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Antifungal Activities Of Novel Series Of Azetidinyl And Thiazolidinone Derivatives Along With There Characterization.

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KEYWORDS
Anti- Fungalactivities, Heterocyclic, azetidinyl, thiazolidinone.

ABSTRACT:
(N ' substituted aryl hydrazine) indole 3-carbohydrazine- N"- azetidinyl. (6 and its derivative) was synthesized through the interaction of (N ' substituted aryl hydrazine) indole 3-carbohydrazine with chloro acetyl chloride and (N ' substituted aryl hydrazine) indole 3-carbohydrazine- N"-thiazolidinone (5 and its derivative) was synthesized through the interaction of (N ' substituted aryl hydrazine) indole 3-carbohydrazine with the mercapto acetic acid in presence of anhydrous zinc dichloride. Elemental analyses and spectrum research were used to establish the compounds' structures. The effectiveness of the newly created compounds as antifungal agents against Aspergillus flavus, Aspergillus niger, and Aspergillus fumigatus Candida krusei, Candida albicans, and Candida parapsilosis C. glabrata HO5 was assessed.

Introduction

Our goal was to prepare derivatives of thiazolidin-4-ones combined with an indole ring system in a molecular framework and to investigate the therapeutic benefit of this combination due to the wide range of biological activities displayed by thiazolidin-4-ones and indole. In medicinal chemistry, indole derivatives are a significant class of therapeutic agents that include anticancer1, antioxidant2, antirheumatoidal3, and anti-HIV4 properties. They also play a critical role in the immune system5, and they are effective free radical scavengers6. The anticonvulsant, hypnotic, antitubercular, anticancer, and antiviral properties of thiazolidinones are well known. The review of the literature provided sufficient biological profiles for the aforementioned moieties. With these factors in mind, our research focused on creating some novel derivatives with these nuclei.

Experimental

Melting points were calculated using the METTAR TOLEDO melting point apparatus, and the values were not corrected. Iodine vapour was used as a visualizing agent during the thin layer chromatography (TLC) monitoring of reactions on pre-coated silica gel G plates. On the JASCO V-530 UV/Vis spectrophotometer, UV spectra were captured. Using the KBr pellets technique, IR spectra were captured on the SIMADZU IR INSTRUMENT . The BRUCKER FT-NMR-300MHz FT spectrophotometer was used to record PMR spectra with DMSO as the solvent and TMS as the internal standard. In ppm, the chemical shift was specified. The Finnigan MAT 8230 mass spectrometer was used to record the mass spectra. Table No. 1 displays the physical characterization of the synthesized compounds. The elemental analysis of all elements done using CARLO-ERBA-1108 elemental analyser.

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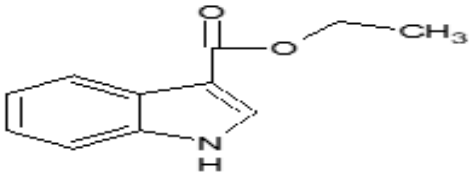
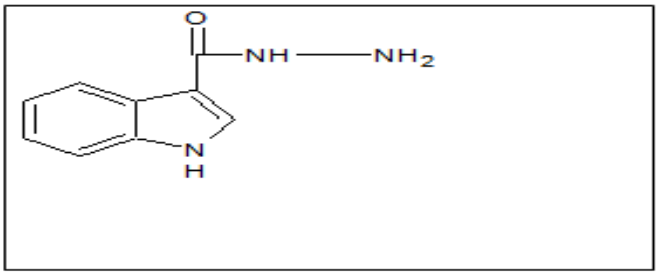
Step I Synthesis of Indole-3-carboxylic acid ester.



