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Research Article

A CONVENIENT AND ECOFRIENDLY SYNTHESIS OF FLUORINE CONTAINING INDOLE NUCLEUS AS A POTENTIAL PHARMACOLOGICAL AGENT

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ABSTRACT

When 3-acetyl-2-phenyl indole reacts with DAST in dry $CHCl_3$ at 0^0 C it results substituted 1,1-difluoroethane. The synthesized compounds have been characterized by elemental analysis and spectral data (IR, NMR and Mass). All the synthesized compounds have been screened for anti microbial activities.

Keywords: Indole, DAST, Elemental analysis, Antimicrobial

INTRODUCTION

Many of organofluorine compounds have unique chemical property that may be incorporated to useful biological activities [1-5] .Introduction of fluorine into the indole moiety is reported to enhance drug persistence by increasing its solubility in lipid material and fat deposits in human body [6]. Fluorinated indoleacetic acid derivatives have been prepared as anti-inflammatory drugs [7]. Fluorine containing indoles and allied derivatives show various biological activities such as antibacterial and antifungal [8,9], plant growth regulators [10], tillering promoters for gramineous plants [11], antiserotonin adrenolytic, psychotic and dopadecarboxylase inhibition activities [12]. Selective and new methods of fluorination have made it possible to synthesize various types of heterocyclic compounds of pharmaceutical importance. DAST is one of the highly selective fluorinating agents [13] for replacing hydroxyl groups and carbonyl oxygens with fluorine under very mild and controlled conditions. Having these concepts in mind and in continuation to our work on organofluorine compounds [14-17] , we have undertaken a comprehensive program for developing better antimicrobial agents and have synthesized a number of new 1-(N-alkyl-2-aryl-indol-3-yl)-1,1-difluoroethanes and screened them for their antibacterial and antifungal activities.

MATERIALS AND METHODS

General

Melting points of all the synthesised compounds were determined in open capillary tubes and are uncorrected. The IR spectra (υ_{max} in cm^{-1}) were recorded on a Perkin Elmer -557 model. ^1H NMR spectra were recorded with Brucker spectrometer (200 MHz) dissolved in $CDCl_3$ (TMS as internal standard) .Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapours or by irradiation with ultra violet lights (254 nm). The reactions were placed according to the literature methods [18].

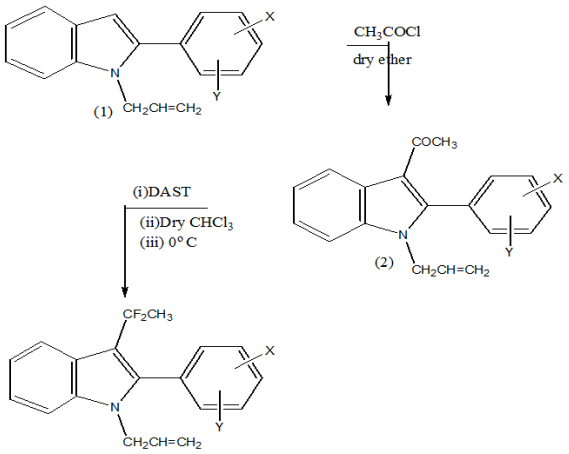
1-(N-alkyl-2-aryl-indol-3-yl)-1,1-difluoroethanes

A solution of N-alkylindole (1) (10mmol) in ether (20ml) was added to acetylchloride drop wise and refluxed for 3-4 hrs. The solution was poured on crushed ice and filtered. A solution of DAST (10 mmol) in dry chloroform (15ml) was added dropwise in the solution of acetylindol (2) (5mmol) in dry chloroform (15ml) at 0^0 C under nitrogen atmosphere with constant stirring 15-20 minutes. It was further stirred for 25-30 days at 20^0 C and then refluxed for 3-6 hrs. When all DAST was consumed, the dark brown reaction mixture was poured over crushed ice, extracted with chloroform. The extract was washed with saturated solution of sodium carbonate followed by water. Dried over sodium carbonate and chloroform was removed under reduced pressure. The resultant was purified by recrystallization from pet ether: Benzene.

