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Synthesis of azetidinonyl substituted 1, 3, 4-thiadiazole-2-yl derivatives as antibacterial activity

Joseph Valarmathy[**], Lazarus Samueljoshua[1], Govindasamy Rathinavel[2], Loganathan Senthilkumar[1]

[**]Department of Pharmaceutical Chemistry, Nandha College of Pharmacy, Erode, Tamilnadu, India
[1]Department of Pharmaceutical Chemistry, Padmavathi College of Pharmacy, Dharmapuri, Tamilnadu, India
[2]Prist University, Thanjavur, Tamilnadu, India

Abstract

Some new 3-chloro-4-(phenyl substituted)-1-[5-pyridin-4-yl)-1,3,4-thiadiazol-2yl] azetidine 2-one derivatives (5a-e) have been synthesized by the reaction of INH(1) with potassium thio cynate. On further condensation with conc H_2SO_4 to form 5-(pyridine-4-yl)-1,3,4-thiazol-2-amine. The compound react with various aldehyde which on cyclo addition with chloroacetyl chloride and triethylamine in DMF. These compounds were characterized by their spectral data. The title compounds were found to be efficient antibacterial agents on evolution.

Key words: Thiadiazole, Azetidinone, Antibacterial activity, Cup plate method.

INTRODUCTION

A number of 1,3,4-thiadiazoles and azetidinone derivatives have been reported to possess antibacterial activity[1-3]. These are found to possess various biological activities viz Antitubercular, analgesic, anti-inflammatory, antimicrobial, anthelmintic and pesticidal activity[4-8]. In view of such reports, we now report the synthesis of some 3-chloro-4-(phenyl substituted)-1-[5-(pyridine-4yl)-1,3,4-thiadiazol-2yl] azetidin 2-one and antibacterial activity associated with them. The required 5-(pyridine-4yl)-1,3,4-thiadiazol-2-amine(3) has been synthesized by reacting isonicotinohydrazide with potassium thiocynate, on further cyclo condensation with conc H_2SO_4 . The compound was reacting with various aromatic aldehyde in

the presence of ethanol which on further cyclo addition with chloroacetyl chloride and triethylamine in DMF.

RESULTS AND DISCUSSION

All the synthesized compounds have been screened for antibacterial activity against *B.subtilis, S.facilis, S.aureus, P.mirabilis, K.pneumonia,* and *S.typhi* by cup plate method. Oxytetracyclin was used as standard for antibacterial activity. The results indicate that these compounds were active against all the six organisms. Compound 5d exhibited significant activity and compound 5b, 5c, 5e exerted equal potency against *B.subtilis.* Compound 5b and 5e exhibited significant activity and compound 5c, 5d exerted equal potency against *S.facilis.* Compound 5a, 5b, 5c and 5e exhibited significant activity and compound 5d exerted equal potency against *S.aureus.* Compound 5b and 5e almost equal potency against *Pmirabilis.* Compound 5e exhibited significant activity and compound 5a, 5c and 5d exerted equal potency against *K.pneumoniae.*

MATERIALS AND METHODS

Experimental

The synthesis of the title compounds is given in scheme1. Melting were determined by using open capillary method and are uncorrected. The purity of the synthesized compounds was finally ascertained by TLC on silica gel-G plate. The structure of the synthesized compounds was confirmed by IR and NMR. IR spectra were recorded on Perkin Elmer FTIR-283 in KBr phase. ^{1}H NMR spectra were recorded on Bruker-400.

Isonicotinyl thiosemicarbazide

A mixture of isonicotinic acid hydrazide(1) (0.1 mol), potassium thiocyanate(0,2 mol) in methanol were refluxed for 4h.The reaction mixture was poured into crushed ice, filtered and the solid product was recrystallized from ethanol[9-13].