A mixture of 80.6 gm, (0.50 mole) of indole-2-carboxylic acid,200 ml of ethanol, 200 ml of dichloromethaneand 25 ml of concentrated sulphuric acid was refluxed for 8 hrs and cooled to –5 to - 10°C using dry ice, The contents were poured into 300 ml of ice cold water. The organic layer at the bottom was separated out and dichloromethane was distilled off to get the crude product. The high vacuum distillationof this crude product afforded the pure compound which is crystallized from methanol. The purity ofthe ester was established by single spot on the TLC plate AND OTHERS INCLUDED DATA, The solvent system used was methanol : chloroform (3:1).[excess of ethanol recover from the water using distillation]

Yield is 89%
Melting point = 172-174 °C;
IR (FTIR/ FTNIR-ATR): 1705 cm-1 (C=O), 3351 cm-1 (N-H)
1 H-NMR (CDCl3) δ: 9.06 (1H, s, indole H-1), 7.74 (1H, d, J=7.6 Hz, indole H-4), 7.45-7.34 (3H, m, indole H-6, phenyl H-2,6), 7.30-7.25 (4H, m, indole H-5,7, phenyl H-3,5), 7.18 (1H, m, indole H-9), 2.98-2.91 (1H, m, CH(CH3) 2), 1.28 (3H, s, CH3), 1.26 (3H, s, CH3)
Calc for [C_{11} H_{11} N O_2]: C-69.89; H-5.9 ; N-7.5 , O- 16.9;
Found : C- 69.90; H-5.80;N- 7.95,O-16.89
MS: $[M]^+$,at M/z=189 .

Step II Synthesis of Indole-3-carbohydrazide



To 47.5 g,(0.5mol)of Indole-3-carboxylicacid ester in 250 ml ethanol, 30.5 Gm of 98% hydrazine hydrate was added in drops with constant stirring and the mixture was refluxed for 9 hrs . After cooling, the solution was poured on to crushed ice. The solid separated was filtered, dried and recrystallised from ethanol. The purity of the compound was established by single spot on the TLC plate And other included data. The solvent system used was ethanol : chloroform (3:1).
Yield is 60%
Melting point = 192-194 °C;
IR (FTIR/ FTNIR-ATR): 1715 cm-1 (C=O), 3280 cm-1 (N-H), (C-N)-1243, (N-N)-1524

1 H-NMR (CDCl3) δ: 9.16 (1H, s, indole H-1), 7.34 (1H, d, J=7.6 Hz, indole H-4), 7.48-7.24 (3H, m, indole H-6, phenyl H-2,6), 7.15-7.25 (4H, m, indole H-5,7, phenyl H-3,5), 7.48 (1H, m, indole H-9), 2.88-2.91 (1H, m, CH(CH3) 2), 1.23 (3H, s, CH3), 1.20 (3H, s, CH3) , 4.42 (d-2H, NH CH2).
Calc for [C_9 H_9 N_3 O_1]: C-61.61; H-5.15 ; N-24.03 , O- 9.1;
Found : C- 61.70; H-5.20;N- 23.93 ,O-9.06,
MS: $[M]^+$,at M/z=175

Journal of Chemical Health Risks

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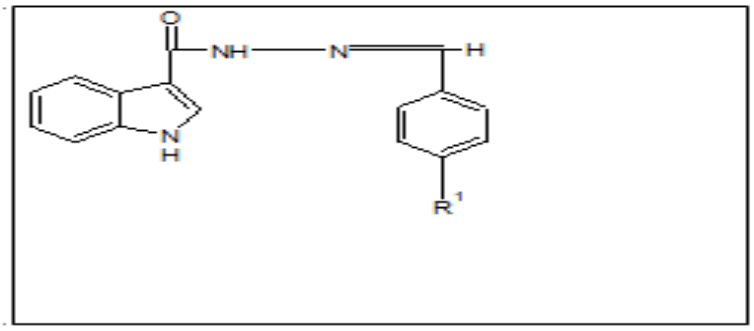
Step III Synthesis of (N ' substituted aryl hydrazine) indole 3-carbohydrazine

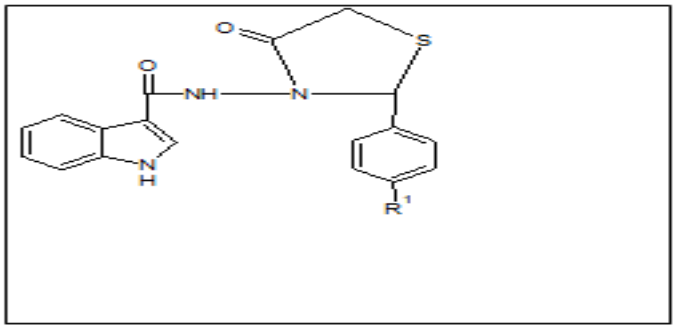


Indole-3-carbohydrazide 35 Gm(0.20mol) taken into 50 ml of MDC and aryl aldehyde(0.30mol) were added into above mass in 2 hrs with maintin temp of 35 ^{o}c in a 250 ml beaker and the mixture was refluxed for 8 hrs.

