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Synthesis, molecular properties and anthelmintic activity of some schiff bases of 1, 3, 4 thiadiazole derivatives

Bijo Mathew*, Shyam Sankar Vakketh and Shyam. Sasi. Kumar

Department of Pharmaceutical Chemistry, Grace College of Pharmacy, Palakkad, Kerala

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ABSTRACT

Our research concentrates on the synthesis of some Schiff bases of 5-phenyl substituted, 2-amino 1, 3, 4 thiadiazole derivates. The synthesis involves reaction between various aryl carboxylic acids with thiosemicarbazide in presence of dehydrating agent like Conc. H_2SO_4 to form 5-phenyl substituted, 2-amino 1, 3, 4 thiadiazole derivates. These derivatives on further treatment with various aldehydes to form Schiff base. The structures of the compounds were confirmed by IR, ^{1}HNMR and elemental analysis. The physicochemical properties involve determination of drug-like property of the synthesized compounds. It is based on the ***Lipinski's rule of 5*** *and can be determined by using* ***molinspiration cheminformatics*** *software. All the synthesized compounds showed zero violation of Lipinski's rule of five, which indicates good bioactivity and bioavailabilty.The anthelmintic activity of those compounds was investigated by method described in details by Kuppast and Nayak.Parameters under study were mean paralysis and mean lethal time in Pheretima posthuma. All the compounds having significant activity than standard drug except compounds* ***3b, 3c*** *and* ***3d.***

Key Words: Schiff base, 1,3,4 thiadiazole, Lipinski's rule of five, molinspiration, cheminformatics, *Pheretima posthum.*

INTRODUCTION

The biological activity of a compound depends up on their molecular structure. The interesting biological activities of a novel heterocyclic like Thiadiazole have stimulated considerable research work(1). There are number of five membered heterocyclic containing nitrogen and sulphur atom, have turned out to be a potential chemotherapeutic and pharmacotherapeutic agents. The biological profile of 1,3, 4-Thiadiazole derivatives is very extensive. The compounds

with azomethine linkages were also shown to possess an array of biological activities such as antifungal, antibacterial, and anti-inflammatory activity (2,3)

From these findings our work is designed for the synthesis of 5-phenyl substituted, 2-amino 1, 3, 4 thiadiazole derivates and determination of its molecular properties by suitable computational programmes and evaluation of its anthelmintic activity.

MATERIALS AND METHODS

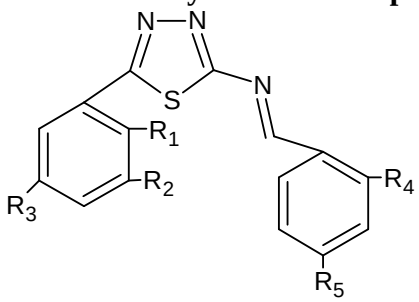
Melting points of all the synthesized compounds were determined by open capillary tube method and are uncorrected. The purity of all compounds was checked by TLC technique and iodine as the visualizing agent. IR spectra were recorded on FT-IR spectrophotometer (Shimadzu) by using KBr pellets technique. ^{1}H-NMR was recorded on DRX-300 MHz FT spectrophotometer by using DMSO as solvent and TMS as internal standard. The chemical shift was expressed in δ ppm. Molecular properties of the synthesized compounds were calculated by Molinspiration software (MI Chemoinformatics, SK-84104 Bratislava, Slovak Republic).

1) Synthesis of 2-amino, 5-(phenyl substituted) 1, 3, 4-thiadiazole

A mixture of thiosemicarbazide, 0.1mol and aryl substituted carboxylic acid 0.1mol, and conc. H_2SO_4 (5ml) in 50 ml of ethanol was refluxed for 2 hours. The resultant product was transferred in to a beaker and poured on to crushed ice. The solid separated out was filtered, washed with cold water and recrystallized from ethanol (4,).