RESULT AND DISCUSSION

2-Phenylindole (1) was referred to acetylation with acetylchloridein dry ether to give 3-acetylated phenylindoles (2). This acetylated indole (2) and DAST were refluxed in chloroform at 0^0 C, to give 1-(N-alkyl-2-aryl-indol-3-yl)-1,1-difluoroethanes (3). (scheme 1). The physical and analytical data of all the compounds reported in this paper (4a-i) are shown in Table-1.

Schme-1



X: H; 4-Cl; 4-Br; CH_3;3-Cl; 4-F; Y: H; Cl

Antimicrobial activity

All the newly synthesized compounds 4a-i have been screened for their antibacterial action against *Klebisella pneumonia* (Gram positive bacterium) and *Escherichia coli* (Gram negative bacterium) and for antifungal action against *Aspergillus flavus* and *Aspergillus niger* at different concentrations by the disc diffusion method [19]. Results were compared to Streptomycin and Betadine as reference drugs respectively. The results are tabulated in Tables 2 and 3.

Table 1: The characteristic data of the compounds (4a-i)

Compd No.	X	Y	Molecular formula	M. P. (°C)	Yield %	Elemental Analysis % Found (Calculated)			
						C	H	N	F
4a	H	H	$C_{19}H_{13}F_2N$	81	73	77.26 (77.28)	5.06 (5.08)	4.72 (4.74)	12.88 (12.89)
4b	4-Br	H	$C_{19}H_{14}BrF_2N$	122	78	60.95 (60.96)	3.72 (3.74)	3.73 (3.74)	10.17 (10.16)
4c	4-F	H	$C_{19}H_{14}F_3N$	128	69	72.83 (72.84)	4.46 (4.47)	4.45 (4.43)	12.13 (12.14)
4d	4-CH_3	H	$C_{20}H_{17}F_2N$	117	83	77.65 (77.66)	5.48 (5.50)	4.51 (4.53)	12.27 (12.29)
4e	3-Cl, 4-F	H	$C_{19}H_{13}ClF_3N$	151	66	65.59 (65.61)	3.73 (3.74)	3.99 (4.02)	16.39 (16.40)
4f	H	Cl	$C_{19}H_{14}ClF_2N$	203	79	69.18 (69.19)	4.23 (4.24)	4.23 (4.24)	11.51 (11.53)
4g	4-Br	Cl	$C_{19}H_{13}BrClF_2N$	177	71	55.79 (55.81)	3.15 (3.18)	3.40 (3.42)	9.28 (9.30)
4h	4-CH_3	Cl	$C_{20}H_{16}ClF_2N$	108	69	69.84 (69.86)	4.63 (4.65)	4.05 (4.07)	11.04 (11.06)
4i	3-Cl, 4-F	Cl	$C_{20}H_{12}Cl_2F_2N$	169	78	62.80 (62.82)	3.13 (3.14)	3.64 (3.66)	9.95 (9.94)

Table 2: Inhibitory zone (diameter) mm of synthesized compounds (4a-i) against tested bacterial strains by disc diffusion method

