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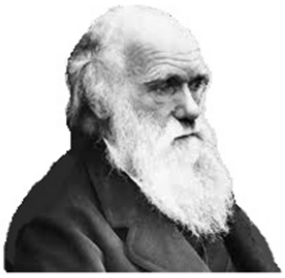

World News of Natural Sciences

An International Scientific Journal

WNOFNS 54 (2024) 9-16 EISSN 2543-5426

Synthesis, spectral studies and antimicrobial activity of thiosemicarboximide derivatives containing pyridine nucleus

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ABSTRACT

The Thiosemicarboximide derivatives of **(5a-5j)** were synthesized by the condensation of Chalcone derivatives **(4a-4j)** with H_2N-NH-CS-NH_2 in the presence of glacial acetic acid. The structures of newly synthesized compounds were confirmed based on ^{1}H-NMR, mass spectra, and IR data. All the newly synthesized compounds were screened for their antibacterial activity against Gram +ve Bacteria *Bacillus subtilis, Staphylococcus aureus*, and Gram –ve Bacteria *Escherichia coli, Pseudomonas aeruginosa* and Fungi *Aspergillus niger*.

***Keywords*:** Thiosemicarboximide derivatives, Pyridine, Anti-microbial activity

1. INTRODUCTION

The introduction to the compound pyridine aims to present a comprehensive overview, emphasizing its significance as a heterocyclic compound[1,2]. This exploration includes an examination of its unique structural attributes and the broad spectrum of applications it holds in diverse fields ranging from medicinal chemistry to pharmaceuticals and materials science[3-5]. Over the past two decades, organic fluorination chemistry has emerged as a crucial method for obtaining biological Active compounds[6]. Furthermore, the FDA has approved ten fluorinated drugs[7]. Several therapeutic actions suggest derivatives of thiosemicarboximides may be

(Received 20 February 2024; Accepted 17 March 2024; Date of Publication 19 March 2024)

significant treatments for disorders of the central Nervous system & infections induced by thiosemicarboximides based medicines have been documented as bacteria, a pain reliever, and an anti-allergen[8,9]. New pharmaceutical structures and bioactive molecules may be synthesized using thiosemicarboximides as intermediaries[10]. Clinically active pharmacological moieties such as Thioacetazone and Triapine are used as anticancer drugs that have shown promise in combating DNA viruses, the most prevalent of which are orthodox[11].

Thiosemicarboxmide derivatives possesses remarkable pharmaceutical importance and biological activities. Thiosemicarboxmide derivatives have been reported to be active Anti-malarial activity[12], Anticancer activity[13], Anti-tumor activity[14], Anti-convulsant activity[15], Antimicrobial activity[16], Anthelmintic activity[17], Antifungal activity[18], Anti-rheumatics activity[19] etc. On the basis of these results prompted us to synthesized some new Thiosemicarboxmide derivatives. This paper outlines the synthesis of Thiosemicarboxmide derivatives **5a-5j**. It includes a study on their biological activities. The antimicrobial activity was determined by the cup plate method at a concentration of 50 µg/ml using DMSO as a solvent[20]

2. EXPERIMENTAL

All the chemicals used in the reaction Sigma-Aldrich. Thin-layer chromatography (TLC) using precoated silica gel GF254 plates from E-Merck Co. was used to monitor the reactions, and UV light exposure allowed the chemicals to be observed. The melting points of synthesized compounds were measured in open glass capillaries are uncorrected. Tetramethylsilane was used as an internal standard for the ^{1}H NMR spectra of the synthesized compounds, which were recorded on a Bruker 400-MHz NMR spectrometer in DMSO-d6 solvent. The compound's IR spectra were recorded using the KBr pellet technique on the SHIMADZU-FTIR-8400 spectrophotometer. A water mass spectrometer was used to record the mass spectra.

2. 1. General procedure for the synthesis of 1-{4'-[(3''-methyl)-4''-(2''',2''',2''' trifluoroethoxy)pyridin-2''-yl)methoxyphenyl}-3-(3'''',4''''-dimethoxyphenyl) prop-2-en-1-one.(4c)

The procedure involved dissolving 1-{4'-[(3"-methyl)-4"-(2"',2"',2"'-trifluoroethoxy)pyridin-2"-yl]methoxyphenyl}ethan-1-one in methanol, and adding 3,4- Dimethoxy benzaldehyde to the solution, followed by the addition of a catalytic amount of 20% aq. NaOH solution. The mixture was then stirred for 24 hours at room temperature,the completion of the reaction was confirmed using TLC. The resulting mixture was poured into crushed ice. filtered and dried, crystallized in methanol. Yield 78% (Light yellow solid). M.P: 178 °C