Mobile phase for TLC- Ethanol: Ethylacetate 9:1

Table : 1 detail of synthesized compounds



Compound	R_1	R_2	R_3	R_4	R_5
3a	OH	H	H	H	Cl
3b	OH	H	H	H	CH_3NCH_3
3c	OH	H	H	OH	H
3d	OH	H	H	H	OCH_3
3e	OH	NO_2	NO_2	H	Cl
3f	$OCOCH_3$	H	H	H	Cl
3g	H	H	H	H	H
3h	H	NO_2	H	H	Cl
3i	H	NO_2	H	OH	H
3j	H	NO_2	H	H	H

2) Synthesis 5-phenyl-*N*-[(1*E*)-phenylmethylidene]-1,3,4-thiadiazol-2-amine

The substituted Thiadiazole derivatives 0.01 mol was dissolved in 30 ml of ethanol containing few drops of sulphuric acid. The appropriate aldehyde 0.01 mol was added to the reaction mixture. It was refluxed around 45 minutes, cooled and then poured in to crushed ice. The solid obtained was filtered, washed with water and recrystallized with ethanol(5,6).The details of the synthesized compounds were shown in table no: 1. The physical characterization of the synthesized compounds were shown in table no:2

Table 2: Physical parameters and elemental analysis of synthesized compounds

Compound	MF	MW	MP(^{0}C)	Rf	Elemental analysis calculated(found)		
					C	H	N
3a	$C_{15}H_{10}ON_3SCl$	315.78	138	0.31	57.05 (57.21)	3.19 (3.23)	13.31 (13.27)
3b	$C_{17}H_{16}ON_4S$	324.40	143	0.34	62.94 (62.54)	4.97 (4.61)	17.27 (17.02)
3c	$C_{15}H_{11}O_2N_3S$	297.33	162	0.41	60.59 (60.99)	3.73 (3.89)	14.13 (14.27)
3d	$C_{16}H_{13}O_2N_3S$	311.36	136	0.22	61.72 (61.93)	4.21 (4.51)	13.50 (13.37)
3e	$C_{15}H_8O_5N_5SCl$	405.77	154	0.51	44.40 (44.62)	1.99 (1.92)	17.26 (17.39)
3f	$C_{17}H_{12}O_2N_3SCl$	357.81	112	0.54	57.06 (57.23)	3.38 (3.31)	11.74 (11.61)
3g	$C_{15}H_{11}N_3S$	265.33	98	0.46	67.90 (67.63)	4.18 (4.09)	15.84 (15.70)
3h	$C_{15}H_9O_2N_4SCl$	344.78	60	0.42	52.25 (52.05)	2.63 (2.41)	16.25 (16.41)
3i	$C_{15}H_{10}O_3N_4S$	326.33	108	0.48	55.21 (55.38)	3.09 (3.18)	17.17 (17.32)
3j	$C_{15}H_{10}O_2N_4S$	310.33	94	0.38	58.05 (58.33)	3.25 (3.16)	18.05 (18.22)

Compound. 3a

IR (KBr,cm^{-1}): 3059.53(Ar-CH),1375.30(OH-bend),1166.98(Ar-Cl),1594.23(C=N str), 690 (C-S-C linkage in thiadiazole)

Compound. 3b

IR (KBr,cm^{-1}): 3049.53(Ar-CH),1350.36(OH-bend),1166.98(Ar-Cl),1594.95(C=N str),1461.94 (Ar-N$(CH_3)_2$,690.47 (C-S-C linkage in thiadiazole)

