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Synthesis and Identification of some New Sulphadiazine Derivatives

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ABSTRACT

This research involves the synthesis of some new pyrazolines and pyrimidines from sulphadiazine derivatives. Firstly was converted sulphadiazine to 4-(acetamido)-N-(pyrimidin-2-yl) benzene sulfonamide (ASDZ) by reacting ulphadiazine with acetic anhydride in presence of some drops of sulfuric acid. Then, Chalcones were prepared from the reaction of (ASDZ) with aromatic aldehydes in basic medium to prepare (A,B,C,D and E) compounds. Chalcones derivatives were reacted with phenyl hydrazine and 2,4-dinitro phenyl hydrazine to prepare pyrazoline derivatives (A_{PH}, B_{PH},C_{PH}, D_{PH}, E_{PH}, A_{NPH}, B_{NPH}, C_{NPH}, D_{NPH} and E_{NPH}). Also pyrimidine derivatives were synthesized by reactionbetween Chalcones and uear, thiouear and guaniden (A_U, B_U, C_U, D_U, E_U, A_{Th}, B_{Th}, C_{Th}, D_{Th}, E_{Th}, A_G, B_G, C_G, D_G and E_G). The synthesized compounds have been measured by their melting points, and characterized by C.H.N. analysis, FT-IR and ^{1}H-MNR (for some of them) spectroscopy.

Keywords: sulphadiazine, Pyrazolines, pyrimidine,Claisen-Schmidt condensation, Chalcones.

INTRODUCTION

Many heterocyclic compounds due to their specific activity are employed in the treatment ofmany infectious diseases. Their use in the treatment is attributed to their inherent toxicity to various pathogens. Among a wide range of heterocyclic compounds that have been explored for the development of pharmaceutically important molecules, pyrazolines constitute an interesting class of heterocycles due to their synthetic versatility and effective biological activities such as anticancer[1], antioxidant[2], antibacterial[3], antifungal[4] antidepressant[5-7], anti-inflammatory[8], anticonvulsant[9] antitumor[10] analgesic[11] properties. Many chemotherapeutically important sulfa drugs like sulphadiazine (silver sulphadiazine), sulphathiazole, sulphamerazine and so forth, posses (-SO_2NH-) moiety, which is an important toxophoric functional group[12,13]. Zinc sulphadiazine products were more effective against Gram positive and Gram negative bacteria as well as fungi. These compounds displayed apotential value in wound healing. The toxicity of zinc sulphadiazine derivative was much lower than that of silver sulphadiazine[14]. Generally there are two reactive sitesin sulphadiazine, one is the aromatic amine and the other is sulphonamide [15]. Therefore, the main work of the modified sulphadiazine has been focused on the aromatic amine due to its relatively high reaction activity [16,17].

MATERIALS AND METHODS

All chemicals were used supplied from Merck, BDH and Fluke Chemicals Company. The melting points were recorded using thermometer melting point apparatus, UK. The elemental analyses were recorded using E.A.G.E.R.-100, Carlo Erba, Italy. FT.IR spectra were recorded using Fourier transform infrared SHIMADZU FT.IR-8400S infrared spectrophotometer by KBr disc.^{1}H-NMR were recorded on Fourier transform Bruker spectrometer, operating at 400 MH_Z.

Methods

Synthesis of 4-(acetamido)-*N*-(pyrimidin-2-yl) benzene sulfonamide (ASDZ)[18]: A mixture of sulphadiazine (0.01 mol) (2.5 g) and acetic anhydride (20 mL) with few drops of concentrated sulfuric acid was refluxed for (2 h) at (60-70) ^{o}C. The initial content of the reaction is a suspension, then it was a clear solution after the temperature reaching above 60 ^{o}C. TLC showed that the reaction was completed by using benzene: ethanol in 4:1. After the completion of the reaction, the reaction mixture was added into crushed ice water with stirring. The formed solid product was separated by filtration and recrystallized from ethanol.

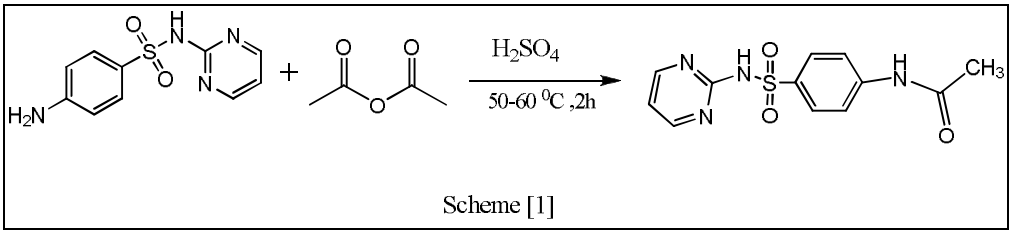
General procedure for synthesis chalcones (A,B,C,D,E)[19]: To a stirred mixture of 0.01 mol ASDZ and 0.01 mol aromatic aldehydes in 25 mL ethanol in ice water path, 40% NaOH aqueous solution was added portion-wise after which stirring was continued for further 2-3 h. TLC showed that the reaction was completed by using benzene: ethanol (8:2). The colored precipitate formed was filtered and washed with 3% aqueous HCl, then with distilled water and recrystallized from ethanol.