colour of reaction mass get changes after 8.00 hrs then after excess of mdc had been distilled out and the remaining bottom slurry mass have to cool upto 5 ^{0} c the solid formed was separated by filtration, washed with coldethanol and recrystalised from ethanol. Purity of the product was established by single spot on the TLC plate as well as using reverse phase HPLC. The solvent system used was methanol : chloroform (3:1).
Yield is 52%
Melting point = 207-214 °C;

IR (FTIR/ FTNIR-ATR): 1725 cm-1 (C=O), 3295 cm-1 (N-H), (C-N)-1220, (N-N)-1540, (C-C of aromatic)-1550-59, (C=N)-1585,
1 H-NMR (CDCl3) δ: 9.12 (1H, s, indole H-1), 7.21 (1H, d, J=7.6 Hz, indole H-4), 7.28-7.14 (3H, m, indole H-6, phenyl H-2,6), 7.52-7.56 (4H, m, indole H-5,7, phenyl H-3,5), 7.37 (1H, m, indole H-9), 2.78-2.80 (1H, m, CH(CH3) 2), 1.31 (3H, s, CH3), 1.26 (3H, s, CH3) , 4.82 (d-2H, NH CH2), 4.76 (d, IH, N=CH-Ar-R)
Calc for [$C_{16}H_{12}N_3O_1$]: C-73.28; H-4.95 ; N-16.04 , O- 6.13;
Found : C- 73.40; H-5.00;N- 16.13 ,O-6.16,
MS: $[M]^+$,at M/z=262

Step IV Synthesis (N ' substituted aryl hydrazine) indole 3-carbohydrazine- N"-thiazolidinone .



Method 01
Take 26 gm (0.1)mole of (N ' substituted aryl hydrazine) indole 3-carbohydrazine into 100 ml 4 neck Rbf along with 150 ml DMS and pinch of Anhydrous zinc di chloride added into to above reaction mass after that at 20^{0} c mercapto acetic acid [0.15 mole] added within 2.00 hrs and after addition reflex the reaction mixture for 16 hrs and continuously monitor the reaction with TLC after that cool the rexn mass and pour into crushed ice so solide pricipitate separating out and filter the solid and recrystalised with ethyl alcohol.
Yield is around 36%
Method 02
A mixture **of (N ' substituted aryl hydrazine) indole 3-carbohydrazine** (1mM) in DMF and 1 ml of mercapto acetic acid with a pinch of Zinc chloride was taken in a 100 ml beaker and the reaction mixture was zapped inside a microwave oven at 20^{0} c for 3 min. The solution was then diluted with ice cold water and solid formed was separated and recrystallized from ethanol.
Reaction complies about 80%
Melting point = 188-198 °C;
IR (FTIR/ FTNIR-ATR): 1725 cm-1 (C=O), 3295 cm-1 (N-H), (C-N)-1220, (N-N)-1540, (C-C of aromatic)-1550-59, (C=N)-1585, (CH2)-2920 , (C-S-C)-850
1 H-NMR (CDCl3) δ: 9.19 (1H, s, indole H-1), 7.11 (1H, d, J=7.6 Hz, indole H-4), 7.38-7.34 (3H, m, indole H-6, phenyl H-2,6), 7.72-7.78 (4H, m, indole H-5,7,

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phenyl H-3,5), 7.44 (1H, m, indole H-9), 2.88-2.93 (1H, m, CH(CH3) 2), 1.46 (3H, s, CH3), 1.34 (3H, s, CH3) , 4.76 (d, IH, N=CH-Ar-R), 3.55 (S,CH2 of thia-azolidinone) + 4.55 (d.2H) NHCH2) 6.62 (S.IH.Ch-Aromatic).