ompound No.	Mean value of area of inhibition in mm 1000 ppm IZ (IA)		Mean value of area of inhibition in mm 800 ppm IZ (IA)		Mean value of area of inhibition in mm 400 ppm IZ (IA)		Mean value of area of inhibition in mm 200 ppm IZ (IA)	
	E. coli	*K. Pneumonia*	*E. coli*	*K. pneumoniae*	*E. coli*	*K. pneumoniae*	*E. coli*	*K. pneumoniae*
eptomycin	9.4	10.2	9.2	10.0	8.8	9.2	8.2	8.9
4a	10.2 (1.08)	9.1 (0.89)	8.9 (0.96)	9.8 (0.98)	7.3 (0.82)	8.6 (0.93)	6.1 (0.74)	7.3 (0.82)
4b	12.1 (1.31)	8.4 (0.82)	10.1 (1.09)	7.6 (0.76)	8.6 (0.97)	7.2 (0.78)	7.2 (0.87)	5.2 (0.58)
4c	8.1 (0.86)	7.3 (0.71)	7.6 (0.82)	5.8 (0.58)	5.4 (0.61)	5.7 (0.61)	6.3 (0.76)	6.0 (0.67)
4d	8.3 (0.91)	12.1 (1.18)	6.9 (073)	8.6 (0.86)	5.9 (0.67)	8.1 (0.88)	7.1 (0.86)	7.8 (0.87)
4e	8.8 (0.93)	13.3 (1.30)	8.1 (0.86)	9.8 (0.98)	7.2 (0.81)	9.1 (0.98)	6.9 (0.84)	8.8 (0.98)
4f	17.3 (1.84)	16.4 (1.60)	9.8 (1.06)	12.4 (1.24)	11.3 (1.28)	10.6 (1.15)	9.4 (1.14)	11.6 (1.32)
4g	18.1 (1.92)	16.9 (1.65)	13.2 (1.43)	13.6 (1.36)	13.8 (1.56)	13.4 (1.45)	11.1 (1.35)	12.0 (1.34)
4h	16.7 (1.77)	18.1 (1.77)	16.1 (1.75)	13.8 (1.38)	12.4 (1.40)	13.9 (1.51)	12.3 (1.50)	13.8 (1.55)
4i	11.5 (1.22)	11.2 (1.09)	10.2 (1.10)	11.1 (1.11)	9.9 (1.12)	8.4 (0.91)	8.9 (1.08)	7.6 (0.85)

IZ= Inhibition area (zone) excluding diameter of disc; AI (Activity Index) = Inhibition area of sample/inhibition area of standard

Table 3: Inhibitory zone (diameter) mm of synthesized compounds (4a-i) against tested fungal strains by disc diffusion method

pound o.	Mean value of area of inhibition in mm 1000 ppm IZ (IA)		Mean value of area of inhibition in mm 800 ppm IZ (IA)		Mean value of area of inhibition in mm 400 ppm IZ (IA)		Mean value of area of inhibition in mm 200 ppm IZ (IA)	
	A. flavus	*A. niger*	*A. flavus*	*A. niger*	*A. flavus*	*A. niger*	*A. flavus*	*A. niger*
tadine	10.2	11.2	9.3	10.9	9.0	9.6	8.1	8.9
4a	10.0 (0.98)	10.3 (0.91)	9.1 (0.97)	9.6 (0.88)	9.2 (1.02)	7.8 (0.81)	8.3 (1.02)	6.9 (0.77)
4b	9.8 (0.96)	9.1 (0.81)	9.0 (0.96)	8.8 (0.80)	8.4 (0.93)	8.0 (0.83)	7.6 (0.93)	6.4 (0.71)
4c	7.1 (0.69)	10.2 (0.91)	8.2 (0.88)	8.9 (0.81)	7.8 (0.86)	8.2 (0.85)	6.9 (0.85)	5.9 (0.66)
4d	14.1 (1.38)	12.4 (1.10)	13.1 (1.40)	11.3 (1.03)	12.1 (1.34)	10.3 (1.07)	9.2 (1.13)	7.6 (0.85)
4e	12.2 (1.19)	16.1 (1.43)	11.9 (1.27)	14.6 (1.33)	10.2 (1.13)	13.1 (1.36)	10.1 (1.24)	10.3 (1.15)
4f	13.3 (1.30)	14.9 (1.33)	12.6 (1.35)	12.9 (1.18)	11.8 (1.31)	11.1 (1.15)	10.8 (1.33)	9.6 (1.07)
4g	15.1 (1.48)	13.8 (1.23)	14.3 (1.53)	11.3 (1.03)	12.4 (1.37)	10.3 (1.07)	11.2 (1.38)	9.0 (1.02)
4h	14.3 (1.40)	13.6 (1.21)	13.5 (1.46)	11.5 (1.05)	13.2 (1.46)	10.8 (1.12)	11.5 (1.41)	8.6 (0.96)
4i	16.2 (1.58)	15.3 (1.36)	14.3 (1.53)	13.8 (1.26)	11.6 (1.28)	12.8 (1.33)	12.2 (1.50)	10.2 (1.14)

IZ= Inhibition area (zone) excluding diameter of disc; AI (Activity Index) = Inhibition area of sample/inhibition area of standard

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