General procedure for the synthesis of pyrazoline[20]: A stirred solution of chalcones (A,B,C,D and E 0.01 mol) in 15 mL EtOH (96 %) was added to 0.01 mol phenyl hydrazine or hydrazine Hydrate and KOH (0.2g in 2.5 mL of EtOH) at 50-60 ^{o}C. The reaction mixture was heated to reflux for 8 h. The progress of the reaction was monitored by TLC (benzene: ethanol, 8:2). The EtOH was removed under reduced pressure and precipitate recrystallized from ethanol.

General procedure for synthesis of pyrimidine[21]: A stirred solution of chalcone (A,B,C,D and E 0.01 mol) in 15 mL EtOH (96 %) was added to 0.01 mol urea , thiourea or guanidine and 0.2g KOH in 2.5 mL of EtOH) at 50-60 ^{o}C. The reaction mixture was heated to reflux for 6 h. The progress of the reaction was monitored by TLC (benzene: ethanol, 8:2). The EtOH was removed under reduced pressure and precipitate recrystallized from ethanol.

RESULTS AND DISCUSSION

Synthesis and identification of 4-(acetamido)-*N*-(pyrimidin-2-yl) benzene sulfonamide (ASDZ): The key intermediate compound[ASDA] were prepared first by the condensation of sulfadiazine with acetic anhydride in the presence of concentration sulfuric acid Scheme 1.

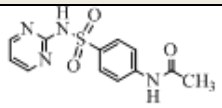


Scheme [1]

The synthesized compound [ASDA] was characterized by [C.H.N.S.] analysis, and the result of experimental percentages was a good agreement with the calculated percentages of elements shown in

table 1. This is a good evidence for formatting our compounds. The FT-IR spectra of this compound showed disappearance of two absorption bands at 3425 cm^{-1} and 3357 cm^{-1} of the asymmetric and symmetric stretching vibrations of (-NH_2) group of sulfadiazine [22] and appearance of the band at 1678 cm^{-1} of stretching vibration of (C=O) carbonyl group . The absorption band at 3309 cm^{-1} was due to a stretching vibration of (N-H) secondary sulfonamide. All of these absorption bands are good evidence to the formation of 4-(acetamido)-*N*-(pyrimidin-2-yl)benzene sulfonamide, ASDZ compound.^{1}H-NMR spectrum (δ ppm), figure 1 of 4-(acetamido)-*N*-(pyrimidin-2-yl)benzene sulfonamide, ASDZ showed the following characteristic chemical signals in DMSO- d_6 as a solvent. 3H of N-COC<u>H</u>$_3$, 2.285 , Ar-<u>H</u> 6.886-8.728 , 1H of N-<u>H</u>$_{sulfonamide}$ 11.549, 1H of N-<u>H</u>$_{amide}$ 10.285.

Table 1. C.H.N.S analysis data and some physical properties of synthesized compound ASDZ.

Com. No.	Structural formula and molecular formula	C.H.N.S. data Calculated found				M.P. ^{0}C	Yield %	R_f
		C%	H%	N%	S%			
ASDZ	 $C_{12}H_{12}N_4O_3S$	49.31 49.12	4.14 4.08	19.17 19.07	10.97 10.88	202-204	88	0.71

