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SYNTHESIS AND ANTIFUNGAL ACTIVITY OF 1-SUBSTITUTED-3-(2-(6-CHLOROBENZOTHIAZOL-2-YL) HYDRAZONO) - 4, 5/5, 6/5, 7-DIMETHYLINDOLIN-2-ONES

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ABSTRACT

*A series of 1-substituted- 3-(2-(6-chlorobenzothiazol-2-yl) hydrazono)- 4, 5/ 5, 6/ 5, 7-dimethylindolin-2-ones (**1-15**) have been synthesised by the reaction of 2-hydrazino-6-chlorobenzothiazole and 1-substituted 4,5/5,6/5,7-dimethylindolin-2,3-diones. Structures of the compounds have been established with the help of elemental analysis and spectral data (IR, ^{1}H-NMR and Mass). Compounds have also been screened for their antifungal potential against human pathogenic fungi. Many of the compounds showed good antifungal activity against Aspergillus fumigatus.*

Keywords: Indolin-2,3-dione, Schiff base, antifungal activity.

Introduction

Isatins (1*H*-indole-2, 3-diones) and their derivatives possess wide variety of biological activities viz., anthelmintic[1], antiinflammatory[2], analgesic[3], antimalarial[4], antioxidant[5], anti-epileptic[6], anticonvulsant[7], antitubercular[8], cytotoxic[9,] antimicrobial[10], antifertility[11], CNS depressant[12] and enzyme inhibitory[13]. Benzothiazole derivatives have also been shown to possess anticancer[14], antiinflammatory, analgesic[15], antimycobacterial[16], antiplasmodial[17], anticonvulsant[18], anti HIV[19], antidiabetic[20] and antimicrobial[21] activities. Number of review articles have been published on the chemistry and biological potential of indolin-2, 3-diones[22] and benzothiazoles[23]. In the light of biological activity profile of indolin-2, 3-diones and

benzothiazoles and in continuation of our work on indolin-2, 3-dione derivatives[24], synthesis and antifungal potential of 1-substituted-4, 5/5,6/5,7 dimethylindolin-2,3-diones is being reported here.

2-Amino-6-chlorobenzothiazole was obtained by orthothiocyanation of 4-chloroaniline with potassium thiocyanate in glacial acetic acid which on reaction with hydrazine hydrate in ethylene glycol gave 2-hydrazino-6-chlorobenzothiazole. Acid catalysed condensation of 2-hydrazino-6-chlorobenzothiazole with 1-substituted-4, 5/5, 6/5, 7 dimethylindolin-2, 3-diones in equimolar proportions, gave 1-substituted-3-(2-(6-chlorobenzothiazol-2-yl) hydrazono)- 4, 5/5, 6/5, 7-dimethylindolin-2-ones. 4, 5 and 5, 6-dimethylindolin 2, 3-diones were synthesised by the reaction of 3,4-dimethylaniline with chloral hydrate and hydroxylamine hydrochloride to get isonitrosoacetanilide intermediate which on cyclization with concentrated sulfuric acid gave a mixture of 4,5-and 5,6-dimethylindolin-2, 3-diones while 5,7-dimethylindolin-2,3-dione was obtained by using 2,4-dimethylaniline. 4, 5 and 5, 6-dimethylindolin 2, 3-diones were separated using the method of Varma and Singh[25]. 1-methyl, ethyl, acetyl and benzyl 4, 5/5, 6/5, 7-dimethylindolin-2, 3-diones were prepared by the reaction of the respective indolin-2, 3-diones with dimethyl sulphate, ethyl bromide, acetic anhydride and benzyl bromide.

Antifungal activity

Compounds **1-15** were screened for their antifungal potential against human pathogenic fungi viz: *Candida albicans* (CA), *Cryptococcus neoformans* (CN), *Candida parapsilosis* (CP), *Trichophyton mentagrophytes* (TM) and *Aspergillus fumigatus* (AF) using tube dilution method at a maximum concentration of 100μg/mL in DMSO and Minimum Inhibitory Concentration (MIC) values were determined in μg/mL. Fluconazole was taken as standard drug. Antifungal activity data are shown in Table-1. All the compounds were found to be inactive against *Cryptococcus neoformans*, and showed MIC of no significance against *Candida albicans*. However, many of the compounds showed good antifungal activity against *Aspergillus fumigatus.* No systematic increase or decrease in antifungal potential of compounds was observed in terms of substituents, hence no SAR could be established.

