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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF NOVEL COMPOUNDS OF DIETHYL (((5 - ((1H - PYRAZOL - 1 - YL) METHYL) - 1, 3, 4 - THIADIAZOL - 2 - YL) AMINO) (4 - SUBSTITUTED PHENYL) METHYL) PHOSPHONATES

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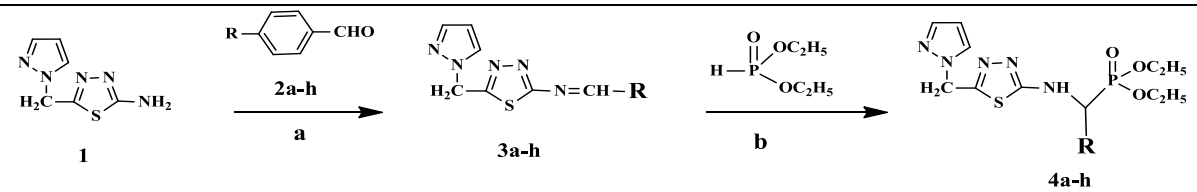
ABSTRACT

New novel derivatives of Synthesis of 5 - ((1H-pyrazol - 1 - yl) methyl) - N - (4 - substitued benzylidene) -1, 3, 4 - thiadiazol - 2 - amines (3a - h). were prepared by condensation of we have reported the synthesis and characterization of Diethyl (((5 - ((1H - pyrazol - 1 - yl) methyl) - 1, 3, 4 - thiadiazol - 2 - yl) amino) (4 - substituted phenyl) methyl) phosphonates (4a - h). The newly synthesized compounds were characterized by IR, 1H-NMR, 13C-NMR, mass spectra & Elemental analysis. The newly synthesized compounds were screened for their Biological activity.

KEYWORDS: 1,3,4-thiadiazole, Antibacterial and Antifungal activity, spectral data.

INTRODUCTION



Scheme: VI. 1: Proposed synthetic scheme for the preparation of (4a-h).

MATERIALS AND METHODS

All the chemicals used in the present investigation were purchased from Sigma-Aldrich Chemicals Company, Inc.USA. And used without further purification. TLC was performed on aluminum sheet of silica gel 60F254, E-Merk, Germany using iodine as visualizing agent. Melting point was determined in open capillary tubes on Mel-Tempapparatus and are

uncorrected. Column chromatography was performed on silica gel with different solvent systemsas eluents to afford the pure compound.[1-4] The IR Spectra were recorded as KBr pellets on Perkin-Elmer 1000 units, instruments. All 1H and ^{13}C-NMR spectra were recorded on a Varian XL-300 spectrometer operating at 400MHzfor 1H -NMR and 75 MHz for ^{13}C-NMR were recorded on a Varian XL-spectrometer operating at161.89MHz.[5-8] The compounds were dissolved in DMSO-d6 and Chemical shifts were referenced to TMS (1H and^{13}C-NMR). Mass spectral data was recorded on FAB-MS instrument at 70ev with direct inlet system. Elemental analysis were recorded on a Carlo Erba 1108 elemental Analyzer[9-10], Central Drug Research Institute, Lucknow, India.

RESULTS AND DISCUSSION

1. Synthesis of 5-((1H-pyrazol-1-yl) methyl)-N-(4-substitued benzylidene)-1, 3, 4-thiadiazol-2-amines (3a-h)

The Synthesis and characterization of 5-((1H-pyrazol-1-yl)-1, 3, 4-thiadiazol-2-amine (1) prepared by Equimolar quantities of 5-((1H-pyrazol-1-yl)-1, 3, 4-thiadiazol-2-amine (1) and Benzaldehyde (**2a)** were dissolve in absolute alcohol, to this three drops of acetic acid was added, then heated on a steam bath for 5-6 hours at 100^{o}C. After standing for 24hours at room temperature, the product was dried and recrystalised from warm absolute alcohol, the separated solid was identified as 5-((1H-pyrazol-1-yl)methyl)-N-benzyidene-1,3,4-thiadiazol-2-amine**(3a)**, mp134-136^{o}C and yield70%.

