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Synthesis and antibacterial activity of 5-chloro-N-cyclohexyl- 6-thio substituted-nicotinamide derivatives

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ABSTRACT

A new route for the synthesis of 5-chloro-N-cyclohexyl-6-thio substituted-nicotinamide derivatives is reported. The antibacterial activity of all the synthesized compounds (4a-h) has been performed against gram positive and gram-negative bacteria. The compound 4c has found excellent antibacterial activity. The newly synthesized compounds are characterized by spectral data.

Keywords: Substituted-nicotinamide, antibacterial, cyclohexylamine, thiols.

INTRODUCTION

Importance of hetero cyclic compounds has long recognized in the field of synthetic organic chemistry. It is well known that heterocyclic compounds containing nitrogen and sulphur exhibit a wide variety of biological activity [1]. A series of pyridine derivative were evaluated for antitumor activities [2]. Nicotinamide has been shown to be beneficial in the treatment of papular and pustular acne, as well as improvement of skin cancer[3]. Nicotinamide or nicotinic acid has been used to treat diseases such as hypercholesterolemid and schizophrenia [4-7]. Nicotinamide and its derivatives are also used to prevent type-1 diabetes in animal model and humans showed cytotoxic properties [8-9].

On the other hand 6–chloro–3-substituted pyridine are very important class of heterocycles and are widely used in pharmaceutical and agrochemical industry [10-12]. The increasing interest in the chemistry of nicotinamide and its substituted derivatives result from the wide possibilities and their practical application for obtaining biologically active agents. Derivatives of S-protected triazole and diazole exhibit high anti-inflammatory activity [13] Our interest is to search antibacterial activity of S- protected derivatives of nicotinamide. An attempt has been made to understand the antibacterial behavior of these compounds *in vitro*.

MATERIALS AND METHODS

Experimental

IR spectra (cm⁻¹) were recorded on a Shimadzu, 460 IR spectrophotometer in KBr pellets. ¹H NMR spectra (ppm) were recorded on 300 MHz Bruker Spectrometer with TMS as an internal standard. All compounds were purified by column chromatography using CHCl₃: methanol (90:10) as an eluent.

5,6-Dichloronicotinoyl chloride (compound 2):

5,6-dichloro nicotinic acid (0.03 M) & SOCl₂ (0.1 M) was refluxed using catalytic DMF on water bath for half an hour. The reaction mixture was cooled, concentrated to afford titled compound in quantitative yield.

Synthesis of 5,6-Dichloro-N-cyclohexyl nicotinamide (compound 3):

In cold condition cyclohexylamine was treated with nicotinoyl chloride in DCM using triethylamine as a base and maintained at room temperature. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was concentrated, poured on crushed ice. The solid obtained was filtered and washed with water. Solid dried at 40 0 C [14]

5-chloro-N-cyclohexyl-6-(2H-imidazol-2-ylsulfanyl)-nicotinamide (compound 4a):

A mixture of 5, 6-dichloro-*N*-cyclohexylnicotinamide and 2*H*-imidazole-2-thiol (**3**) was refluxed in DMF in the presence of anhydrous potassium carbonate at 80 $^{\circ}$ C. Progress of reaction was monitored by TLC. After completion of reaction (3.0 hr), the reaction mixture was poured on crushed ice. The solid obtained was filtered and washed with water. Solid dried in at 40 $^{\circ}$ C. Further purification was performed by column chromatography using CHCl₃: methanol (90:10) as an eluent, m.p. 222 $^{\circ}$ C.

¹HNMR δ (ppm):1.44– 1.70 (m, 10 H, cyclohexyl), 3.54 (m, 1H, cyclohexyl), 7.30 – 8.35 (m, 3H, imidazolyl), 8.56 – 8.70 (m, 2H,pyridyl), m/z: (m+1), 337.

Synthesis of 5-chloro-N-cyclohexyl-6-(pyridin-2-ylthio) pyridine-3-carboxamide (4e)

¹HNMR δ (ppm):1.0-2.0(m,10H,Cyclhexyl), 3.8-4.0(m, 1H,Cyclohexyl) 6.2 (S,1H,-NHCyclohexyl), 7.2- 8.8(M,6H, Pyridinyl) m/z: (m+1),348

RESULTS AND DISCUSSION

The mixture of 5,6-dichloro nicotinic acid and $SOCl_2$ with catalytic amount of DMF was refluxed for half an hour to get the 5,6-dichloro nicotinoyl chloride. This 5,6-dichloro nicotinoyl chloride was treated with cyclohexylamine in DCM containing triethylamine as a base. The obtained product was treated with substituted thiols in DMF containing anhydrous potassium carbonate. The reaction mixture was poured on crushed ice to get the title compounds, which were purified by column chromatography using CHCl₃: methanol (90: 10) as an eluent.

