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Synthesis, Characterisation and Antimicrobial studies of 4, 6-Disubtuted phenyl - (5-subsutied phenyl -1, 3, 4-thiadiazol-2-yl) -1, 4, 5, 6-tetrahydro pyrimidine-2-thiols

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Abstract : A new series of 4,6-disubtuted phenyl - (5-subsutied phenyl -1,3,4-thiadiazol-2-yl)-1,4,5,6-tetrahydro pyrimidine 2-thiols were synthesized by the condensation of 1-(5-substitued phenyl -1,3,4-thidiazole-2-yl)thiourea and substituted chalcones. The structures of the new compounds have been established by spectral and analytical data. Some of the compounds were screened for their antibacterial and antifungal activity. A few compounds showed potent activity comparable with that of the standard drugs.
Keywords : Antibacterial activity, antifungal activity, pyrimidine-2-thiols, thiourea and chalcones.

Introduction:

Pyrimidines represent an important class of heterocycles and their structural framework is not only a key constituent of nucleic bases, alkaloids, and numerous pharmacophores with variety of potent biological activities. Pyrimidines occupy a distinct and unique place in medicine, large array of pyrimidine nonnucleoside derivatives possess a variety of pharmacological properties. These properties include anticancer[1-2], antiviral[3-5], antibacterial[6-7], antifungal[8-9], antiprotozoal[10-11], antihypertensive[12-13], antihistaminic[14], anti-inflammatory[15-16] and central nervous activities[17-18]. The previous workers[19] have studied the reaction of chalocnes with thiourea and reported the products as 2-mercaptopyrimidines. This promoted us to study the reaction of substituted chalocnes with substituted thiadiazole thiourea derivatives using ethyl alcohol as solvent using different conditions. Such reactions resulted in the formation of a novel 4,6-disubtuted phenyl - (5-subsutituted phenyl-1, 3, 4-thiadiazol-2-yl)-1,4,5,6-tetrahydro pyrimidine 2-thiols. The synthetic route followed for obtaining the title compounds is outlined in Schemes-1, 2, and 3.

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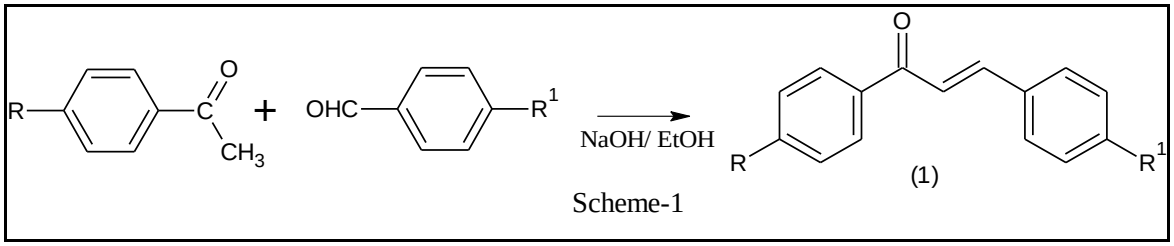
Reaction scheme:

Synthesis of chalcones (1):

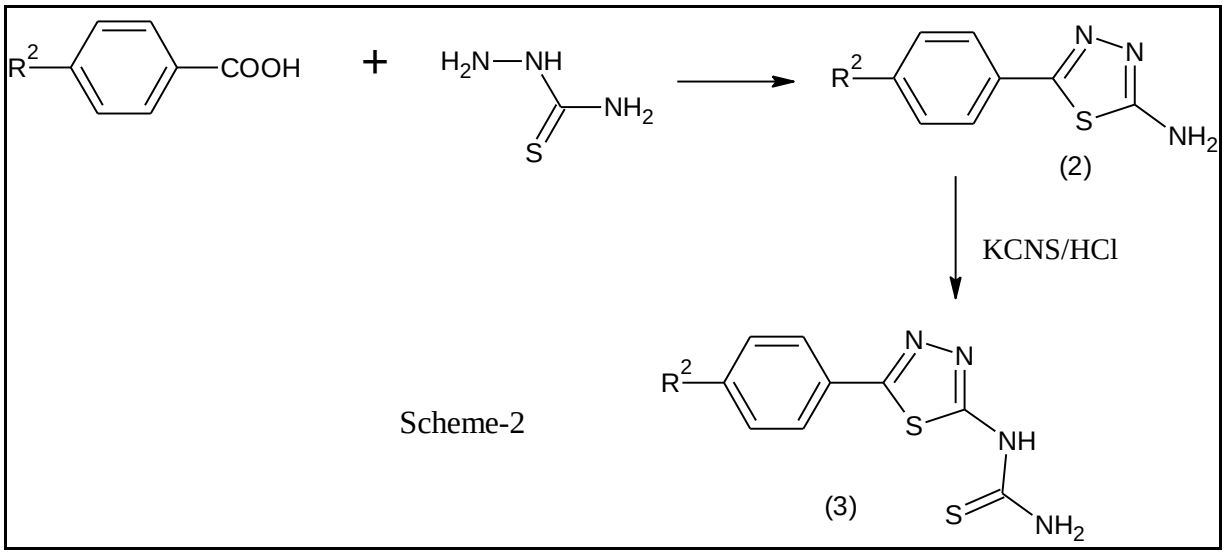
Substituted Chalcones (1) were prepared by the condensation of substituted acetones and substituted benzaldehydes in the presence of sodium hydroxide and ethanol according to the procedures in the literature[20].