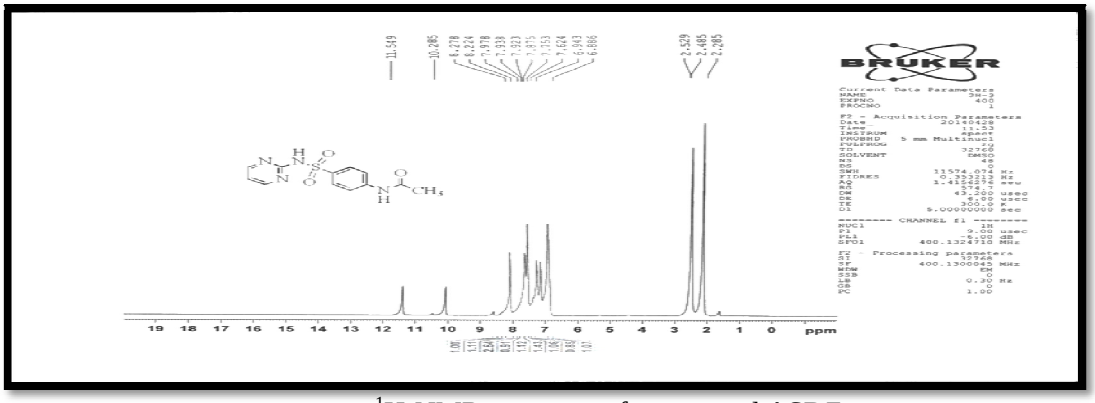
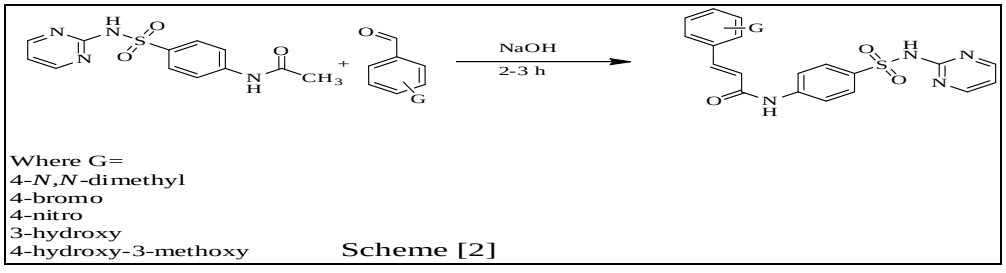


Figure 1. ^{1}H-NMR spectrum of compound ASDZ

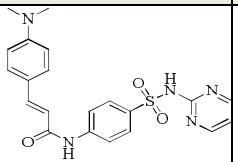
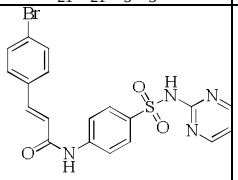
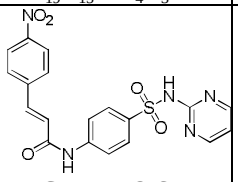
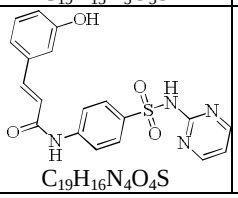
Synthesis and identification of chalcones [A,B,C,D,E] : Chalcones are synthesized by Claisen-Schmidt condensation of SDZA and aromatic benzaldehyde derivatives by base catalyzed followed by dehydration to yield the desired chalcones, scheme 2.

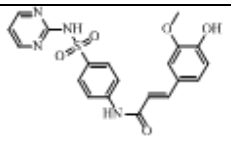


The synthesized compounds were characterized by Bayer test and the result was positive. That is a good evidence for preparing our compounds [A,B,C,D and E]. The C.H.N.S. analysis of these compounds accepted agreement with the calculated percentages of elements shown in the table 2. FT-IR spectra showed the remaining of the bands between 1660to1664 cm^{-1} of the stretching vibration of carbonyl (C=O)

group, with the remaining of absorption band at 1550 cm^{-1} of the stretching vibration of (C=N) group of hetero aromatic ring of pyrimidine [23]. The appearance absorption band at 1575-1591 cm^{-1} of the stretching vibration of (C=C) group. The appearance of the strong absorption band at 3415,3384 cm^{-1} to the OH group in D, E compounds, 1064 cm^{-1} to the (C-N) in (A) compound, (648) cm^{-1} to the (C-Br) stretching of B compound, 1370 cm^{-1} due to the (NO_2) stretching group of C compound . All these absorption bands are another good evidence to formation [A,B,C,D and E].^{1}H-NMR spectrum (δ ppm),of compound A showed the following characteristic chemical signals ((DMSO- d_6)as solvent: 6H of N-(CH_3)$_2$ 3.32, Ar-H 6.654-8.304 , 1H of CO-CH=CH 6.512, 1H of CO-CH=CH 6.654 ,1H of (N-H)$_{sulfonamide}$ 11.416, 1H of (N-H) $_{amide}$ 9.954. ^{1}H-NMR spectrum (δ ppm), figure 2 of compound B showed the following characteristic chemical signals ((DMSO- d_6)as solvent: Ar-H 6.801-8.682 , 1H of CO-CH=CH 6.592, 1H of CO-CH=CH 6.762, 1H of (N-H)$_{sulfonamide}$ 11.649, 1H of (N-H) $_{amide}$ 9.971. ^{1}H-NMR spectrum (δ ppm), of compound C showed the following characteristic chemical signals ((DMSO- d_6)as solvent: Ar-H 7.444-8.837, 1H of CO-CH=CH 6.927, 1H of CO-CH=CH 6.950, 1H of (N-H)$_{sulfonamide}$ 11.571, 1H of (N-H) $_{amide}$ 9.677. ^{1}H-NMR spectrum (δ ppm),of compound D showed the following characteristic chemical signals ((DMSO- d_6)as solvent: Ar-H 6.654-8.304 ,1H of CO-CH=CH) 6.512, 1H of CO-CH=CH 6.548, 1H of (N-H)$_{sulfonamide}$ 11.664, 1H of (N-H) $_{amide}$ 9.954, 1H of OH 9.654. ^{1}H-NMR spectrum (δ ppm),of compound E showed the following characteristic chemical signals ((DMSO- d_6)as solvent: 3H of (O-(CH_3) 3.353, Ar-H 6.757-8.701, 1H of (CO-CH=CH) 6.602, 1H (CO-CH=CH) 6.757, 1H (N-H)$_{sulfonamide}$ 11.669 1H of (N-H) $_{amide}$ 9.983, 1H of (OH) 9.101.