The other compounds **(3b-h)** were prepared by employing the above described procedure between **(1)** and 4-sbstituted benzaldehydes **(2b-h)**. The structure of **3a-h** was established by IR, ^{1}H-NMR, ^{13}C-NMR, mass data and elemental analysis elemental analysis.

IR Spectra: ($\bar{\nu}/\delta$, cm^{-1})

The IR spectra of 5-((1H-pyrazol-1-yl)methyl)-N-benzyidene-1,3,4-thiadiazol-2-amine **(3a)** was recorded in the 4000-400 Cm^{-1} range in KBr pellet reflect the molecular structure and showed characteristic bands around 3052 (stretching of Ar-H), 2940 and 2895 (CH_3,CH_2aliphatic stretching), 1627 (stretching of C=N thiadiazole),1375-1487 (stretching vibrations of pyrazole ring), 1039 (N-N of thiadizole), 695 Cm^{-1} (stretching of C-S-C of thiadizole). **1**

^{1}H-NMR: (δ, ppm)

The ^{1}H-NMR (400MHz) Spectra of 5-((1H-pyrazol-1-yl)methyl)-N-benzyidene-1,3,4-thiadiazol-2-amine **(3a)** was recorded in DMSO-d_6 showed the following signals at δ, ppm 4.99 (S, 2H , -CH_2 – flanked between pyrazol and thiadizol),6.22(q,1H,$H_a$of pyrazole ring),7.28(d,1H,H_b of pyrazole ring),7.52-7.83 (m,4H,-CH-of phenyl ring),7.80(d,1H,Hc of pyrazole ring),8.59(s,1H,-N=CH – flanked between 1,3,4-thiadiazole ring and phenyl group).

synthesis of Diethyl(((5-((1H-pyrazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl)amino) (4-substituetd phenyl)methyl) phosphonates (4a-h)

A mixture of 5-((1H-pyrazol-1-yl) methyl)-N-benzyidene-1, 3, 4-thiadiazol-2-amine **(3a)** and diethyl phosphite (0.50 mol, 0.004 mol) in anhydrous toluene (15 ml) was added drop wise. The reaction mixture was stirred at room temperature for 0.5hrs, after which the mixture was heated under reflux for 4-6 hrs. The reaction was monitored by TLC on silica gel using petroleum ether, ethyl acetate (1:2V/V).After completion o f the reaction, the solvent was removed by rota evaporator and the resulting residue was purified by Colum chromatography on silica gel (100-200 mesh) and ethyl acetate –hexane, (3:7 ratio) as eluent to afford pure Diethyl(((5-((1H-pyrazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl) amino) (phenyl) methyl phosphonate **(4a)**. mp152-154^{o}C and yield 70%.

The other compounds **(4b-h)** were prepared by employing the above described procedure between **(3b-h)** and diethyl phosphite. The structure of **4a-h** was established by IR, ^{1}H-NMR, ^{13}C-NMR, mass data and elemental analysis elemental analysis.

IR Spectra: ($\bar{\nu}$/δ, cm^{-1})

The IR spectra of Diethyl(((5-((1H-pyrazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl) amino) (phenyl) methyl phosphonate **(4a)** recorded in the 4000-400 Cm^{-1} range in KBr pellet reflect the molecular structure and showed characteristic bands around 3052 (stretching of Ar-H), 2940 and 2895 (aliphatic –CH_2 stretching) , 1670 (stretching of C=N thiadiazole),1375-1487 (stretching vibrations of pyrazole ring),1217-1251 (stretching of P=O functional group)[1,2], 1039 (N-N of thiadizole), 1019(stretching of P-O-C(aliphatic), 742-758(stretching of P-$C_{(Aliphatic)}$ of ester group)[3,4], 695 Cm^{-1} (stretching of C-S-C of thiadizole).