Scheme-1

Synthesis of 2-amino-5-substituted aryl-1,3, 4-thiadiazoles (2) and 1-(5-substitued phenyl-1,3,4-thidiazol-2-yl)thioureas(3):

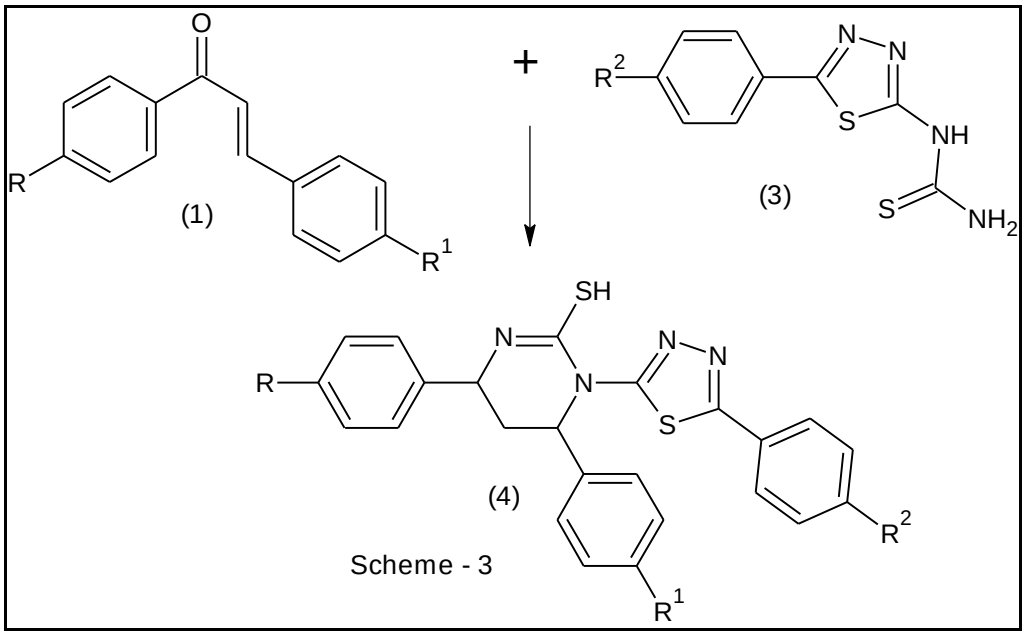
2-Amino-5-substituted aryl-1,3,4- thiadiazoles **(2)** were prepared by the reaction of substituted Benzoic acids and thosemicarbazide in the presence of concentrated sulphuric acidas per the literature method[21].2-Amino-5-substituted aryl-1,3, 4-thiadiazoles **(2)** on reaction with ammonium thiocyanate in presence of hydrochloric acid yields 1-(5-substituted phenyl -1, 3, 4-thiadiazol-2-yl) thioureas **(3).**



Scheme-2

Synthesis of 4,6-disubtituted phenyl- 5-subsutied phenyl -1,3,,4-thiadiazol-2-yl)- 1,4,5,6-tetrahydro pyrimidine 2-thiols (4):

1-(5-Substitued phenyl -1, 3, 4-thiadiazol-2-yl) thioureas **(3)** on condensation with substituted Chalcones **(1)** yields 4,6-disusbtituted phenyl-(5-susbtituted phenyl -1, 3, 4-thiadiazol-2-yl)- 1,4,5,6-tetrahydro pyrimidine 2-thiols**(4).**



Scheme - 3

Experimental Section:

Melting points (^{0}C) were determined by open capillary and are uncorrected. The purity of compounds was monitored by TLC using silica gel. IR spectra were recorded on a NICOLET AVATAR 330 FTIR Spectrophotometer. The^{1}H-NMR spectra was recorded using AC Bruker 400 MHz Spectrophotometer and chemical shift valves are given on delta scale relative to TMS as internal reference. Mass spectra were recorded on Shimadzu 2010A LC-MS system.