Table 2. C.H.N.S. analysis data and some physical properties of synthesized compounds [A,B,C,D,E]

Com. No.	Structural formula and molecular formula	C.H.N.S. data Calculated found				M.P. ^{0}C	Yield %	R_f
		C%	H%	N%	S%			
A	 $C_{21}H_{21}N_5O_3S$	59.51 59.49	4.99 4.98	16.57 16.51	7.53	116-118	81	0.67
B	 $C_{19}H_{15}BrN_4O_3S$	49.56 49.52	3.19 3.18	12.18 12.17	6.89 6.88	98-100	83	0.64
C	 $C_{19}H_{15}N_5O_5S$	56.36 56.32	4.25 4.24	13.19 13.12	7.46 7.5	103-105	85	0.65
D	 $C_{19}H_{16}N_4O_4S$	57.6 57.52	4.011 4.03	14.13 14.11	7.99 7.98	107-109	80	0.64

E	 $C_{20}H_{18}N_4O_5S$	56.27 56.22	4.26 4.23	13.14 13.12	7.5 7.48	101-103	78	0.7

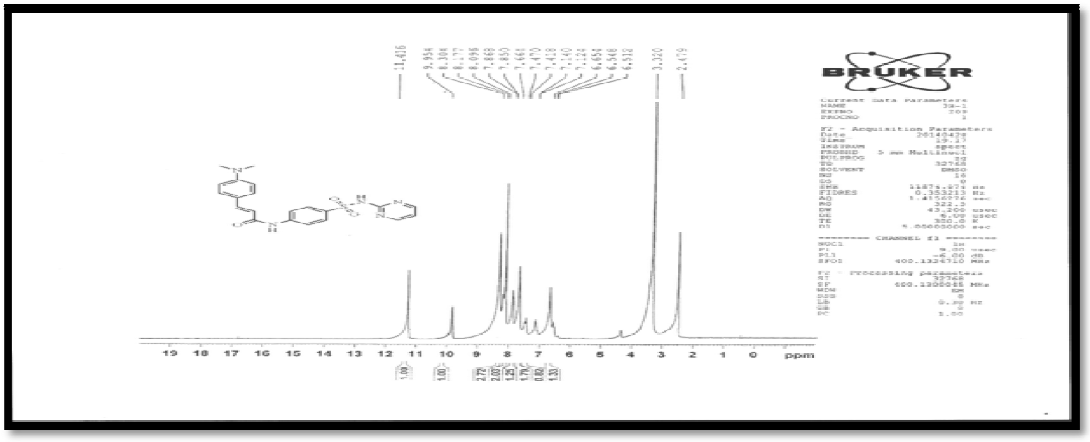
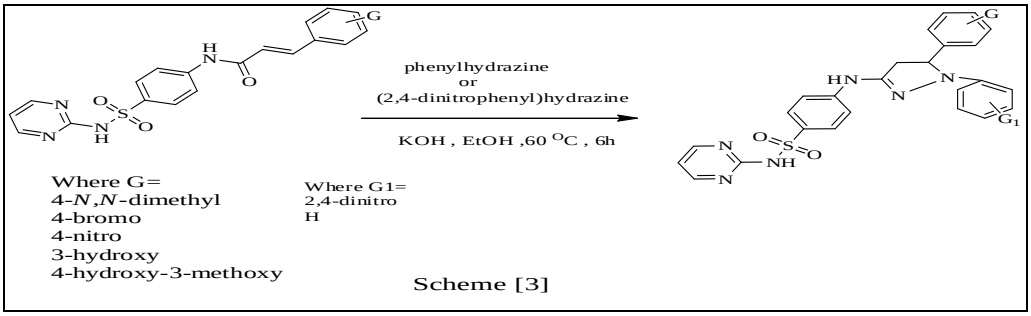