The antibacterial activity of all the synthesized compounds (**4a-h**) has been performed against gram positive and gram-negative bacteria. Antibacterial activity was studied using paper disc method. Test solution of sample and standard were prepared as 20 and 40 mg/ml in dimethyl formamide (DMF). Paper disc (6 mm) was immersed in seeded agar. The solution was dropped to the filter paper disc. The zone for each test and standard solution was measured in mm.

Antibacterial Activity

Nutrient agar media or the requisite composition viz. peptone (2.5 g), beef extract (0.5 g), agaragar (10 g) and distilled water (500 ml) and pH of the medium was adjusted to 6.6 for the preparation of media. All the above ingredients (except – agar – agar) were weighed and dissolved in distilled water (250 ml). After gentle heating, all ingredients were dissolved. After complete dissolution of ingredients more distilled water and weighed quantity of agar-agar were added. Then it was filtered through cotton to obtain a clear solution. The mixture was autoclaved for 30 min at a pressure of 1-5 kg/cm². All the glass apparatus were cleaned with chromic acid and then sterilized by keeping in oven and cooled to 37 ± 1^{0} C and homogeneous suspension was prepared by transferring aseptically. A loopful of all the corresponding microorganism from fresh subculture into agar medium followed by vigorous shaking, 20 ml of this medium was poured into each sterilized Petri dish under aseptic conditions and allowed to set.

Entry	R	Yield (%.)	Melting point (°C)	Elemental analysis (%) Calculated (found)		
				С	Н	N
4a	$\mathbb{N}_{\mathbb{N}}$	75	222	53.49 (52.19)	5.09 (4.86)	16.63 (15.86)
4b	∑ N I	85	166	54.77 (53.96)	5.46 (5.13)	15.97 (14.68)
4c	S N	80	146	52.23 (51.96)	4.93 (4.23)	11.42 (10.96)
4d	H ₂ N N-N	80	165	45.46 (41.86)	4.36 (4.16)	18.93 (18.15)
4e	⟨k	75	126	58.20 (57.58)	5.22 (4.90)	12.08 (11.56)
4f		87	180	62.33 (61.86)	5.52 (5.15)	8.08 (7.85)
4g	S N→}	90	176	50.91 (49.89)	4.56 (4.14)	11.87 (11.10)
4h	N	82	195	55.09 (54.86)	4.91 (4.16)	16.06 (15.98)

Test solution and streptomycin having concentration 40 mg/ml and 20 mg/ml were prepared in DMF. The paper disc (6 mm) was immersed in seeded agar containing petri dishes. The solution was dropped into the filter paper disc. The inhibition zone for each test solution was measured in mm.



Table 2: Antibacterial activity of 5-Choloro-N-Cyclohexyl-6-thio substituted nicotinamide Derivatives 4a-4h

		Zone of Inhibition in mm*				
		Gram +ve		Gram -ve		
Entry	Concentration (mg/ml)	S. aureus	S. Typhi	S. mutans	E. coli	
4.0	20	11	10	11	-	
4a	40	11	15	12	15	
4h	20	10	10	10	18	
40	40	14	12	12	23	
4.5	20	16	15	18	-	
40	40	22	15	22	23	
4.4	20	10	10	8	10	
40	40		10	11	12	
4.5	20	10	12	12	10	
40	40	12	16	15	12	
1£	20	11	14	12	13	
41	40	12	15	14	15	
10	20	13	10	12	11	
4g	40	14	12	13	13	
416	20	10	12	11	10	
411	40	11	13	12	11	
Strantomucin	20	18	18	16	16	
Sueptomychi	40		22	20	22	

* Average of three determinations

The synthesized compounds were tested for their antibacterial activity against *E. Coli*, *S.Typhi*. *Streptococcus mutans* and *S. aureus* using streptomycin as standard drug. The biological activity of these compounds have been evaluated by filter paper disc method. The zone of inhibition are presented in Table–2. Compound 4c were found to be more active against *S. aureus*, *S. mutans E. coli*.

CONCLUSION

The compound **4c** is found to be more active against *S. aureus*, *E. coli* and *S. mutants*. The influence of methyl group in 4th position of thiazole ring of compound **4c** showed good activity compared to other synthesized compounds. From this it can be concluded that the methyl group at 4th position may be responsible for good antibacterial activity.

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