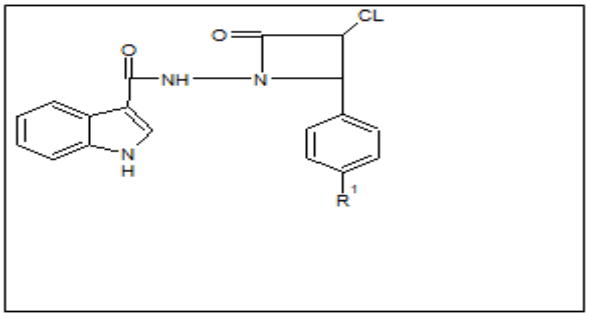
Calc for [C_{18} H_{14} N_3 O_2 S]: C-64.51; H-4.78 ; N-12.54

Found : C-64.63, H-4.80; N- 12.63

MS: $[M]^+$,at M/z=335

Some derivatives of compound 5 series given in table.

Step V Synthesis (N ' substituted aryl hydrazine) indole 3-carbohydrazine- N"- azetidinyl.



Take 26 gm (0.1)mole of (N ' substituted aryl hydrazine) indole 3-carbohydrazine into 100 ml 4 neck Rbf along with 250 ml dry Benzene ,chloro acetyl chloride17 gm (0.15 mole) added into reaction mass at 35 ^{0} c and allow the reaction mixture to stirred for 3.0 hrs and allow to reflux for 10 hrs after completion of reaction on TLC ,hydrochloride salt of TEA is filtered out and after the filtration excess of solvent removed by solvent recovery under vacuumed reaming bottom mass after solvent recovery quince in ice cold water at 0 to -5 degree c .

Molecule 6 : M.P.218 to 221°C, Yield 28 %,

IR (FTIR/ FTNIR-ATR): 1735 cm-1 (C=O), 3255 cm-1 (N-H), (C-N)-1230, (N-N)-1530, (C-C of aromatic)-1530-49, (C=N)-1525, (CH2)-2980 , (c-cl) 750.

1 H-NMR (CDCl3) δ: 9.10 (1H, s, indole H-1), 7.25 (1H, d, J=7.6 Hz, indole H-4), 7.48-7.44 (3H, m, indole H-6, phenyl H-2,6), 7.67-7.69(4H, m, indole H-5,7, phenyl H-3,5), 7.35 (1H, m, indole H-9), 2.78-2.83 (1H, m, CH(CH3) 2), 1.46 (3H, s, CH3), 1.30 (3H, s, CH3) , 4.56 (d, IH, N=CH-Ar-R), 3.55, 4.55 (d.2H) NHCH2) 6.62 (S.IH.Ch-Aromatic), 4.90 (d,1h,ch-cl).

Calc for [C_{18} H_{13} N_3 O_2 cl]: C-63.81; H-3.84 ; N-12.40

Found : C-63.73, H-3.80; N- 12.43

MS: $[M]^+$,at M/z=337.5

Journal of Chemical Health Risks
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JCHR (2024) 14(1), 3231-3238| ISSN:2251-6727