Spectral analysis: IR (KBr pallet) in CM^{-}

3036 (C-H str. Aromatic), 2952 (C-H Asym. Alkane), 2880 (C-H Sym. Alkane), 1654 (C=O str. Ketone), 1599 (CH=CH str. Vinyl), 1580 (C=C Str. Aromatic), 1470 (C-H Def. Alkane), 1211 (C-O-C Ether), 1103 (C-F Halide). ^{1}H NMR (DMSO, 400 MHz) in δPPM: 8.37 (Doublet, 1H of -CH), 8.16 (Doublet, 2H of -CH), 7.8 (Doublet, 1H of –CH), 7.6 (Doublet, 1H –CH), 7.5 (Singlet, 1H –CH), 7.3 (Doublet, 2H –CH), 7.1 (Doublet, 2H –CH), 7.0 (Doublet, 1H

–CH), 5.3 (Multiplet, 2H –CH_2), 4.9 (Singlet, 2H –CH_2), 3.87 (Singlet, 3H –OCH_3), 3.82 (Singlet, 3H –OCH_3), 2.24 (Singlet, 3H –CH_3). MS: at M/Z = 486, 470, 354, 285, 204, 191, 181, 106, 79. Analytical calculated for Molecular formula $C_{26}H_{24}F_3NO_5$ is Calcd C: 64.06 %, H: 4.96 %, F: 11.69 %, N:2.87 %, O: 16.41 Found C: 64.01 %, H: 4.92 %, F: 11.62 %, N: 2.78% , O: 16.38%.

Similarly, other (**4a-4j**) were synthesized. Chalcones physical data and antimicrobial activities was published in *World Journal of Pharmaceutical Research* 2024, 13(3), 899-908. DOI: 10.20959/wjpr20243-31128

2. 2. General procedure for the synthesis of 1-{1'-4''- [(3'''-methyl)-4'''-(2'''',2'''',2''''-trifluoroethoxy)pyridine-2'''-yl]methoxy phenyl}-3'-(3''''',4'''''-dimethoxyphenyl)-prop-2'-ene-1'-hydrazino thiamide. (5c)

A solution of 1-{4'[(3"-methyl)-4"-(2"',2"',2"'-trifluoroethoxy)pyridin-2"-yl]methoxy) phenyl}-3-(3"",4""-dimethoxyphenyl)-prop-2-ene-1-one (3.19 gm, 0.01M), Methanol (20 ml) and Thiosemicarboximide (1.39 gm, 0.02M) refluxed in an oil bath for 6 hrs. at 120 °C temp. After the successful completion of reaction, the reaction mixture was poured into ice cold water. Filtered it, dried it. The product was crystallised in Methanol. m.p.172 °C, Yield 81 %.

Spectral analysis: IR (KBr pallet) in CM^{-}

3316 (N-H str.), 3076 (C-H str.Aromatic), 2959 (C-H Asym. Alkane), 2867 (C-H Sym. Alkane), 1647 (C=N str.), 1583 (N-H bending), 1477 (C=C Str. Aromatic), 1453 (C-H Def. Alkane), 1244 (C-O-C Ether), 1334 (C-F Halide), 1034 (>C=S str.). ^{1}H NMR (DMSO, 400 MHz) in δPPM: 10.70 (Singlet, 1H -NH), 8.46 (Singlet, 2H of -NH_2), 8.18 (Doublet, 1H of -CH),7.84 (Doublet, 2H of –CH), 7.62 (Doublet, 1H –CH), 7.58 (Doublet, 1H –CH), 7.1 5 (Doublet, 2H –CH), 6.88 (Doublet, 1H –CH), 6.78 (Singlet, 1H –CH), 5.85 (Doublet,1H -CH), 5.34 (Singlet, 2H –CH_2), 4.99 (Multiplet, 2H –CH_2), 3.82 (Singlet, 3H –OCH_3), 3.71 (Singlet, 3H –OCH_3), 2.23 (Singlet, 3H –CH_3). MW = 560 ($C_{27}H_{27}F_3N_4O_4S$; Required: C, 57.85 %; H, 4.85%; F, 10.17%; N, 9.99%; O, 11.42%; S, 5.72%; found: C, 57.83%; H, 4.81%; F, 10.13%; N, 9.93%; O, 11.38%; S, 5.68%)