(Pyridine-4yl)-1,3,4-thiadiazol-2amine

A mixture of (2) (0.1mol), and 5ml of conc. H_2SO_4 were taken in a 50ml beaker and the reaction mixture was kept at room temperature for 2-5h. The reaction mixture was then poured over ice water and recrystallized from ethanol.

(3) IR (KBr cm^{-1}) 3307, 3277, 3280(NH), 1587(C=N), 690(C-S-C); H^1 NMR: 6.71-7.40, (m, 5H, Ar-H), 6.72-7.54(m, 4H, Ar-H), 5.61(s, 2H, NH_2).

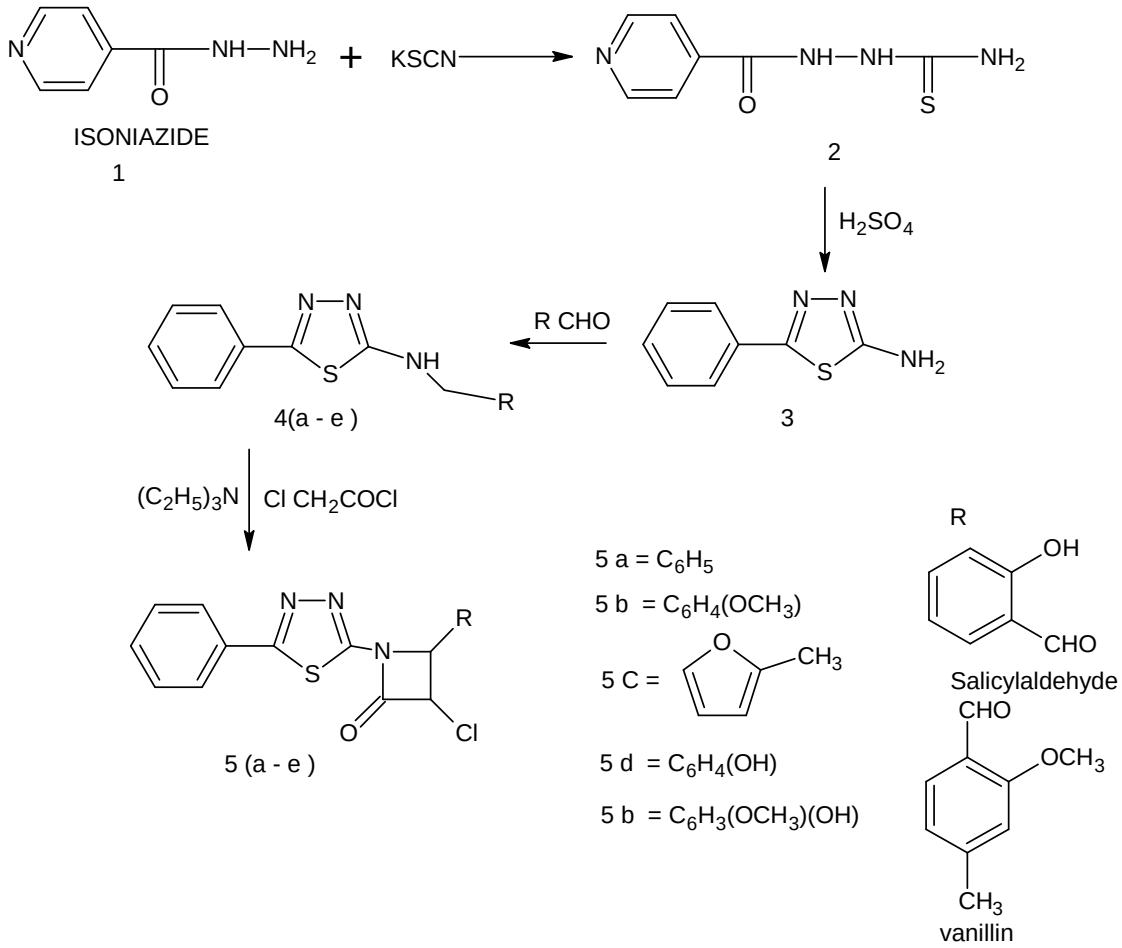
(Pyridine-4yl)-1,3,4-thiadiazol-2amine benzylidene substituted(4a-e)

A mixture of (3) (0.1 mol) and aromatic aldehyde (0.001 mol) were dissolved in 30ml of ethanol containing few drops of glacial acetic acid. The reaction was refluxed for 5h. Cooled and then poured into crushed ice and the resultant solid was recrystallized from ethanol[14].