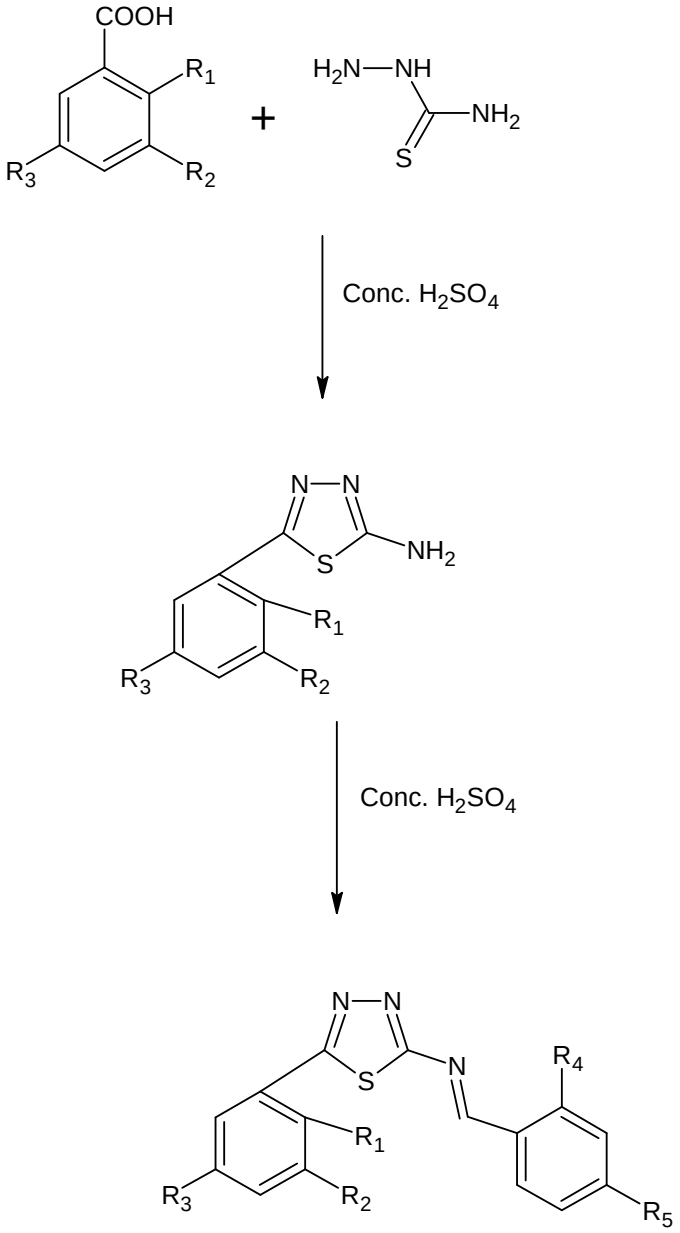
Compound. 3c

IR (KBr,cm^{-1}): 3023.53(Ar-CH),1296.36(OH-bend),1614.15(C=N str),700.41 (C-S-C linkage in thiadiazole)

Compound. 3d

IR (KBr,cm^{-1}): 3039.53(Ar-CH),1281.33(C-O str),2921.96(Methyl CH str), 1244.0(Asymmetric C-O-C str)694.33(C-S-C linkage in thiadiazole)

Scheme



Compound. 3e

IR (KBr,cm^{-1}): 3026.58(Ar-CH),1358.36(OH-bend),1166.85(Ar-Cl),1600.42(C=N str),1527.52 (Ar-NO_2),679.68 (C-S-C linkage in thiadiazole); ^{1}H NMR(DMSO):4.5(1H,s,-OH),1.5(1H,s, N=CH),7.1-7.8(4H.d,CH-Aryl).8.4-8.9(4H,d,CH-$Aryl_2$)

Compound. 3f
IR (KBr,cm^{-1}): 3046.22(Ar-CH),1614.13(C=N str),1533.30 (Ar-NO_2),668.78 (C-S-C linkage in thiadiazole); ^{1}H NMR(DMSO):2.3(1H,s, N=CH),7.5-7.89(4H.d,CH-Aryl).8.3-8.9(4H,d,CH-Aryl$_2$)