Figure 2. ^{1}H NMR spectrum of compound A

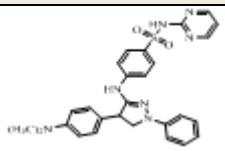
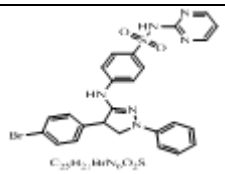
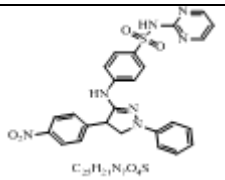
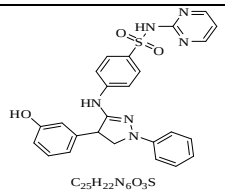
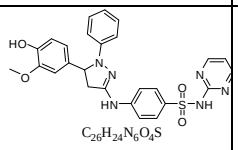
Synthesis and identification of pyrazolines: The chalcones [A,B,C,D and E] were further reacted with 2,4-di nitrophenyl hydrazine or phenyl hydrazine in ethanol absolute to yield the corresponding pyrazoline derivatives by the following reaction: Scheme 3.



Scheme [3]

The C.H.N.S analysis of synthesized compounds (A_{PH} , B_{PH} ,C_{PH} , D_{PH} , E_{PH} , A_{NPH} , B_{NPH} , C_{NPH} , D_{NPH} and E_{NPH}) was accepted agreement with the calculated percentage of elements shown in tables 3 and 4. The FT-IR spectra showed the appearance of absorption band at 3344-3460 cm^{-1} of the symmetric stretching vibration of (-NH-) group of all compounds and the disappearance of stretching vibration bands between 1637 to 1664 cm^{-1} was due to the stretching vibration of (C=O) group, and disappearance stretching vibration bands between 1550-1600 $cm^{-1}$was due to the stretching vibration (C=C) of benzylic group of all compounds. The remaining of the strong absorption band at 3349-3460 cm^{-1} to the OH group in (D_{PH}, E_{PH}, D_{NPH} and E_{NPH}) compound. All of these absorption bands are another good evidence to prepare pyrazoline derivatives (A_{PH} , B_{PH} ,C_{PH} , D_{PH} , E_{PH} , A_{NPH} , B_{NPH} , C_{NPH} , D_{NPH} and E_{NPH}).^{1}H-NMR spectrum (δ ppm), Figure [3] of compound [A_{PH}] showed the following characteristic chemical signals: ((DMSO- d_6)as solvent. 6H of (N-(C<u>H</u>$_3$)$_2$ 3.016, 1H of (C<u>H</u>)$_{pyrazoline\ ring}$ 3.029, 2Hof (C<u>H$_2$</u>)$_{pyrazoline\ ring}$ 3.378, ((Ar-<u>H</u>) 6.467-8.304), 1H (N-<u>H</u>)$_{sulfonamide}$ 11.616, 1H (N-<u>H</u>) $_{amide}$ 9.929. ^{1}H-NMR spectrum (δ ppm), of compound [B_{NPH}] showed the following characteristic chemical signals :((DMSO- d_6)as solvent (Ar-<u>H</u>) 6.532-8.040, 1H of (C<u>H</u>)$_{pyrazoline\ ring}$ 3.081, 2H of (C<u>H$_2$</u>)$_{pyrazoline\ ring}$ 3.737, 1H of (N-<u>H</u>)$_{sulfonamide}$ 11.632, 1H of (N-<u>H</u>) $_{amide}$ 9.831.

Table 3. C.H.N.S analysis data and some physical properties of pyrazoline derivatives (A_{PH} , B_{PH} ,C_{PH} , D_{PH} , E_{PH})

Com. No.	Structural formula and molecular formula	C.H.N.S. data Calculated found				M.P. ^{0}C	Yield %	R_f
		C%	H%	N%	S%			
A_{PH}	 $C_{27}H_{27}N_7O_2S$	63.1463 .12	5.3 5.23	19.09 18.92	6.24 6.21	128-130	86	0.67
B_{PH}		54.65 54.62	3.85 3.83	15.3 15.22	5.84 5.79	120-122	81	0.63
C_{PH}		58.24 57.98	4.11 4.07	19.02 18.99	6.22 6.17	126-128	85	0.59
D_{PH}	 $C_{25}H_{22}N_6O_3S$	61.71 61.67	4.56 4.45	17.27 17.22	6.59 6.51	117-119	88	0.65
E_{PH}	 $C_{26}H_{24}N_6O_4S$	60.45 60.42	4.68 4.63	16.27 16.12	6.21 6.19	113-115	82	0.55