3-Chloro-4-(phenyl substituted)-1-[5-(pyridine-4yl)-1,3,4-thiadiazol-2yl] azetidin 2-one (5a-e)

Compound (4) (0.01 mol) was dissolved in ethanol (40ml) and triethylamine (0.02 mol) was added to it. Chloroacetyl chloride (0.02 mol) was introduced dropwise over a period of 1h with constant stirring. The reaction mixture was refluxed for 2h. After cooling, the reaction mixture was washed with water and recrystallized from ethanol[15-17].

Scheme 1



5a. IR (KBr cm^{-1}) 2842.56 (Ar-H), 1692.27 (C=O), 1587.13 (C=N), 700.033 (C-Cl), 620.96 (C-S-C); ^{1}H NMR: 7.0-7.4 (m, 5H, pyridyl-H), 4.1(d, 1H, CH of azetidinone), 3.6(d, 1H, CH-Cl).

5b. IR (KBr cm^{-1}) 2814.23 (Ar-H), 1655.27 (C=O), 1578.28 (C=N), 1290.14 (Ar-CH), 1169.78 (C-O), 714.033 (C-Cl), 620.966 (C-S-C); ^{1}H NMR :7.7-8.1 (m, 4H, pyridyl-H), 7.0-7.3 (m, 4H, Ar-H), 3.96 (s, 3H, -OCH_3), 3.4(d, 1H, CH of azetidinone), 2.6(d, 1H, CH-Cl).

5c.IR (KBr cm^{-1}) 2842.56 (Ar-H), 1674.27 (C=O), 1587.13 (C=N), 769.458 (C-Cl), 700.033 (C-S-C); ^{1}H NMR:7.6-8.0 (m, 4H, pyridyl-H), 6.8-7.2(m, 3H, Furan-H), 3.9(d, 1H, CH of azetidinone), 3.4(d, 1H, CH-Cl).

5d.IR (KBr cm^{-1}) 3663.17 (-OH), 2858.56 (Ar-H), 1696.27 (C=O), 1587.13 (C=N), 1128.51 (C-N), 769.458 (C-Cl), 685.033 (C-S-C); ^{1}H NMR: 7.7-8.1 (m, 4H, pyridyl-H), 7.0-7.3 (m, 4H, Ar-H), 4.6(s, 1H, OH), 3.4(d, 1H, CH of azetidinone), 2.6(d, 1H, CH-Cl).

5e.IR (KBr cm^{-1}) 3498.24 (-OH), 2842.56 (Ar-H), 1684.27 (C=O), 1593.13 (C=N), 1467.56 (Ar-CH), 1290.14 (C-O-C), 700.033 (C-Cl), 620.966 (C-S-C); ^{1}H NMR: 7.7-.8.1 (m, 4H,

pyridyl-H), 7.0-7.3 (m, 3H, Ar-H), 4.6(s, 1H, OH), 3.9 (s, 3H, OCH_3), 3.4 (d, 1H, CH of azetidinone), 2.6(d, 1H, CH-Cl).

Table 1

Compound	Zone of inhibition (in mm)					
	B.subtilis	*S.facilis*	*S.aureus*	*P.mirabilis*	*K.pneumoniae*	*S.typhi*
5a	18	20	25	17	20	19
5b	20	28	22	19	-	20
5c	20	22	26	15	20	15
5d	25	22	21	14	21	18
5e	20	31	28	20	31	16

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