (%): C=68.25 ; H=4.40 ; N= 10.05; S=11.44 ; ^{1}H-NMR (DMSO-*d*6 , δ ppm): 2.50 (3H, s, CH3), 6.95-7.71 (8H, d-d, arH), 9.01 (1H, s, CHO).

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Synthesis of chalcones [III]$_{a-f}$

Equi-molar quantities of different 4-substituted acetophenone (0.01mol) and aldehyde[II] (0.01 mol) were dissolved in 20mL of alcohol. Sodium hydroxide solution (0.02mol) was added slowly (and the mixture becomes cold), then the mixture was poured onto 400mL of ice water with stirring. The precipitate obtained was filtered after kept in refrigerator for 24 hrs. washed and re-crystallized from chloroform .

3-{4-[5-(4`-tolyl)-1,3,4-thiadiazole-2-yl] phenyl}-2-propene-1-one-phenyl[III]$_a$ .Dark orange , re-crystallized from chloroform. Yield 80%, mp 198-200 ˚C. UV(chloroform , nm, λmax): 297.5. IR (KBr, υ, cm^{-1}): 1650(C=N), 1636 (C=O), 1625(CH=CH) ; Anal. Calcd. (%) for $C_{24}H_{18}N_2OS$: C= 75.39 ; H=4.71 ; N=7.32; S=8.37. found (%): C=75.45 ; H=4.98 ; N= 7.22; S=8.54

3-{4-[5-(4`-tolyl)-1,3,4-thiadiazole-2-yl] phenyl}-2-propene-1-one-3``-nitrophenyl[III]$_b$ .Pale brown, re-crystallized from chloroform. Yield 85%, mp 182-184 ˚C. UV(chloroform , nm, λmax): 297. IR (KBr, υ, cm^{-1}): 1669(C=N) ,1636 (C=O), 1616(CH=CH), 1516 and 1346 (3-NO_2) ; Anal. Calcd. (%) for $C_{24}H_{17}N_3O_3S$: C= 67.44 ; H=3.98 ; N=9.83; S=7.49. found (%): C=67.49 ; H=3.92 ; N= 9.85; S=7.55; ^{1}H-NMR (DMSO-*d*6 , δ ppm): 2.69 (3H, s, CH3), 7.25-7.86(12H,d,t,s,C-H arm.), 7.81-7.86(H,t,C-H arm.), 8.37-8.49(2H,d,CH=CH).

3-{4-[5-(4`-tolyl)-1,3,4-thiadiazole-2-yl] phenyl}-2-propene-1-one-4``-nitrophenyl[III]$_c$ .Pale yellow, re-crystallized from chloroform. Yield 82%, mp 204 ˚C. UV(chloroform , nm, λmax) :299.5. IR (KBr, υ, cm^{-1}): 1670(C=N), 1635(C=O), 1610(CH=CH) , 1510 and 1339 (4-NO_2) ; Anal. Calcd. (%) for $C_{24}H_{17}N_3O_3S$: C= 67.44 ; H=3.98 ; N=9.83; S=7.49. found (%): C=67.04 ; H=4.06 ; N= 9.89; S=7.92.

3-{4-[5-(4`-tolyl)-1,3,4-thiadiazole-2-yl] phenyl}-2-propene-1-one-4``-bromophenyl[III]$_d$ .Pale orange, re-crystallized from chloroform. Yield 78%, mp 214-215 ˚C. UV(chloroform , nm, λmax) :298. IR (KBr, υ, cm^{-1}): 1665(C=N), 1635(C=O), 1613(CH=CH) , 692 (4-Br) .

3-{4-[5-(4`-tolyl)-1,3,4-thiadiazole-2-yl]phenyl}-2-propene-1-one-4``-hydroxyphenyl[III]$_e$ .Pale yellow, re-crystallized from ethanol. Yield 80%, mp 208-209 ˚C. UV(chloroform , nm, λ max) :296. IR (KBr, υ, cm^{-1}): 1670(C=N), 1636(C=O), 1612(CH=CH) , 3269 (4-OH)

3-{4-[5-(4`-tolyl)-1,3,4-thiadiazole-2-yl] phenyl}-2-propene-1-one-4``-aminophenyl[III]$_f$ .Pale yellow, re-crystallized from acetone. Yield 75%, mp 218 ˚C. UV(chloroform , nm, λ max) :295.5. IR (KBr, υ, cm^{-1}): 1648(C=N), 1638(C=O), 1628(CH=CH) , 3287 and 3100 (4-NH_2); Anal. Calcd. (%) for $C_{24}H_{19}N_3OS$: C= 72.54; H=4.78; N=10.57; S=8.06. found (%): C=72.82 ; H=4.69 ; N=10.65 ; S=8.12. ; ^{1}H-NMR (DMSO-*d*6, δ,ppm):2.37(3H,s,CH_3),7.5-7.94(12H,d-d,C-Harm.),8.12-8.26(2H,d,CH=CH), 6.24(2H,s,NH_2).