General procedure for synthesis of Chalcones (1):

A mixture of substituted acetophenones (0.01 mole) and aryl aldehydes (0.01 mole) was stirred in 90% ethanol (30 mL) and then an aqueous solution of potassium hydroxide (15 ml) was added to it. The mixture was kept overnight at room temperature and then it was poured into crushed ice and acidified with dilute hydrochloric acid. The chalcones derivative precipitates out as solid. Then it was filtered and crystallized from ethanol.

General procedure for synthesis of 2- amino -5- substituted aryl -1,3,4- thiadiazoles (2):

Amixture of thiosemicarbazide (0.01 mole), substituted benzoic acid (0.01mole) and conc. H_2SO_4 refluxed for two hours and poured into crushed ice. The resulting solid collected by filtration, washed with water, dried and recrystallized from ethanol

General procedure for synthesis of 1-(5-substitued phenyl-1,3,4-thiadiazole-2-yl)thioureas (3):

A mixture of 2- amino -5- substituted aryl -1, 3, 4- thiadiazoles (0.01 mole), ammonium thiocyante (0.02 mole) conc. HCl (1 ml) and water (20 ml) mixture refluxed for 3 hours. After cooling, the resulting solid collected by filtration, washed with water, dried and recrystallized from ethanol.

Synthesis of 4,6-disubtituted phenyl-(5-substituted phenyl -1, 3, 4-thiadiazol-2-yl)- 1,4,5,6-tetrahydro pyrimidine-2-thiols (4):

Substituted chalcones (0.01 mole) and 1-(5-substitued phenyl-1,3,4-thidiazole-2-yl) thioureas (0.02 mole) and KOH (0.02 mole; 1.12g) were taken in a 100 ml round bottom flask. To the above reaction mixture ethanol (30 ml)was added. Reaction mixture was refluxed for 3 hours using water condenser. It was then cooled and poured in cold water. Acidified with dil. HCl filtered washed with water and dried. The product was recrystallized from ethanol to get the product

Results and Discussions:

The synthesis of the target compounds **4a-l** was accomplished by condensation of substituted chalcones with various 1-(5-substitued phenyl-1,3,4-thidiazole-2-yl) thioureas in ethanol as shown in the scheme-3. The characterization data of the synthesized compounds (**4a-4l**) was collected and presented in Table-1.The overall yield of compound exceeds 70%. The products were characterised on the basis of their M.P,TLC, FT-IR, ^{1}HNMR and LC-MS.

Spectral data of titled compounds (4):

4b. FT-IR(KBr)νcm^{-1}:3121.5 (Ar-H stretch), 823.3 (C-Cl stretch), 2984.7 (2-CH_3 stretch), 1596.6 (Ar C=C stretch), 1512.6 (C=N stretch), 1463 (-S=C-N stretch), 1233 (C=S stretch), 3344 (N-H stretch).

^{1}HNMR(DMSO, 400 MHz, δ ppm): 3.3 (s, 1H, Ar-SH), 7.4-7.9 (m, 13H, ArH), 3.42- 3.47 (q, 2H, CH_2), 8.07-8.34 (m, 2H, 2-CH), 2.51 (s, 6H, $N(CH_3)_2$).

Mass (m/z): 505.

4f. FT-IR(KBr)νcm^{-1}: 3100 (Ar-H stretch), 852.56 (C-Cl stretch), 761.91 (C-Br stretch), 1591.33 (Ar C=C stretch), 1491.03 (C=N stretch), 1423.51 (-S=C-N stretch), 1280.78 (C=S stretch), 3300 (N-H stretch).

^{1}HNMR(DMSO, 400 MHz, δ ppm): 3.3 (s, 1H, Ar-SH), 7.0-7.7 (m, 12H, ArH), 3.40-3.44 (q, 2H, CH_2). 7.86-7.95 (m, 2H, 2-CH).

Mass (m/z): 541.

4g. FT-IR(KBr)νcm^{-1}:3180.3 (Ar-H stretch), 728.8 (C-Br stretch), 1441.2 (Ar-NO_2 stretch), 1594.1 (Ar C=C stretch), 1512 (C=N stretch), 1441 (-S=C-N stretch), 1233 (C=S stretch), 3321 (N-H stretch).

^{1}HNMR(DMSO, 400 MHz, δ ppm): 3.3 (s, 1H, Ar-SH), 7.56-7.58 (m, 12H, ArH), 3.4-3.44 (q, 2H, CH_2), 7.93-7.95 (m, 2H, 2-CH).