Compound. 3g
IR (KBr,cm^{-1}): 3023.26(Ar-CH),1591.16(C=N str), 668.78 (C-S-C linkage in thiadiazole)

Compound. 3h
IR (KBr,cm^{-1}): 3086.58(Ar-CH),1165.05(Ar-Cl),1597.34(C=N str),1545.59 (Ar-NO_2),695.78 (C-S-C linkage in thiadiazole); ^{1}H NMR(DMSO):1.81H,s, N=CH),7.5-8.2(4H.d,CH-Aryl).8.4-8.9(4H,d,CH-Aryl$_2$)

Compound. 3i
IR (KBr,cm^{-1}): 3066.58(Ar-CH),,1593.38(C=N str), 1565.39 (Ar-NO_2),669.68 (C-S-C linkage in thiadiazole); ^{1}H NMR(DMSO):4.4(1H,s,-OH),1.6(1H,s, N=CH),7.6-7.9(4H.d,CH-Aryl).8.4-8.8(4H,d,CH-Aryl$_2$)

Compound. 3j
IR (KBr,cm^{-1}): 3064.58(Ar-CH),,1614.13(C=N str), 1549.39 (Ar-NO_2),662.68 (C-S-C linkage in thiadiazole); ^{1}H NMR(DMSO):2.3 (1H,s, N=CH),7.5-7.9(4HCH-Aryl).8.3-8.9(4H,d,CH-Aryl$_2$)

Table :3 Determination of molecular properties from molinspiration software

Compound	Log p	TPSA	Number of non-Hydrogen atom	M W	No of Hydrogen bond acceptor	No of Hydrogen bond donors	No of rule- 5 violation	Number rotatable bonds	Molar volume
3a	4.514	58.376	21	315.78	4	1	0	3	254.074
3b	3.941	61.614	23	324.409	5	1	0	4	286.44
3c	3.779	78.004	21	297.339	5	2	0	3	286.456
3d	3.895	67.61	22	311.366	5	1	0	4	266.083
3e	4.338	150.024	27	405.779	10	1	0	5	300.742
3f	4.28	64.453	24	357.82	5	0	0	5	290.585
3g	4.106	38.148	19	265.341	3	0	0	3	232.52
3h	4.79	83.972	23	344.783	6	0	0	4	269.39
3i	3.982	104.2	23	326.377	7	1	0	4	263.872
3j	4.04	83.972	22	310.338	6	0	0	4	255.854

Where TPSA- Total polar surface area

Lipinski's Rule of Five is a rule of thumb to evaluate drug likeness .or determines if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally activedrug in humans. The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism and excretion(7). Lipinski's Rule of 5 states that, in general, an orally active drug has(8):

- Not more than 5 hydrogen bond donors(OH and NH groups)
- Not more than 10 hydrogen bond acceptors(notably O and N)

- Not more than 15 rotatable bonds
- A molecular weight under 500g/mol
- A partition coefficient log P (mi.LogP) less than 5

The results of the molecular properties of the synthesized compounds were shown in the table no: 3

Anthelmintic activity screening

The synthesized compounds were tested for Anthelmintic activity screening according to the method described in details by Kuppast and Nayak. *Pheretima posthuma* (earth worms obtained from the Botanical garden of Grace College of pharmacy, kerala.).of nearly equal size (6cm±1) were selected randomly for present study. The worms were acclimatized to the laboratory condition before experimentation. The earthworms were divided into four groups of six earth worms each. Albendazole first dissolved in minimum amount of ethanol and diluted with normal saline solution to obtained 0.1% w/v, 0.2% w/v, 0.5% w/v, 1% w/v were served as a standard and poured in to a Petridishes.