Results and Discussion

2-Amino-1,3,4-thiadiazole derivatives was synthesized from condensation of tuloic acid with thiosemicarbazide in $POCl_3$. The FTIR absorption spectrum gives two bands at 3258cm^{-1} , 3180 cm^{-1} related to NH_2 group, 3020cm^{-1} for CH aromatic, peak at 1628cm^{-1} due to C=N of thiadiazole ring , para substituted in benzene ring indicated by a good bending band at 813cm^{-1}. The UV-VIS spectroscopy exhibited λ_{max} at 296.5 nm.

The new aldehyde[II] was synthesized from reaction of 2-amino-1,3,4-thiadiazole with bezaldehyde in a preoperative conditions . FTIR spectrum of this compound showed a good

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stretching band at 1692 cm^{-1} dueto aldehydic carbonyl and two vibration bands at 2750 cm^{-1} and 2820 cm^{-1} for C-H aldehydic stretching. The UV-VIS spectroscopy exhibited λ_{max} at 294.5 nm. ^{1}HNMR spectrum (in DMSO) of synthesized [II](Figure 2), showed a signal (sharp) at δ 9.01 ppm for one proton could be attributed to the aldehydic protone, three doublets between δ (6.95-7.71)ppm due to the eight aromatic protons and a singlet signals at δ 2.50ppm due to three protons of CH_3 group.

By claisen-schmidt condensation of aldehyde[I] and 3- or 4-substituted acetophenone using base catalyzed followed by dehydration led to produce new chalcones [III]. The structural assignments of the chalcones $[III]_{a-f}$ based on C.H.N.S analysis and their spectral data (FTIR, UV and ^{1}HNMR spectroscopy). The FTIR specta indicated the disappearance of two bands which could be attributed to asymmetric and symmetric stretching vibration of CH of aldehydic group, besides, two peaks appearance around (1638-1635)cm^{-1} and around (1628-1610)cm^{-1} due to of C=O, C=C (CH=CH) stretching vibrations, respectively. The ^{1}HNMR of chalcone $[III]_b$ (Figure 3) showed the following features: two pairs of doublet in the region δ8.37-8.49 ppm which could be attributed to two protons of CH=CH group. doublet of doublets , singlet and triplet appeared in the region δ7.25-7.86 ppm due to twelve protons of benzene rings having different substituents at positions 3- or 4-, a sharp signal appearance in the spectrum at δ 2.69ppm due to three protons of CH_3 group. The ^{1}HNMR of chalcone $[III]_f$ showed the following features: two pairs of doublet in the region δ8.12-8.26 ppm which can be attributed to two protons of CH=CH group, three doublets appeared in the region δ7.50-7.94ppm due to twelve protons of benzene rings having different substituents at positions I,4. Also the spectrum show two peaks as a sharp signals at δ 2.37ppm and a broad signal at δ 6.24ppm for three protons of CH_3 group and one proton of NH_2 group, respectively.

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Antibacterial activity

The agar diffusion method [23] was used well to evaluate the antibacterial activity for synthesized compounds, with [10^{-3}M] concentration for each compound. The microorganisms were spread on Muller -Hinton agar by cottons wab. .The plates were incubated for 24 hrs at 37 ^{0}c the inhibition zone was measuring to evaluate the antibacterial activity for the synthetic compounds. The result of activities of the synthesis compounds[II] and $[III]_d$ possess moderate to high specific activity (inhibition) against Burkholderia, E.coli, Shigella , Serratia and Acinetobacter . The compound [II] which is contains CHO group showed a higher activity than chalcones. The antibacterial activity data, as in Table 1and Figure 3, may be explained depending on the molecular structure and nature of the substituted group. Also, We can observe differences in the biological activity of the synthesized compounds against different types of bacteria, that could be related to cell membrane permeability or other genetic factor [24].

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Table (1): Inhibi tion Zones of Compounds [II]-[III]$_{a-f}$.

Comp. No.	*Burkholderiacepacia* Gram(-)	*Escherichia coli* Gram(-)	*Staphyous aureas* Gram(+)	*Shigellad ysentria* Gram(-)	*Serratia marcescens* Gram(-)	*Acinetobacter sp.* Gram(-)
[II]	12	22	10	13	_	17
[III]$_a$	_	_	_	_	_	_
[III]$_b$	_	_	_	_	12	_
[III]$_c$	_	_	_	_	12	_
[III]$_d$	11	19	_	12	_	13
[III]$_e$	_	_	_	_	_	_
[III]$_f$	_	16	_	14	_	_
Control DMSO	_	_	_	_	_	_

Key of symbols :

1. active (slightly) = + 5 – 10mm,
2. active (Moderately) = ++ 11 – 15mm
3. active (Highly) = +++ more than 15mm .

