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Design, synthesis and evaluation of carbazole derivatives as potent antifungal

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Abstract
An antimicrobial is a substance that kills or inhibits the growth of microbes such as bacteria, fungi, or viruses. Antimicrobial drugs either kill microbes (microbicidal) or prevent the growth of microbes (microbistatic). Carbazole (Dibenzopyrrole) is an aromatic heterocyclic organic compound. It has a tricyclic structure, consisting of two six-membered benzene ring fused on either side of a five-membered nitrogen-containing ring. The compound's structure is based on the indole structure but in which a second benzene ring is fused onto the five-membered ring at the 2-3 position of indole. Carbazole and its derivatives are used in organic synthesis and vermicides or fungicides as they inhibit the action of certain microorganisms. Carbazole is also having the anti tubercular and anticancer activity. The microbiological assay is based upon a comparison of the inhibition of growth of micro-organisms by measured concentrations of the synthesized compound to be examined with that produced by known concentrations of a standard drugs having a know activity. Agar well diffusion method was used for anti-fungal activity. Fluconazole and Itraconazole were used as a positive control. Sample solution (1mmol) poured into the bored well. It was incubated for 4 days and it was observed after every 24 hours that there was zone of inhibition.

Keywords: carbazole, antifungal, fluconazole, itraconazole, zone of inhibition

Introduction

An antimicrobial is a substance that kills or inhibits the growth of microbes such as bacteria, fungi, or viruses. Antimicrobial drugs either kill microbes (microbicidal) or prevent the growth of microbes (microbistatic).
An Ideal Antimicrobial should be Quick acting, few side effects, Quick "kill" of the pathogen, Broad spectrum in action, Water soluble
Main Classes of Antimicrobials are Antibiotics and synthetic antibacterial agents (antibacterial agents), Antivirals, Antifungals, Antiparasitic.
Carbazole (Dibenzopyrrole) is an aromatic heterocyclic organic compound. It has a tricyclic structure, consisting of two six-membered benzene ring fused on either side of a five-membered nitrogen-containing ring. The compound's structure is based on the indole structure but in which a second benzene ring is fused onto the five-membered ring at the 2-3 position of indole.

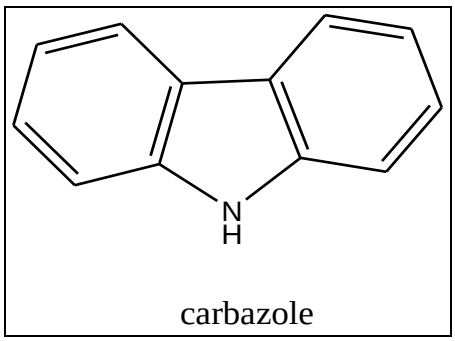

Fig 1

It inhibit sterol 14-α-demethylase, a microsomal cytochrom P450 depended enzyme system and thus impair the biosynthesis of ergosterol for the cytoplasmic membrane and lead to accumulation of 14-α methyl sterol. This methyl sterol may distrupt the close packaging of the acyl chains of phospholipids, impairing the function of certain membrane bound enzyme system such as ATPase and enzyme of electrone transport system and thus inhibiting growth of the fungi.
Carbazole and its derivatives are used in organic synthesis and vermicides or fungicides as they inhibit the action of certain microorganisms. Carbazole is also having the anti-tubercular and anticancer activity.

Experimental Methods and Materials

Synthesis of newer compounds

1. ***Synthesis of 1-(9h-Carbazole-9-Yl)-2-Chloroethanone***

Chloroacetyl chloride (3.81ml, 0.04 moles) was added to a solution of Carbazole (8.00 g, 0.04 mole) in acetone (60 ml) and the reaction mixture was refluxed in 500ml round bottom flask for 6 to 7hr. The solvent was concentrated and kept at room temperature for overnight to get crude product. The product was Recrystallized from ethanol.

2. ***Synthesis of 1-(9h-carbazole-9-yl)-2-hydrazinylethanone***

N-1 Chloro acetyl Carbazole (6.7 g, 0.027 moles) and hydrazine hydrate (1.33 ml, 0.027 moles) in ethanol: dioxan 18:2 v/v (9:1 v/v) mixture was refluxed in 500 ml round bottom flask for 6 to 7 hr. The solvent was concentrated and kept at room temperature for overnight to get product. The product was Recrystallized from chloroform.

3. ***Synthesis of n-1 (arylidene hydrazino acetyl) carbazole***

Hydrazinoacetyl carbazole (1 mole) with different aryl compounds (1 mole) in ethanol: diaoxan 18:2 v/v (9:1 v/v) mixture was refluxed in 500 ml round bottom flask for 13 to 14 hr. It was cooled, filtered, and concentrated to get a solid compound. The product was recrystallized from methanol.