Table 4: Anthelmintic activity of the synthesized compounds

Compounds	Time in min.(mean±SEM) for paralysis				Time in min.(mean±SEM) for paralysis			
	Concentration (%)				Concentration (%)			
	0.1	0.2	0.5	1	0.1	0.2	0.5	1
3a	1.21 ±0.53	1.12 ±0.03	1.02 ±0.23	0.51 ±0.31	4.02 ±0.43	3.55 ±0.17	3.21 ±0.06	2.02 ±0.13
3b	2.32 ±0.41	1.54 ±0.25	1.34 ±0.15	1.23 ±0.03	5.02 ±0.09	4.23 ±0.28	3.58 ±0.37	2.43 ±0.05
3c	2.21 ±0.23	1.58 ±0.44	1.43 ±0.29	1.31 ±0.33	5.23 ±0.40	4.21 ±0.29	3.54 ±0.08	2.51 ±0.17
3d	2.12 ±0.48	1.47 ±0.20	1.28 ±0.38	1.37 ±0.03	5.17 ±0.06	4.12 ±0.23	4.05 ±0.39	2.48 ±0.09
3e	1.02 ±0.47	0.54 ±0.32	0.43 ±0.39	0.35 ±0.28	3.23 ±0.13	2.54 ±0.26	2.23 ±0.35	1.12 ±0.02
3f	1.21 ±0.31	1.27 ±0.13	1.11 ±0.27	0.56 ±0.31	3.55 ±0.16	3.23 ±0.19	3.09 ±0.26	1.32 ±0.18
3g	1.42 ±0.07	1.32 ±0.29	1.15 ±0.53	0.50 ±0.21	4.23 ±0.11	3.52 ±0.37	3.21 ±0.04	1.55 ±0.51
3h	1.35 ±0.38	1.23 ±0.32	1.18 ±0.23	0.54 ±0.43	4.12 ±0.08	3.42 ±0.26	3.31 ±0.12	1.45 ±0.36
I	1.32 ±0.21	1.21 ±0.50	1.12 ±0.23	0.51 ±0.44	3.54 ±0.31	3.43 ±0.17	3.12 ±0.24	1.43 ±0.06
3j	1.21 ±0.43	1.25 ±0.52	1.05 ±0.13	0.52 ±0.35	4.05 ±0.03	3.55 ±0.16	3.21 ±0.01	1.52 ±0.31
Standard (albendazole)	1.35 ±0.32	1.30 ±0.39	1.12 ±0.03	0.55 ±0.41	4.12 ±0.23	4.05 ±0.48	3.55 ±0.04	2.21 ±0.13
Control (DMSO+Normal saline)	-	-	-	-	-	-	-	-

RESULTS AND DISCUSSION

All the synthesized compounds were characterized by recrystallization, TLC, Melting point, elemental analysis, IR, ^{1}HNMR analysis. All the synthesized structures showed satisfactory result. Analysis indicated by the symbols of elements are within ±0.4% of theoretical values. The IR data of the compounds clearly showed a strong C=N stretching band around 1614.31cm^{-1} and a C-S-C linkage in thiadiazole of absorption band around 690.47cm^{-1}.This indicates that the formation of 1,3, 4 thiadiazole derivatives along with a. azomethine linkage The ^{1}HNMR also confirms the presence of shift value at 1.8-2.3and 7.8-8.3 for CH=N,(CH-Aryl) groups respectively.

Physicochemical drug descriptors provide a useful tool for evaluating drug activity(11). Table 3 presents descriptors that are calculated by molinspiration software. The rule of Five provides an accurate and useful determination of bioactivity and bioavailabilty.The 1,3, 4 thiadiazole derivatives were showed zero number of violation of the rule of Five. The anthelmintic activity of those compounds was investigated by method described in details by Kuppast and Nayak.Parameters under study were mean paralysis and mean lethal time in *Pheretima posthuma*. All the compounds having significant activity than standard drug except compounds **3b, 3c** and **3d.** The thiadiazole derivatives with a azomethine linkage posses a potent anthelmintic activity. The molecular properties also reveal the drug-like property of the compounds and in future we can make good moiety from this findings

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