Con: DMSO

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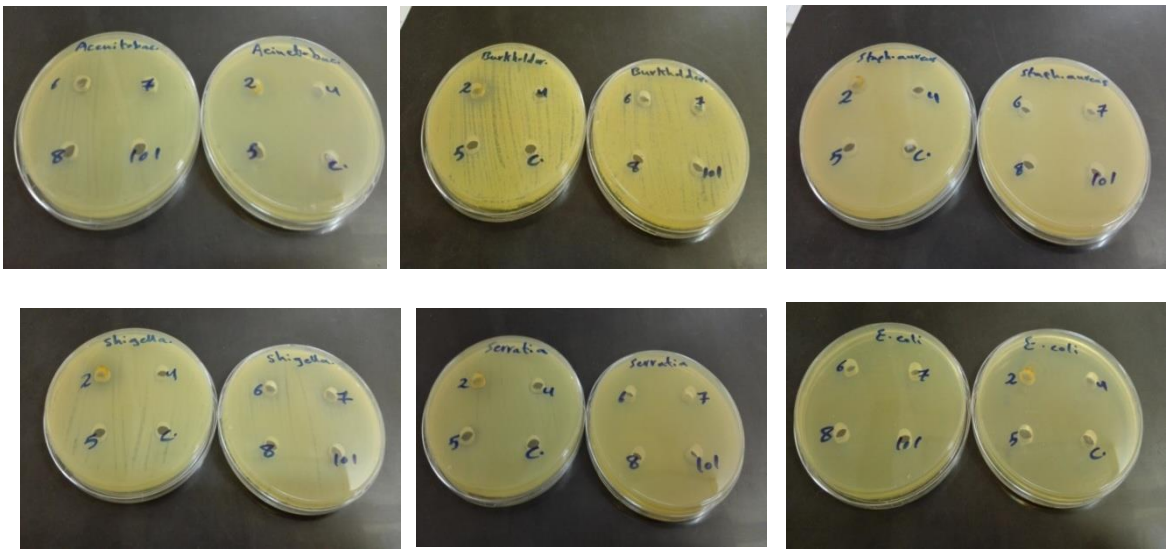

Figure(1): Antibacterial activity of compounds[I]-[III] against Burkholderia, E.coli , Stap . aureus ,Shigella , Serratia and Acinetobater
Symbol: c= control (DMSO); 2=compound [II]; 101=compound [III]a; 5=compound [III]b; 4=compound[III]c; 6=compound [III]d; 7=compound [III]e; 8=compound [III]f.

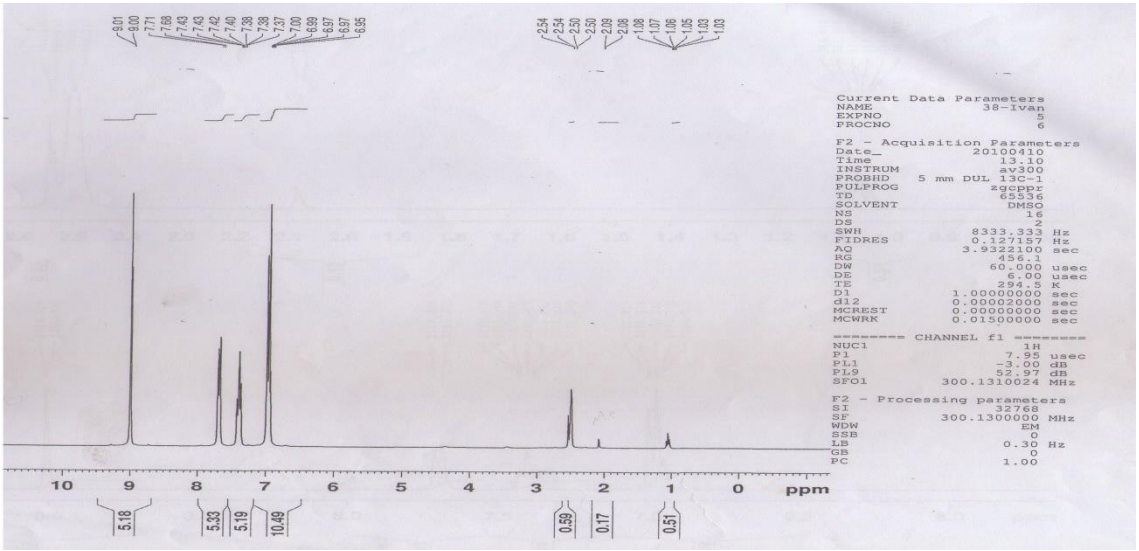

Figure (2): ^{1}HNMR spectrum of compound[II].