^{1}H -NMR: **(δ, ppm)**

The ^{1}H-NMR (400MHz) of Diethyl(((5-((1H-pyrazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl) amino) (phenyl) methyl phosphonate **(4a)** was recorded in DMSO-d_6 showed the following

signals at δ, ppm 1.29(t,6H, 2 x CH_3 groups of diethyl phosphite,J=0.86),3.9(s,1H,-CH- attached to thiadiazol ring),4.0(d,1H,-NH- flanked between thiadizol ring and -CH-), 4.07 (q,4H, 2 x CH_2 groups of diethyl phosphite), 4.99 (S, 2H , -CH_2 – flanked between pyrazole ring and thiadizol ring), 6.22(q,1H,H_b of pyrazole ring),7.23-733 (m,5H,-CH- of phenyl ring), 7.28(d,1H,H_b of pyrazole ring), 7.80(d,1H,H_c of pyrazole ring).

^{13}C- NMR: (δ,ppm)

The ^{13}C- NMR (75 MHz) spectra of Diethyl(((5-((1H-pyrazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl) amino) (phenyl) methyl phosphonate **(4a)** was recorded in DMSO-d_6 showed the following signals at δ,ppm 139.6, 105.9, 129.6 49.8, 168.0, 164.2, 69.6, 136.1, 128.2, 128.5, 126.7, 62.2, 16.3. corresponding to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 , C_8 , C_9& C_{13}, C_{10}& C_{12}, $C_{11,}$ C_{14} & C_{15}, C_{16} & C_{17}.

^{31}P- NMR spectra :((δ, ppm)

The ^{31}P- NMR (161.89MHz) spectra of Diethyl (((5-((1H-pyrazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-yl) amino) (phenyl) methyl phosphonate **(4a)** was recorded in DMSO-d_6 solvent. The ^{31} P NMR spectra of compounds **7a-o** were recorded by taking 85% H_3PO_4 as reference standard.

Mass Spectra

The electron impact mass spectrum of Diethyl(((5-((1H-pyrazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl) amino) (phenyl) methyl phosphonate **(**4a)The mass spectra of **(4a)** exhibited the molecular ion ($M^{7+\cdot}$) ion peak at m/z=515.15.The m/z values of molecular ion indicates that molecule is having odd number of Nitrogens.

Table: VI.7: Mass spectral data of primary fragmented ions for Diethyl (((5-((1H-pyrazol-1-yl)methyl)-1,3,4-thiadiazol-2-yl) amino) (phenyl) methyl phosphonate (4a)

Molecular ion	Lost radical	Primary fragmented ion	m/z values	Relative abundance (R.A) (%)
$C_{17}H_{22}N_5O_5PS(M^{7+\cdot})$ m/z 407.12 (100%)	$\dot{C}_6H_5$	$\overset{+}{C}_{11}H_{17}N_5O_3PS$ 4a(I)	330.08	14.75
	$\dot{C}_{11}H_{17}N_5O_3PS$	$\overset{+}{C}_6H_5$ 4a(II)	77.05	6.6
	$\dot{C}_{11}H_{16}O_3P$	$C_6H_6N_5\overset{+}{S}$ 4a(III)	180.03	6.6
	$C_6H_6\dot{N}_5S$	$\overset{+}{C}_{11}H_{16}O_3PH_2$ 4a (IV)	227.08	12.2
	$C_4H_{10}O_3\dot{P}$	$C_{13}H_{12}\overset{+}{N}_5S$ 4a(V)	270.08	16.7
	$\dot{C}_{13}H_{12}N_5S$	$C_4H_{10}O_3\overset{+}{P}$ 4a(VI)	137.04	4.6
	$\dot{C}_5H_5N_2$	$C_{13}H_{19}N_3O_3\overset{+}{P}S$ 4a(VII)	328.09	16.3

	$\dot{C}_{13}H_{17}N_3O_3P$	$\overset{+}{C}_4H_8N_2$ 4a(VIII)	81.05	4.4
	$C_3H_4N_2$	$\overset{+}{C}_{14}H_{18}N_3O_3PS$ 4a(IX)	339.08	17.2

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