4. *Synthesis of n-1 (arylidine hydrazino acetyl) carbazolo thazolidine-4-ones:*

Thioglycolic acid (1 ml, 0.01 mol), Compounds 4A to 4D (1 mol) and ethanol (30 ml) as a solvent were placed in 250ml round bottom flask. The reaction mixture was refluxed for 13 to 14 hrs. The resultant mixture was kept at room temperature for overnight to get the precipitates. The product was recrystallized using propen – 2-ol as a solvent.

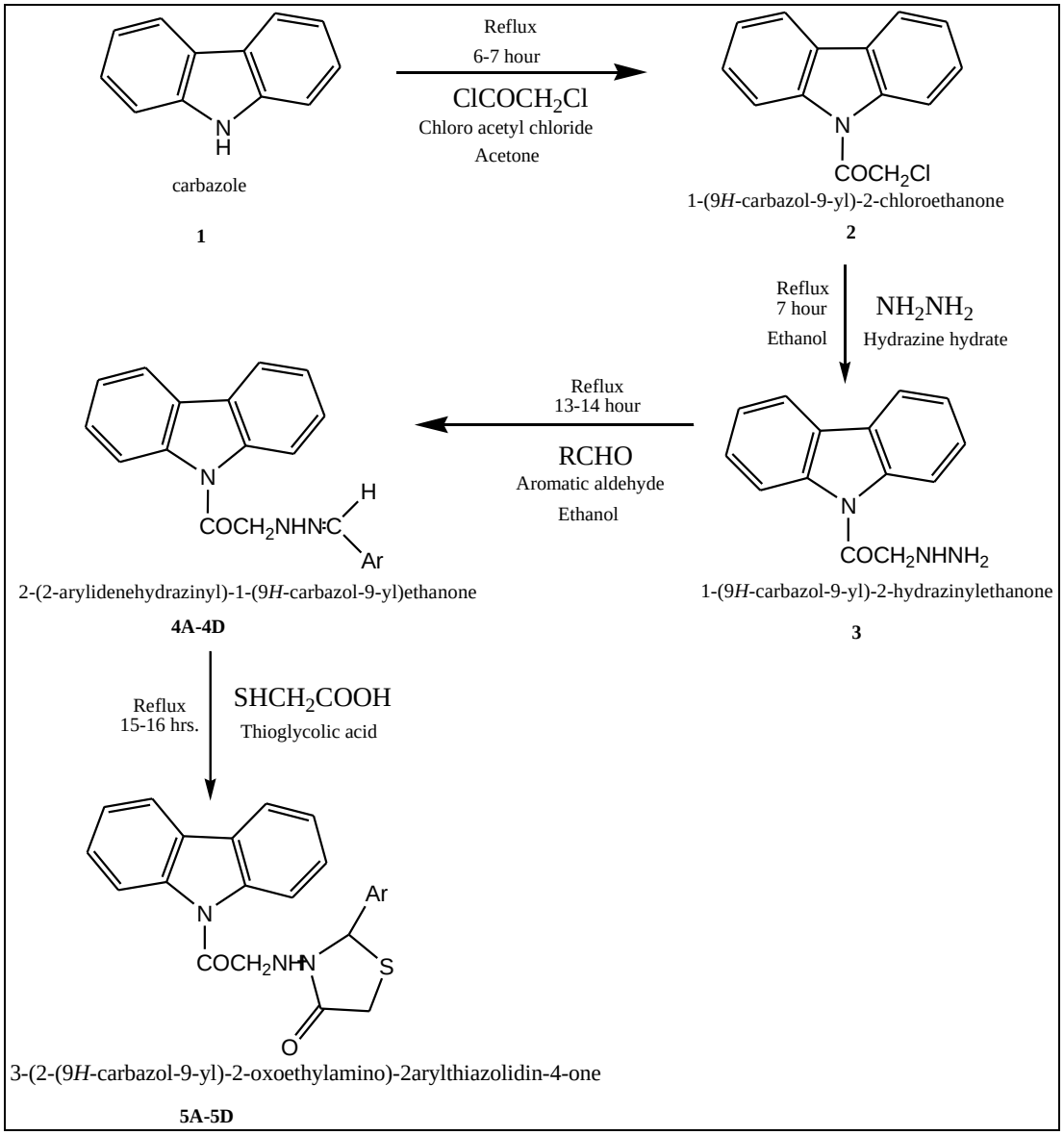

Fig 2: Synthetic scheme for newer compounds

Table 1: Physical characteristics of Schiff's bases:

Comp Code	Ar	Molecular formula	Mol Wt	M. P. (°C)	Yield %	R_f
4A	C_6H_5	$C_{21}H_{17}N_3O$	327.38	216-218	65	*0.75
4B	3-NO_2-C_6H_4	$C_{21}H_{16}N_4O_3$	372.38	209-210	62	**0.37
4C	4-OH-C_6H_4	$C_{21}H_{17}N_3O_2$	343.38	218-220	64	**0.58
4D	4-Cl-C_6H_4	$C_{21}H_{16}ClN_3O$	381.82	210-215	63	*0.56

Mobile phases used for TLC are: * Benzene: methanol (9:1), ** Hexane: ethylacetate (9:1)

Table 2: Physical characteristics of newer compounds:

Comp Code	Ar	Molecular formula	Mol Wt	M. P. (°C)	Yield %	R_f
5A	C_6H_5	$C_{23}H_{19}N_3O_2S$	401.48	193-195	66	*0.61
5B	3-NO_2-C_6H_4	$C_{23}H_{18}N_4O_4S$	446.48	225-228	54	**0.48
5C	4-OH-C_6H_4	$C_{23}H_{19}N_3O_3S$	417.48	243-245	61	**0.36
5D	4-Cl-C_6H_4	$C_{23}H_{18}ClN_3O_2S$	435.93	177-180	55	*0.50

Mobile phases used for TLC are: * Benzene: methanol (9:1), ** Hexane: ethylacetate (9:1)

Spectral characteristics of newer compounds

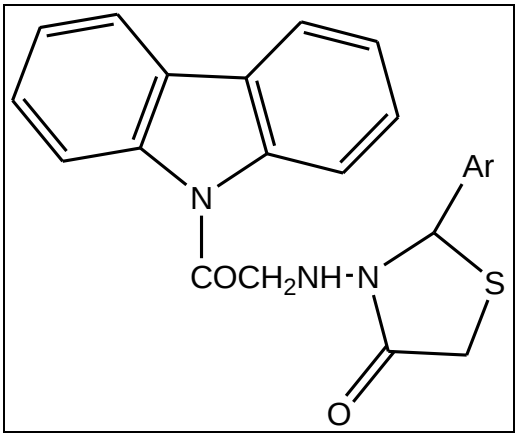

Fig 3

Table 3: Spectral data of newer compounds

Compound	Ar	Mass	IR (cm^{-1})	^{1}H NMR (δ ppm)
5A	C_6H_5	(420) $(M+NH_4)^+$	(-C=O) 1625-1695	3.71 (d, 1H, -NCH) 7.2-7.9 (m, 12H, Ar-H) 3.33-3.64 (s, 2H, thiazolidine -CH_2) 2.48-2.50 (t, 1H, -NH)
5B	3-NO_2-C_6H_4	(464) $(M+NH_4)^+$	(-C=O) 1625-1695 (-NO_2) 1475-1550 (-NH) 3040	3.71 (d, 1H, -NCH) 7.2-7.9 (m, 12H, Ar-H) 3.33-3.64 (s, 2H, thiazolidine -CH_2) 2.48-2.50 (t, 1H, -NH)
5C	4-OH-C_6H_4	(415.48) (M-2)	(-C=O) 1625-1695 (-OH) 3200-3400 (-NH) 3040	3.71 (d, 1H, -NCH) 7.2-7.9 (m, 12H, Ar-H) 3.33-3.64 (s, 2H, thiazolidine -CH_2) 2.48-2.50 (t, 1H, -NH)
5D	4-Cl-C_6H_4	(457) $(M+NH_4)^+$ (M+2)	(-C=O) 1625-1695 (-Cl) 550-750 (-NH) 3040	3.71 (d, 1H, -NCH) 7.2-7.9 (m, 12H, Ar-H) 3.33-3.64 (s,2H, thiazolidine -CH_2) 2.48-2.50 (t, 1H, -NH)

Biological Screening

The inhibition of microbial growth under standardized condition may be utilized for demonstrating the therapeutic efficacy of antibiotics and chemotherapeutic agents. Any subtle change in these agents which may not be detected by chemical methods will be revealed by a change in the anti-microbial activity and hence microbiological assays are very useful for resolving doubts regarding possible change in potency of antibiotics and their preparations. The microbiological assay is based upon a comparison of the inhibition of growth of micro-organisms by measured concentrations of the synthesized compound to be examined with that produced by known concentrations of a standard drugs having a know activity.