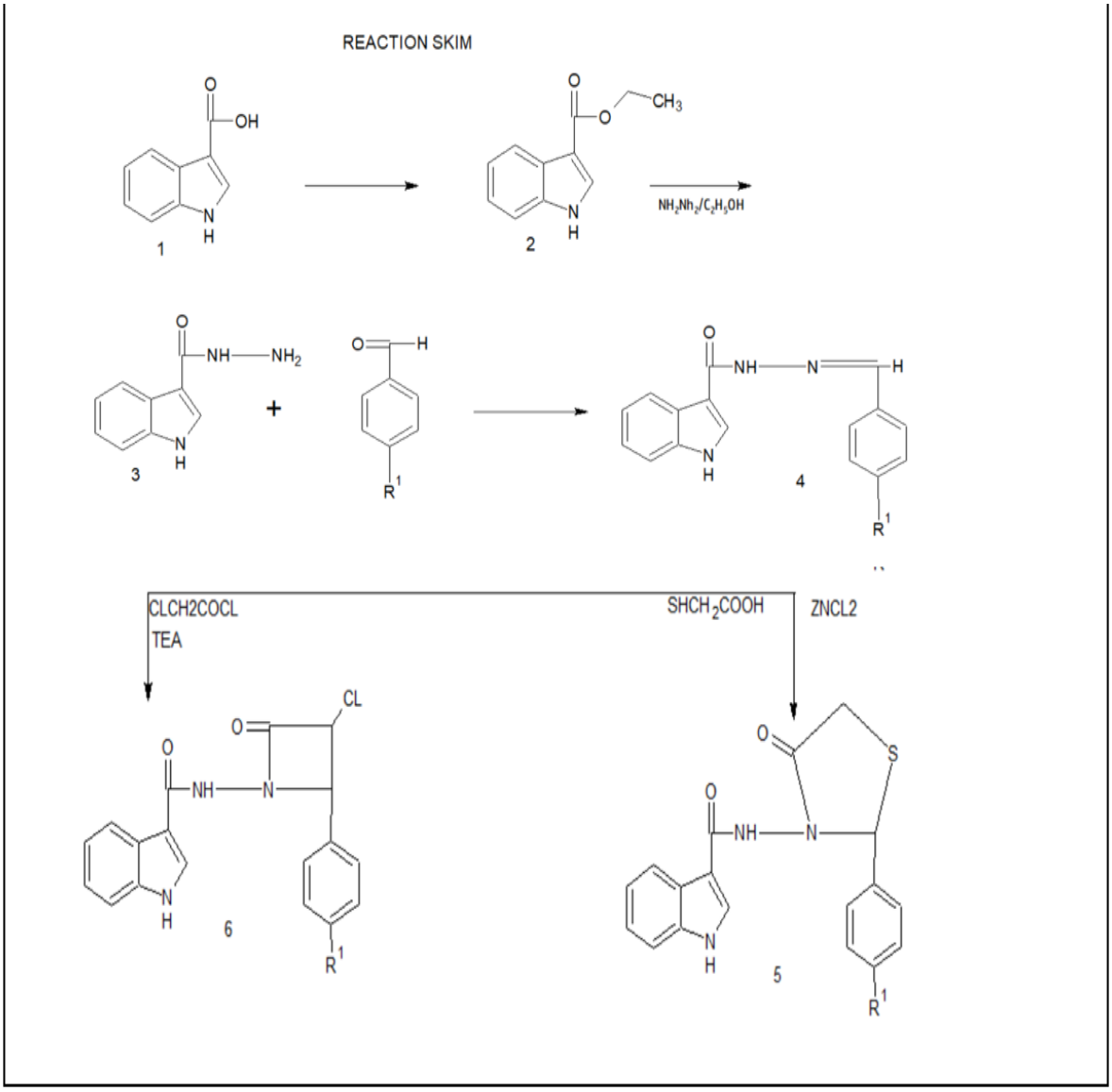

TABLE 01

Comp	R	MP	Yield	Recrystalization	Molecular Formula	Molecular Weight	Elemental Analysis					
						335	C		H		N	
							Calculated	Observed	Calculated	Observed	Calculated	Observed
(5)A	OH	189	36	Ethyl Alcohol	C18H15N303S	352	61.36	61.40	4.26	4.29	11.93	11.94
B	CL	197	29	Methanol	C18H14N3O2SCL	370.5	58.30	58.36	3.78	3.76	11.34	11.37
C	N(CH3)3	184	20	Acetone	C21 H23 N4 O2 S	394	63.96	64.00	5.84	5.89	13.20	13.28
D	OCH3	213	30	MDC	C19H17N303S	366	62.30	62.34	4.64	4.68	11.48	11.44
E	4-OH,3-OCH3	217	39	MDC	C19H17N3O4S	383	59.53	59.59	4.44	4.48	10.97	11.00
F	2,4-F	212	18	EDC	C18H13N3O2SF2	373	57.91	57.95	3.49	3.50	11.26	12.27
G	2-CL,4-F	208	43	EDC	C18H13N3O2SCLF	389.5	55.46	55.50	3.34	3.38	10.78	10.79
H	NO2	200	40	Ethyl Alcohol	C18H14N4O4S	381	56.69	56.73	3.67	3.70	14.70	14.73
I	NHCOCH3	193	28	Ethyl Alcohol	C20H18N4O3S	393	61.07	61.10	4.58	4.60	14.25	14.29
J	CH3	205	35	MDC	C19H17N302S	350	65.14	65.12	4.86	4.88	12.00	12.03
K	COOH	219	44	Toluene	C19H15N3O4S	380	60.00	60.2	3.95	3.98	11.05	11.08
L	COPH	233	18	Toluene	C25 H19 N3 O3 S	440	68.18	68.22	4.32	4.35	9.55	9.59