Table-1 Minimum Inhibitory Concentration MIC (μg/mL) of compounds against fungi

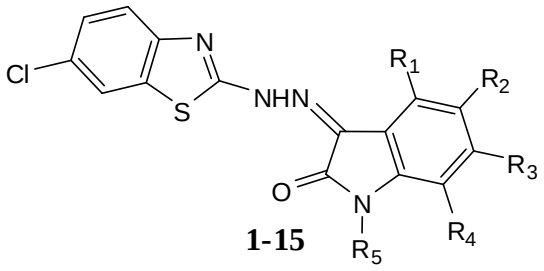
Compd	CA	CN	CP	TM	AF
1	50	>100	50	6.25	3.12
2	12.5	>100	25	3.12	3.12
3	12.5	>100	25	6.25	3.12
4	25	>100	12.5	6.25	6.25
5	12.5	>100	>100	3.12	3.12
6	12.5	>100	12.5	6.25	3.12
7	>100	>100	12.5	6.25	6.25
8	12.5	>100	12.5	3.12	3.12
9	12.5	>100	25	6.25	3.12
10	>100	>100	>100	6.25	6.25
11	12.5	>100	6.25	3.12	3.12
12	12.5	>100	6.25	6.25	3.12
13	50	>100	>100	6.25	6.25
14	12.5	>100	>100	3.12	3.12
15	12.5	>100	>100	6.25	3.12
Fluconazole (Standard drug)	0.5	1.0	2.0	1.0	2.0

Experimental

The melting points were determined in open capillary tubes in sulphuric acid bath and are uncorrected. IR spectra were recorded in KBr on a Perkin Elmer spectrophotometer and frequencies are presented as cm-^{1}. ^{1}H-NMR spectra were recorded on Bruker Avance 300 spectrometer using DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts are expressed in δ (ppm). Mass spectra were recorded on Jeol-JMS-300 spectrometer. Elemental analysis data were obtained on Carlo Erba 1108 analyser. Homogeneity of the compounds was checked on TLC silica gel G plates and spots were located by exposure to iodine vapours. Physical data of the compounds prepared are shown in table-2.

1-substituted-3-(2-(6-chlorobenzothiazol-2-yl) hydrazono) - 4, 5/5, 6/5, 7-dimethylindolin-2-ones 1-15 (General method)

A mixture of 2-hydrazino-6-chlorobenzothiazole (5 mmol) and 1-substituted-4, 5/5, 6/ 5,7-dimethylindolin-2,3-diones (5mmol) in ethanol (30 mL) containing 2-3 drops of glacial acetic acid was refluxed for 3-4h and left over night at room temperature. The solid thus obtained was filtered, washed with methanol and recrystallised from aq. DMF.



1-15

R_1, R_2, R_3, R_4 = H, Me

R_5=H, Me, Et, Ac, Bz

Spectral data of compounds prepared

(1) IR (KBr) cm-^{1}: 3413, 3261 (NH), 1701 (CO), 1605 (C=N), 768 (C-Cl); **^{1}H-NMR (300MHz, DMSO-*d_6*) δppm:** 2.14, 2.33 (s, 6H, 2 x Me), 5.35 (s, 1H, NH), 6.78-8.15 (m, 5H, Ar-H), 12.43 (s, 1H, NH); **MS m/z:** 356 (M^+), 358 (M+2). **(2) IR (KBr) cm-^{1}:** 3411 (NH), 1701 (CO), 1615 (C=N), 768 (C-Cl); **^{1}H-NMR (300MHz, DMSO-*d_6*) δppm:** 2.13, 2.30 (s, 6H, 2 x Me), 2.63 (s, 3H, NMe), 5.35 (s, 1H, NH), 7.00-8.05 (m, 5H, Ar-H); **MS m/z:** 370 (M^+), 372 (M+2). **(4) IR (KBr) cm-^{1}:** 3410 (NH), 1713, 1700 (CO), 1602(C=N), 759(C-Cl); **^{1}H-NMR (300MHz, DMSO-*d_6*) δppm:** 2.14, 2.31 (s, 6H, 2 x Me), 2.41 (s, 3H, COMe), 5.35 (s, 1H, NH), 6.94-8.20 (m, 5H, Ar-H); **MS m/z:** 398 (M^+), 400 (M+2). **(6) IR (KBr) cm-^{1}:** 3410, 3251(NH), 1701 (CO), 1603 (C=N), 761 (C-Cl); **^{1}H-NMR (300MHz, DMSO-*d_6*) δppm:** 3.20 (s, 2H, 2 x Me), 5.35 (s, 1H, NH), 6.88-8.25 (m, 5H, Ar-H), 12.13 (s,1H, NH); **MS m/z:** 356 (M^+), 358 (M+2). **(8) IR (KBr) cm-^{1}:** 3416 (NH), 1712 (CO), 1618 (C=N), 757(C-Cl); **^{1}H-NMR (300MHz, DMSO-*d_6*) δppm:** 2.12- 2.18 (t, 3H, Me), 2.51-2.67 (q, 2H, CH_2Me), 3.20 (s, 2H, 2 x Me), 5.35 (s, 1H, NH), 7.23-8.25 (m, 5H, Ar-H), 12.43; **MS m/z:** 384 (M^+), 386 (M+2). **(11) IR (KBr) cm-^{1}:** 3416 (NH), 1723, 1710 (CO), 1608 (C=N), 757 (C-Cl); **^{1}H-NMR (300MHz, DMSO-*d_6*) δppm:** 2.35 (s, 3H, COMe), 3.20 (s, 6H, 2 x Me), 5.35 (s, 1H, NH), 6.94-8.15 (m, 5H, Ar-H); **MS m/z:** 398 (M^+), 400 (M+2). **(15) IR (KBr) cm-^{1}:** 3412 (NH), 1713 (CO), 1618 (C=N), 767(C-Cl); **^{1}H-NMR (300MHz, DMSO-*d_6*) δppm:** 2.67. 3.09 (s, 6H, 2 x Me), 3.13 (s, 2H, CH_2Ph), 5.35 (s, 1H, NH), 7.04-8.35 (m, 5H, Ar-H); **MS m/z:** 446 (M^+), 448 (M+2).