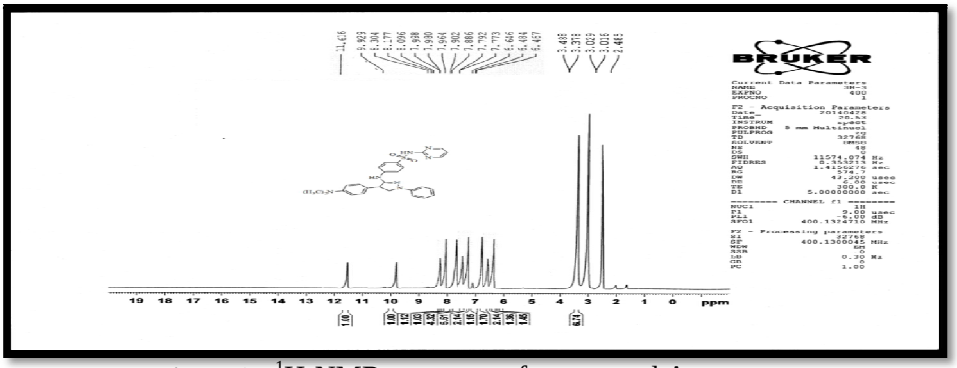
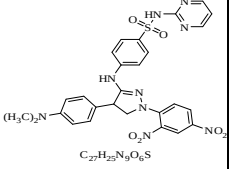
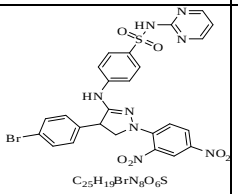
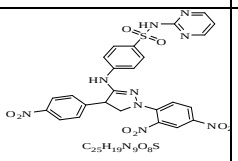
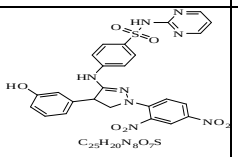
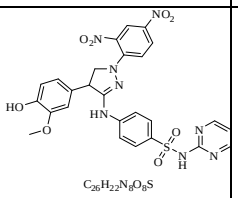
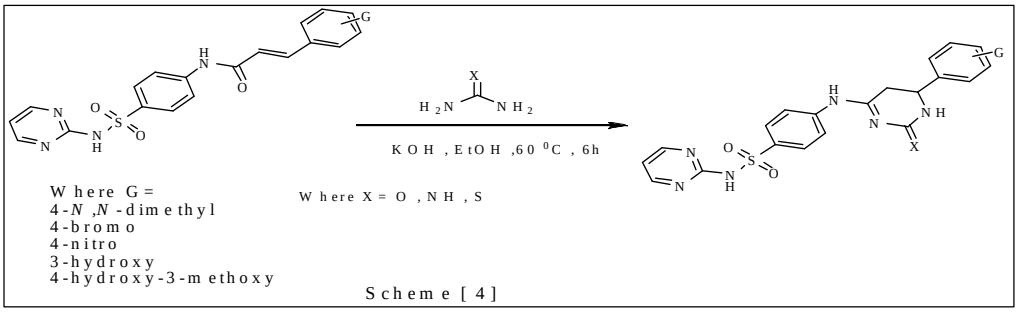


Figure 3. ^{1}H-NMR spectrum of compound A_{PH}

Table 4. C.H.N.S analysis data and some physical properties of pyrazoline derivatives (A_{NPH}, B_{NPH}, C_{NPH}, D_{NPH} and E_{NPH})

Com. No.	Structural formula and molecular formula	C.H.N.S data Calculated found				M.P. ^{0}C	Yield %	R_f
		C%	H%	N%	S%			
A_{NPH}	 $C_{27}H_{25}N_9O_6S$	53.72 53.62	4.17 4.16	20.88 20.78	5.31 5.21	144-146	87	0.72
B_{NPH}	 $C_{25}H_{19}BrN_8O_6S$	46.96 46.91	2.99 2.93	17.52 17.47	5.01 4.97	135-137	89	0.59
C_{NPH}	 $C_{25}H_{19}N_9O_8S$	49.59 49.46	3.16 3.15	20.82 20.77	5.3 5.23	130-132	86	0.62
D_{NPH}	 $C_{25}H_{20}N_8O_7S$	52.08 51.95	3.5 3.43	19.44 19.42	5.56 5.46	137-139	84	0.61
E_{NPH}	 $C_{26}H_{22}N_8O_8S$	51.48 51.46	3.66 3.63	18.47 18.43	5.29 5.22	133-135	79	0.70

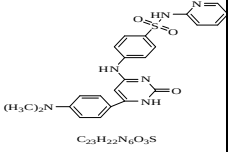
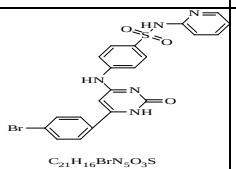
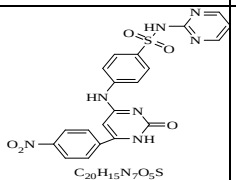
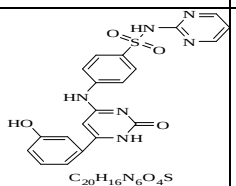
Synthesis and identification of six heterocyclic membered ring (pyrimidines): The chalcones [A,B,C,D and E] were further reacted with urea, thiourea and guanidine in ethanol absolute to yield the corresponding pyrimidine derivatives by the following reaction. Scheme 4.