Table 02

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JCHR (2024) 14(1), 3231-3238| ISSN:2251-6727

COMP	R	MP	YIELD	RECRYSTALIZATION	MOLECULAR FORMULA	MOLECULAR WEIGHT	ELEMENTAL ANALYSIS					
						338.5	C		H		N	
							Calculated	Observed	Calculated	Observed	Calculated	Observed
(6)A	OH	219	28	MDC	C18 H14 N3 O3 cl	355.5	60.76	60.80	3.94	3.95	11.81	11.88
B	CL	222	17	EDC	C18 H13 N3 O2 cl2	374	57.75	57.77	3.48	3.50	11.23	11.25
C	N(CH3)3	234	32	MDC	C21 H22 N4 O2 cl	397.5	63.40	63.40	5.53	5.55	14.09	14.11
D	OCH3	233	28	ETHYLACETATE	C19 H16 N3 O3 cl	369.5	61.71	61.70	4.33	4.30	11.37	11.40
E	4-OH,3-OCH3	240	19	ETHANOL	C19 H17 N3 O4 cl	385.5	59.14	59.15	4.41	4.45	10.89	10.84
F	2,4-F	243	22	ETHANOL	C18 H13 N3 O2 cl F2	375.5	57.52	57.55	3.46	3.48	11.19	11.22
G	2-CL,4-F	254	29	METHANOL	C18 H13 N3 O2 Cl2F	392	55.10	55.15	3.32	3.30	10.71	10.75
H	NO2	220	33	EDC	C18 H13 N4 O4 cl	384.5	56.18	56.19	3.38	3.35	14.56	14.60
I	NHCOCH3	208	27	ETHYLACETATE	C20 H17 N4 O3 cl	396.5	60.53	60.65	4.29	4.33	14.12	14.16
J	CH3	212	22	ETHYLACETATE	C19 H16 N3 O2 cl	353.5	64.50	64.55	4.53	4.57	11.88	11.90
K	COOH	217	26	ETHANOL	C19 H14 N3 O4 cl	383.5	59.45	59.42	3.65	3.62	10.95	11
L	COPH	205	34	ETHANOL	C25 H18 N3 O3 cl	443.5	67.64	67.66	4.06	4.08	9.47	9.5

RESULTS & DISCUSSION

THE POISENED FOOD TECHNIQUE (Gehlot and Vohra, 1998)

Standard drug like fluconazole and Griseofulvin used to identifying the Antifungal Activities of synthesized sample compounds ,10% solution of DIMETHYLSULPHOXIDE prepare in methanol, after that 0.1 gm of substance which have to test and reference compound also dissolved in 10 ml of above prepare solution and make up it with 990 ml czapex dax medium so finally we gets the concentration of 0.1gm per lit.now approx. 20 gm of this prepapre solution pored into 9 centtimeter glass sterile petri dish and settling apply on it.

This sterile plates inoculated with 5 mm plugs of mycelia fungal taken from the freshly growing cultures now incubation at 25^0c taken for 8*24 hrs,after this incubation periods diameter of colony formation taken, Ave inhibition calculation take place with formula (C-T)100/C

Where,

T stands for diameter of fungal colony in tested compound

C stand for diameter of fungal colony in reference standard compound

DISC-DIFFUSION ANTIBIOTIC SENSITIVI- TY TEST OR AGAR DIFFUSION TEST (Pai and Platt, 1995)