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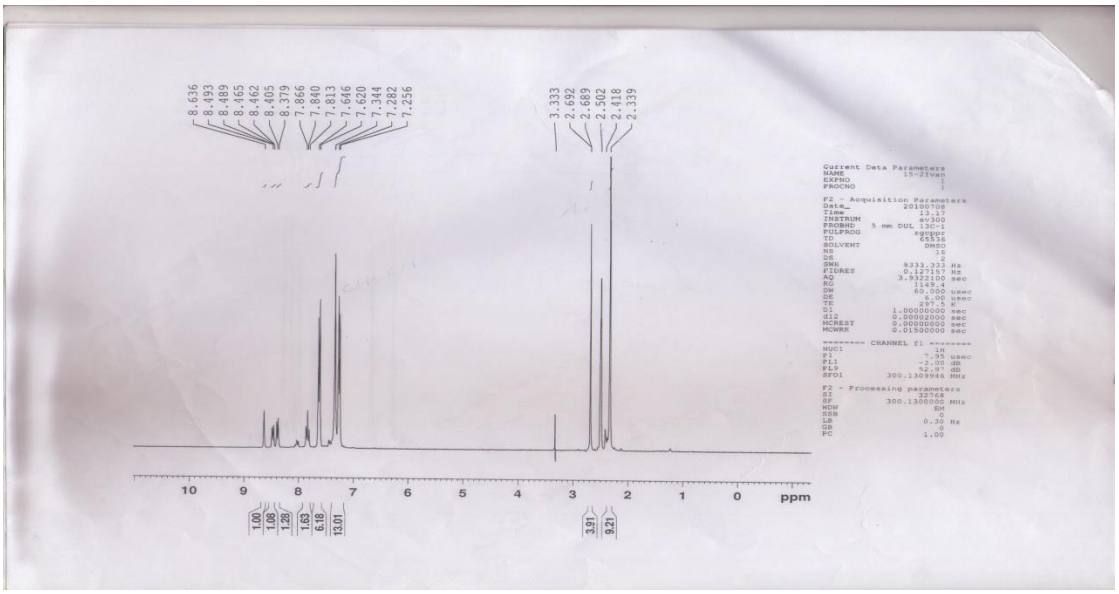
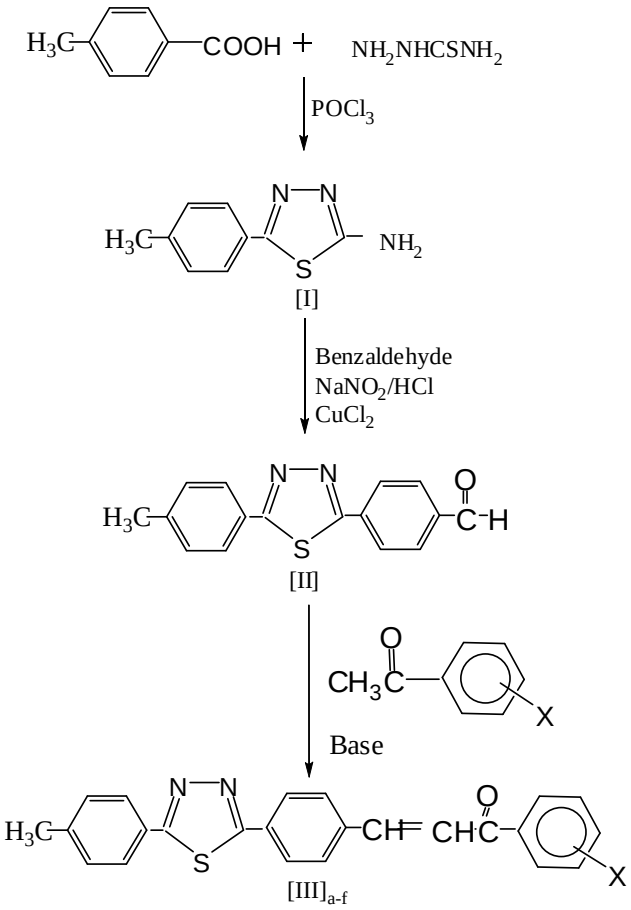


Figure (3): ^{1}HNMR spectrum of compound[III]$_b$.



X= H, 3-NO_2, 4-NO_2, 4-Br, 4-OH and 4-NH_2

Scheme 1. Synthetic route to the prepartion compounds [III]$_{a-f}$.

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