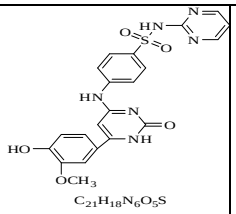
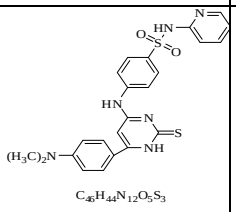
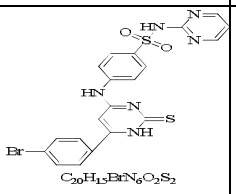
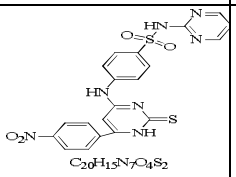
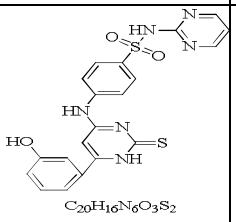
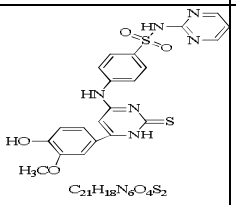
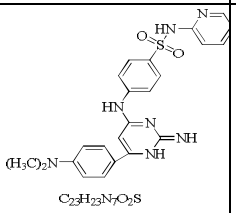


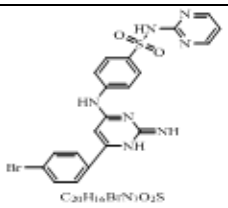
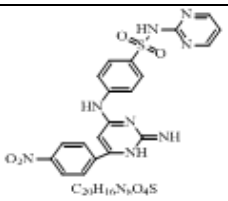
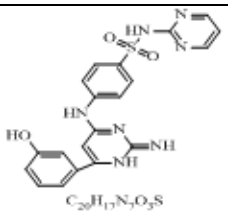
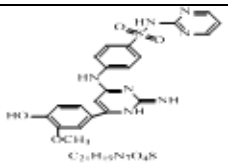
Scheme [4]

The C.H.N.S analysis of synthesized compounds (A_U , B_U , C_U , D_U , E_U , A_{Th} , B_{Th} , C_{Th} , D_{Th} , E_{Th} , A_G , B_G , C_G , D_G and E_G) was accepted agreement with the calculated percentage of elements were shown in table 5. The FT-IR spectra showed the appearance of absorption band at 3348-3464 cm^{-1} of the symmetric stretching vibration of (-NH-)group and the appearance stretching vibration bands at 1664 and 1672 cm^{-1}which was due to the stretching vibration of (C=O) group of oxopyremidine compounds (A_U , B_U , C_U , D_U and E_U), appearance stretching vibration bands between(1415-1417) cm^{-1} due to (C=S) group of thiopyremidine (A_{Th} , B_{Th} , C_{Th} , D_{Th} and E_{Th}) and disappearance stretching vibration bands between (1672-1664) cm^{-1}which was due to the stretching vibration (C=O) of carbnyl group of compounds(A_{Th} , B_{Th} , C_{Th} , D_{Th} , E_{Th} , A_G , B_G , C_G , D_G and E_G). The remaining of the strong absorption bands at 3383-3395 cm^{-1} to the OH group in (D_U, E_U, D_{Th}, E_{Th}, D_G and E_G) compounds . All of these absorption bands are another good evidence of the formation of these compounds.^{1}H-NMR spectrum (δ ppm), of compound C_G showed the following characteristic chemical signals ((DMSO- d_6)as solvent: ((Ar-H) 6.492-8.042), 1H of (C=CH) $_{pyrimidinering}$ 4.931, 1H of (N-H)$_{sulfonamide}$ 11.429 1H of (N-H) 4.492, 1H of (N-H) $_{pyrimidinering}$ 9.482.^{1}H-NMR spectrum (δ ppm) (Figure 4) of compound D_G showed the following characteristic chemical signals ((DMSO- d_6)as solvent :((Ar-H) 6.792-8.691, 1H of (C=CH) $_{pyrimidinering}$ 5.5, 1H of (N-H)$_{sulfonamide}$ 11.649, 1H of (N-H)4.1, 1H (N-H) $_{pyrimidinering}$ 9.322. ^{1}H-NMR spectrum (δ ppm),of compound E_G showed the following characteristic chemical signals ((DMSO- d_6)as solvent: 3H of (O-(CH_3) 3.3, (Ar-H) 6.792-8.442, 1H (C=CH) $_{pyrimidinering}$ 5.89), 1H of (N-H)$_{sulfonamide}$ 11.421, 1H of (N-H) 4.1, 1H of (N-H) $_{pyrimidinering}$ 8.211 , 1H of (OH)9.882.