Mass (m/z): 552.

Biological activity: The antibacterial and antifungal activities of the newly synthesized compounds were assessed by serial dilution method[22] at which there is no turbidity was taken as Minimum Inhibitory Concentration (MIC).

Antibacterial activity

The antibacterial activity of the newly synthesized pyrimidine thiols(**4)** were carried out against two different pathogenic organisms. They are *Staphylococcus aureus*(Gram-positive), *Escherichia coli*(Gram-negative). The results are tabulated in Table-2. The majority of the compounds displayed moderate to good antibacterial activity comparable with that of standard drug Nitrofurazone. Among the compounds tested, **4c, 4g** and **4i** showed significant antibacterial activity comparable with that of standard drug. The better efficacy of **4c, 4g** and **4i**could be due to the presence of the p-chloro, p-bromo and p-nitro phenyl moiety.

Antifungal Activity

Antifungal activity of pyrimidine-thiols**(4)** was carried out on the fungus *Candida albicans.* Fluconazole was engaged as the standard. The results of antifungal activity data are also given in Table-2. Among the compounds tested, the compound**4h**exhibited the highest antifungal activity and all other compounds displayed potent activities comparable with that of standard drug Fluconazole.

Table-1 : Characteristic data of 4,6-disubstituted phenyl-(5-subsutituted phenyl-1, 3, 4-thiadiazol-2-yl)-1,4,5,6-tetrahydro pyrimidine -2-thiols (4):

Compounds	R	R^1	R^2	Molecular.formula	Melting point (^{0}C)	Yield(%)
4a	H	$N(CH_3)_2$	H	$C_{26}H_{23}N_5S_2$	259	60
4b	H	$N(CH_3)_2$	Cl	$C_{26}H_{23}N_5S_2Cl$	260	65
4c	H	$N(CH_3)_2$	NO_2	$C_{26}H_{23}N_6S_2O_2$	230	65
4d	H	$N(CH_3)_2$	OH	$C_{26}H_{24}N_5S_2O$	281	66
4e	H	Br	H	$C_{24}H_{24}N_4S_2Br$	256	66
4f	H	Br	Cl	$C_{24}H_{23}N_5S_2ClBr$	254	63
4g	H	Br	NO_2	$C_{24}H_{23}N_6S_2Br$	291	75
4h	H	Br	OH	$C_{24}H_{24}N_5S_2OBr$	255	77
4i	Br	$N(CH_3)_2$	H	$C_{26}H_{22}N_5S_2Br$	245	67
4j	Br	$N(CH_3)_2$	Cl	$C_{26}H_{22}N_5S_2Cl$	267	66
4k	Br	$N(CH_3)_2$	NO_2	$C_{26}H_{22}N_6S_2BrO_2$	269	75
4l	Br	$N(CH_3)_2$	OH	$C_{26}H_{22}N_5S_2BrO$	257	60

Table-2 : Antibacterial and antifungal activities of4,6-disubstituted phenyl - (5-subsutituted phenyl -1, 3, 4-thiadiazol-2-yl)-1,4,5,6-tetrahydro pyrimidine -2- thiols (4)

Compounds	Antibacterial activity (MIC in μg/ml)		Antifungal activity (MIC in μg/ml)
	Staphylococcus aureus	***Escherichia coli***	***Candida albicans***
4c	3.125	3.125	6.25
4d	12.5	12.5	6.25
4f	6.25	6.25	6.25
4g	3.125	3.125	6.25
4h	6.25	6.25	3.125
4i	3.125	3.125	6.25
Nitrofurazone	6.25	6.25	-
Fluconazole	-	-	6.25

Disc size = 5.5 mm; Duration = 24 h; DMF (Control)

Conclusion:

4,6- Disubtuted phenyl - (5-subsutied phenyl-1, 3, 4-thiadiazol-2-yl)-1,4,5,6-tetrahydro pyrimidine-2-thiols were prepared by the cyclic condensation of substituted chalcones with 1-(5-substitued phenyl-1,3,4-thidiazole-2-yl) thioureas in ethanol. The molar ratio of chalcone and substituted thiourea using ethanol solvent maintained and refluxed for 3 hours for effective condensations. The products were characterized on the basis of their melting point, IR, ^{1}HNMR, Mass spectroscopy. Antimicrobial activity and antifungal activity of tetrahydro pyrimidines with their zone of inhibition (in mm) were carried out.Among the tested compounds **4c**,**4g** and **4i** shown highest antibacterial activity and the compound**4h**shown potent antifungal activity.

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