Table-2 Characterization data of compounds prepared

Compd	R_1	R_2	R_3	R_4	R_5	M.P. (^oC)	Yield %	Elemental analysis % C	H	N	Moleular formula
								Found (Calcd)			
1	Me	Me	H	H	H	>250	67	57.17 (57.22)	3.60 (3.67)	15.63 (15.70)	$C_{17}H_{13}ClN_4OS$
2	Me	Me	H	H	Me	>250	78	58.25 (58.30)	3.90 (4.08)	15.04 (15.11)	$C_{18}H_{15}ClN_4OS$
3	Me	Me	H	H	Et	>250	78	59.24 (59.29)	4.40 (4.45)	14.50 (14.56)	$C_{19}H_{17}ClN_4OS$
4	Me	Me	H	H	Ac	>250	60	57.09 (57.21)	3.73 (3.79)	13.98 (14.05)	$C_{19}H_{15}ClN_4O_2S$
5	Me	Me	H	H	Bz	>250	56	64.40 (64.49)	4.25 (4.28)	12.48 (12.54)	$C_{24}H_{19}ClN_4OS$
6	H	Me	Me	H	H	>250	78	57.16 (57.22)	3.60 (3.67)	15.66 (15.70)	$C_{17}H_{13}ClN_4OS$
7	H	Me	Me	H	Me	>250	78	58.26 (58.30)	3.97 (4.08)	15.04 (15.11)	$C_{18}H_{15}ClN_4OS$
8	H	Me	Me	H	Et	>250	77	59.25 (59.29)	4.41 (4.45)	14.48 (14.56)	$C_{19}H_{17}ClN_4OS$
9	H	Me	Me	H	Ac	>250	70	57.13 (57.21)	3.69 (3.79)	13.90 (14.05)	$C_{19}H_{15}ClN_4O_2S$
10	H	Me	Me	H	Bz	>250	67	64.45 (64.49)	4.23 (4.28)	12.50 (12.54)	$C_{24}H_{19}ClN_4OS$
11	H	Me	H	Me	H	>250	80	57.17 (57.22)	3.63 (3.67)	15.65 (15.70)	$C_{17}H_{13}ClN_4OS$
12	H	Me	H	Me	Me	>250	78	58.24 (58.30)	3.97 (4.08)	15.07 (15.11)	$C_{18}H_{15}ClN_4OS$
13	H	Me	H	Me	Et	>250	78	59.26	4.38	14.49	$C_{19}H_{17}ClN_4OS$

								(59.29)	(4.45)	(14.56)	
14	H	Me	H	Me	Ac	>250	76	57.11	3.70	13.98	$C_{19}H_{15}ClN_4O_2S$
								(57.21)	(3.79)	(14.05)	
15	H	Me	H	Me	Bz	>250	70	64.40	4.23	12.42	$C_{24}H_{19}ClN_4OS$
								(64.49)	(4.28)	(12.54)	

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