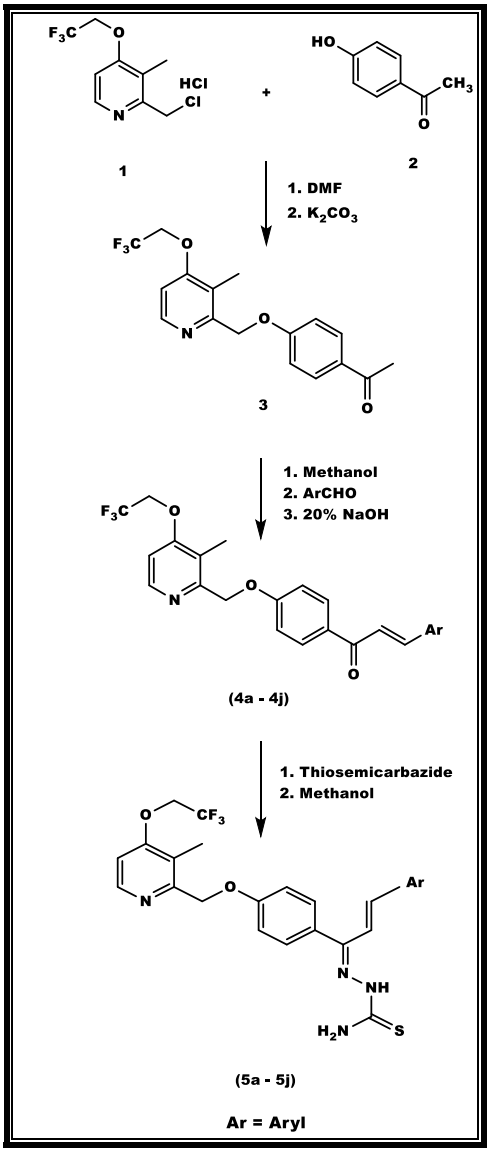
Similarally, other (1-{1'-4"-[(3'"-methyl)-4'"-(2"",2"",2""-trifluoroethoxy)pyridine-2'"-yl]methoxy phenyl}-3'-aryl-prop-2'-ene-1'-hydrazino thiamides Were prepared. The physical data are recorded in Table 1.

Table 1. Physical and Analytical data of (1-{1'-4"-[(3'"-methyl)-4'"-(2"",2"",2""-trifluoroethoxy)pyridine-2'"-yl]methoxy phenyl}-3'-aryl-prop-2'-ene-1'-hydrazino thiamides. (5a – 5j)

Sr No	-Ar	Molecular Formula	M.W	M.P	Yield	% of Nitrogen	
						Calcd	Found
5a	C_6H_5-	$C_{25}H_{23}F_3N_4O_2S$	500	151	88	11.19	11.15
5b	4-OCH_3-C_6H_4-	$C_{26}H_{25}F_3N_4O_3S$	530	169	85	10.56	10.51
5c	3,4 $(OCH_3)_2$ -C_6H_3-	$C_{27}H_{27}F_3N_4O_4S$	560	172	81	9.99	9.93
5d	2-Cl-C_6H_4-	$C_{25}H_{22}ClF_3N_4O_2S$	535	164	78	10.47	10.42

5e	4-Cl-C_6H_4-	$C_{25}H_{22}ClF_3N_4O_2S$	535	169	82	10.47	10.44
5f	4-Br-C_6H_4-	$C_{25}H_{22}BrF_3N_4O_2S$	579	178	79	9.67	9.62
5g	4-F-C_6H_4-	$C_{25}H_{22}F_4N_4O_2S$	518	180	70	10.81	10.78
5h	2-NO_2-C_6H_4-	$C_{25}H_{22}F_3N_5O_4S$	545	170	76	12.84	12.80
5i	3-NO_2-C_6H_4-	$C_{25}H_{22}F_3N_5O_4S$	545	169	69	12.84	12.77
5j	4-OH-C_6H_4-	$C_{25}H_{23}F_3N_4O_3S$	516	188	72	10.85	10.79
Zone of Inhibition measured in mm.							