Table 5. C.H.N.S analysis data and some physical properties of pyrimidine derivatives A_U , B_U , C_U , D_U, E_U , A_{Th} , B_{Th} , C_{Th} , D_{Th} , E_{Th}, A_G , B_G , C_G , D_G and E_G)

Com. No.	Structural formula and molecular formula	C.H.N.S data Calculated found				M.P. ^{0}C	Yield %	R_f
		C%	H%	N%	S%			
A_U	 $C_{23}H_{22}N_6O_3S$	57.01 56.96	4.57 4.53	21.15 21.09	6.92 6.85	185-187	76	0.59
B_U	 $C_{21}H_{16}BrN_5O_3S$	50.61 51.46	3.66 3.63	18.61 18.43	6.43 6.22	170-172	83	0.63
C_U	 $C_{20}H_{15}N_7O_5S$	51.61 51.56	3.25 3.23	21.07 20.96	6.86 6.79	175-177	81	0.66
D_U	 $C_{20}H_{16}N_6O_4S$	55.04 54.95	3.7 3.67	19.26 19.23	7.35 7.25	165-167	85	0.72

E_U		54.07 53.96	3.89 3.83	18.02 17.93	6.87 6.67	160-162	82	0.67
A_{Th}		55.1 54.99	4.41 4.31	20.44 20.4	13.37 13.25	220-222	77	0.55
B_{Th}		46.61 46.56	2.93 2.85	16.31 16.23	12.44 12.32	218-220	88	0.68
C_{Th}		49.89 49.76	3.14 3.11	20.36 20.28	13.32 13.12	206-208	89	0.65
D_{Th}		53.08 52.96	3.56 3.54	18.57 18.53	14.17 14.13	224-226	86	0.57
E_{Th}		52.27 52.26	3.76 3.71	17.42 17.4	13.29 13.21	230-232	90	0.69
A_G		57.13 57.11	4.79 4.73	24.23 24.2	6.93 6.86	195-197	88	0.64

B_G		48.2 48.12	3.24 3.18	19.67 19.63	6.43 6.41	188-190	89	0.67
C_G		51.72 51.69	3.47 3.43	24.13 24.09	6.9 6.89	192-194	86	0.54
D_G		55.16 55.13	3.93 3.89	22.52 22.51	7.36 7.33	180-182	91	0.71
E_G		54.19 54.16	4.11 4.1	21.6 21.02	6.86 6.85	189-191	85	0.60

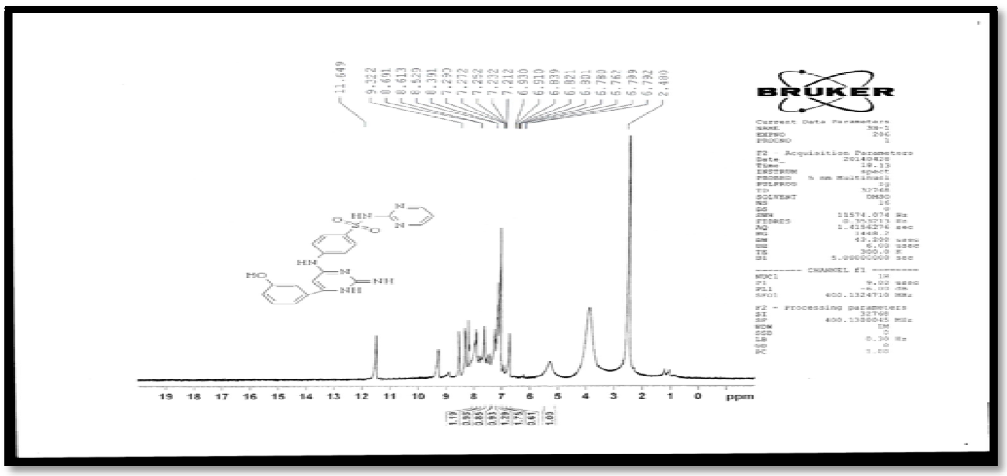


Fig 4. ^{1}H-NMR spectrum of compound D_G

APPLICATIONS

In the present study new derivatives of sulphadiazine were synthesized, and In future we will study their pharmaceutical activity.

CONCLUSIONS

In this research of some new pyrazolines and pyrimidines derivatives were synthesized from sulfadiazine chalcones derivatives, from this work, following conclusion could be drown:Effect of electron-donating and electron-withdrawing in the determination the time of the reaction. The electron-donating group increased the rate of the reaction, therefore the time of the reaction was decreased while the electron-withdrawing group decreased the rate of reaction, therefore the time of reaction was increased. All the synthesized compounds were stable by resonance and having high melting points relatively, this is evidence on the extent stability.

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