Agar disk-diffusion method developed in 1940, it's a official method used in many clinical trials, Every culture was kept on Sbouraud dextrose agar medium kept at 30^0c.this fungi were cultivated overnight in sabouraudbroth,centrifuged to extract the plates ,and then resuspended in clean phosphate buffered saline in order to prepare a homogeneous solution for disc testing, a sterile handheld homogenizer was used to homogenize the fungus plates, then using a bacterial spread to ensure a uniform growth, this suspension was plated on a Sbouraud dextrose agar medium. Various test substance and common medications were impregnated with sterile 6 mm whattmann filter paper discs at a concentration of 100 mg/L

After that, these dishes were positioned in the middle of a medium sabouroud agar plate.one control disc on each of these plates is soaked in 10%dmso/methanol solution, incubation of these plates take place at 30^0c. for each test substance and each standard medication employed, three replicates were used, this plates were taken out after 48 hrs,the radius of the inhibitory zone was measured, and average was computed.

Compound 5(a) and 6(a) which have OH group seems to be lease active for antifungal activities, into series five and six out of all 24 compounds which are synthesised only derivatives with 2,4 di floro substitution ,2 chloro 4 floro substitution ,and derivatives with (-NHCOCH3) substitution seems to be potent activities as antifungal compounds , some of these derivatives contains more activities then the standard compounds which also seems in table .

compound 6(g) which have "one chloro and one floro group" seems highest activity against CANDIDA ALBICANS, similarly 5 (g) and 6(f) have highest activities against CANDIDA ALBICANS ATCC, more active compound for CANDIDA KRUSEL GO3, CANDIDA GLABRATU, CANDIDA PURAPSOLSIS 22019 are 5(i), 5(F)and 6(g) respectively.

OBSERVATIONS

COMPOUNDS	CANDIDA ALBICANS	CANDIDA ALBICANS ATCC	CANDIDA KRUSEL GO3	CANDIDA GLABRATU	CANDIDA PURAPSOLSIS 22019
CONTROL	0	0	0	0	0
FLUCONAZOLE*	29	30	18	18	23
GRISEOFULVIN*	24	26	20	19	26
(5)A	13	1	7	12	-
B	-	-	15	-	14
C	-	23	-	13	12
D	22	13	7	8	9
E	21	-	12	15	20

Journal of Chemical Health Risks

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JCHR (2024) 14(1), 3231-3238| ISSN:2251-6727

F	25	31	17	19	20
G	28	33	18	17	21
H	21	-	-	15	20
I	26	24	19	16	27
J	25	22	14	10	-
K	23	-	17	-	12
L	20	18	15	7	6
(6)A	9	11	6	9	13
B	-	-	15	17	21
C	-	15	17	-	-
D	13	-	12	8	12
E	15	18	11	10	-
F	26	33	15	16	24
G	33	32	16	17	28
H	15	16	8	11	12
I	22	23	12	14	21
J	-	-	14	-	12
K	23	12	-	16	18
L	21	18	-	19	21

Concentration was 100 mg/L, 10%DMSO in methanol, no inhibition zone, std drug use as reference.

CONCLUSION

Table display every pharmacological finding from the current study. The refrence drugs, fluconazole and griseofulvin, as well as compound five A to five L and sevan A to sevan L were all screened for antifungal efficacy against various strains of candida and aspergillus spp.at concentration of 0.1 gm/L, in the series Compound 5(a) and 6(a) which have OH group seems to be lease active for antifungal activities, into series five and six out of all 24 compounds which are synthesised only derivatives with 2,4 di floro substitution ,2 chloro 4 floro substitution ,and derivatives with (-NHCOCH3) substitution seems to be potent activities as antifungal compounds , some of these derivatives contains more activities then the standard compounds which also seems in table ,most powerful chemicals were discovered to be 5F,5G,5I and 6F,6G,6I we also noted that compound 6(g) which have "one chloro and one floro group" seems highest activity against CANDIDA ALBICANS, similarly 5 (g) and 6(f) have highest activities against CANDIDA ALBICANS ATCC, more active compound for CANDIDA KRUSEL GO3, CANDIDA GLABRATU, CANDIDA PURAPSOLSIS 22019 are 5(i), 5(F)and 6(g) respectively.

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