3. REACTION SCHEME



Scheme 1. The synthetic scheme for the preparation of compounds **(5a-5j).**

4. RESULTS AND DISCUSSION

Scheme 1 shows the synthetic pathway used to produce the chalcone derivatives **4a–4j** and Thiosemicarboximide derivatives **5a–5j**. The compound **3** was synthesized by reacting 2-(chloromethyl)-3-methyl-4-(2',2',2'-trifluoroethoxy)pyridine hydrochloride **1** with 4-hydroxy acetophenone **2** in the presence of potassium carbonate and DMF at 90°C. The chalcone derivatives **4a–4j** were prepared by condensation of compound **3** with Aromatic aldehyde using catalytic 20% aq. NaOH in Methanol at room temperature 24 hrs. After recrystallization from methanol, all corresponding chalcones were obtained in 65–87% yield. The Thiosemicarboximide derivatives **5a–5j** were prepared from chalcones **4a–4j** b reacting with H_2N-NH-CS-NH_2 in the presence of glacial acetic acid. The isolated products obtained thiosemicarboximide derivatives in 69-88 % yield. The structures of all newly synthesized compounds **5a–5j** were assigned based on spectral data such as IR, ^{1}H-NMR, and mass spectra.

Antimicrobial Activity

The antimicrobial activity was determined by the cup plate method at a concentration of 50 µg/ml using DMSO as a solvent. The activity was taken by Gram-positive bacteria *Staphylococcus aureus, Bacillus subtilis*, Gram-negative bacteria *Escherichia coli, Pseudomonas aeruginosa,* and anti-fungal activity against *Aspergillus niger*. The zone - of inhibition was measured in mm. The antibacterial activity was compared with the known standard drugs, viz, Streptomycin, Ampicillin, and anti-fungal activity was compared with known standard drugs viz. Nystatin. The zone of inhibition activity results of compounds **(5a-5j)** are shown in Table No. 2 comparable antimicrobial activity represented in Table 3.

Table 2. Antimicrobial Activity of 1-{1'-4''-[(3'''-methyl)-4'''-(2'''',2'''',2''''-trifluoroethoxy) pyridine-2'''-yl]methoxy phenyl}-3'-aryl-prop-2'-ene-1'-hydrazino thiamides. **(5a – 5j)**

Compd	Ar	Antibacterial Activity				Anti Fungal Activity
		Gram +ve bacteria		Gram -ve bacteria		
		B. subtilis	***S. aureus***	***E. coli***	***P. aeruginosa***	***A. niger***
5a	C_6H_5-	13	7	15	6	18
5b	4-OCH_3-C_6H_4-	17	10	8	9	12
5c	3,4 $(OCH_3)_2$ -C_6H_3-	15	11	9	13	13
5d	2-Cl-C_6H_4-	10	17	11	15	17
5e	4-Cl-C_6H_4-	12	9	13	17	8
5f	4-Br-C_6H_4-	10	11	19	13	12
5g	4-F-C_6H_4-	8	7	17	11	16
5h	2-NO_2-C_6H_4-	7	9	18	7	10

5i	3-NO_2-C_6H_4-	11	11	16	12	12
5j	4-OH-C_6H_4-	13	15	17	14	17

Table 3. Compounds **(5a-5j)** showing comparable antimicrobial activity with known standard drugs.

Compounds	**Antibacterial activity**				**Anti fungal activity**
	Gram +ve bacteria		**Gram -ve bacteria**		
	B. subtilis	***S. aureus***	***E. coli***	***P. aeruginosa***	***A. niger***
(5a-5j)	5a	5d	5f	5d	5a
	5b	5j	5g	5e	5d
	5c	-	5h	5j	5g
	5j	-	5j	-	5j
Activity of Known Standard Drugs:					
Streptomycin (50 µg/ml)	26	27	28	20	0
Ampicillin (50 µg/ml)	25	26	26	19	0
Nystatin 50 µg/ml)	0	-	-	-	22
Zone of Inhibition measured in mm.					

5. CONCLUSIONS

In summary, in the present work we have developed 1-{1'-4"-[(3'"-methyl)-4'"-(2"",2"",2""-trifluoroethoxy)pyridine-2'"-yl]methoxyphenyl}-3'-aryl-prop-2'-ene-1'-hydrazino thiamides **(5a – 5j)** were synthesized and characterized based on their physical and spectral data. Thiosemicarboximide derivatives **(5a - 5j)** have been synthesized and some of the compounds **5a, 5d, 5e, 5g, 5j** showed good to remarkable antibacterial and antifungal activity which are compared to known standard drugs e.g. Streptomycin, Ampicillin, Nystatin at the same concentration (50 µg/ml), which are represented in the Table 3.

ACKNOWLEDGMENTS

I am thankful to the Management and the Principal of Shree M. and N. Virani Science College, Chemistry Department, Rajkot, for their kind support and also thankful to NFDD Complex, Deaprtment of Chemistry, Saurashtra University, Rajkot for providingthe spectral data facilities.

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