Antifungal assay

Known amount of sabroud dextrose agar was prepared and 15 ml of it was poured into separate dishes. The fungi was then inoculated and grown for three days. Agar well diffusion method was used. Sabroud dextrose agar poured into the plate and allowed to solidify. A portion of the fungus was spreaded at the centre of the solidified

mixture of agar, radial growth measurement taken after every 24 hours for 4 days. With the help of cork borer, bore two wells in the medium or culture and the not. Fluconazole and Itraconazole were used as a positive control. Sample solution (1mmol) poured into the bored well. It was incubated for 4 days and it was observed after every 24 hours that there was zone of inhibition

Table 4: Comparison of zone of inhibition of sample drug solutions with standard drugs

Compound No.	Ar	Conc. (µmol)	Antifungal activity (cm)	
			Yeast	Mould
			*C. t.	*A. n.
5A	C_6H_5	1000 µmol	0.8	0.8
5B	3-NO_2-C_6H_4	1000 µmol	1.1	1.0
5C	4-OH-C_6H_4	1000 µmol	0.9	0.7
5D	4-Cl-C_6H_4	1000 µmol	0.8	0.9
Fluconazole	-	1000 µmol	1.5	1.6

Where, *C. t. - *Candida tropicans*, *A. n. - *Aspargillous Niger*

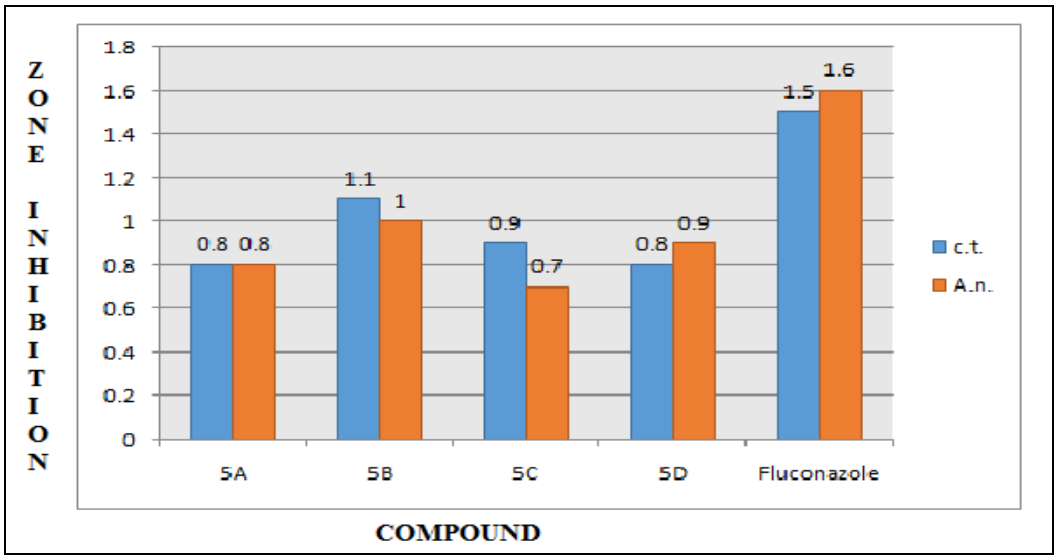

Fig 2: Graph showing antifungal activities of newer compounds.

Result and Discussion

The results of antifungal activities were tabulated, which indicate that different fungal species exhibited different levels of sensitivities towards the different tested compounds and standard drugs. However, none of the derivatives showed a better spectrum of activity than the reference drugs.

Compounds containing chloro substitution (5D) and nitro substitution (5B) had better activity than others in their series, moreover this cyclized compounds were more active than their schiff's bases.

So it is concluded that, compounds having halogen as a part of arylidene structure were more potent than other substituents. Compounds having Electron withdrawing group like Chloro and Nitro gives better antifungal. Compounds having thiazolidine 4-one structure were more active than only their respective Schiff's bases. So thiazolidinone moiety plays an important part to give those compounds more activity then their Schiff's bases.

References

1. Introduction of Carbazole at www.chemicalland21.com.
2. Bonde G, Gaikwad J. Synthesis and preliminary evaluation of some pyrazine containing thiazolines and thiazolidinones as antimicrobial agents. Journal of Bioorganic & Medicinal Chemistry,2004:12:2151-2161.
3. Stevens A, Ichinomiya M, Koshi Y, Horiuchi H. editors, Escape of Candida from Caspofungin inhibition at concentrations above the MIC (paradoxical effect) Accomplished by increased cell wall chitin; evidence for β-1, 6-glucan synthesis inhibition by caspofungin. *Antimicrobial Agents and Chemotherapy*,2006:50:3160-3161.
4. Yaqub G, Hannan A, Usman M, Akbar E, Mateen B. In vitro antifungal and antibacterial activity of carbazoles, *Asian Journal of Chemistry*,2012:24(11):5121-5123.
5. Rosaria O, Maccari R, Ciurleo R, Paoli P, Jacomelli M, Manao G *et al*. 5-Arylidene-2-phenylimino-4-thiazolidinones as PTP1B and LMW-PTP inhibitors. *Bioorganic & Medicinal Chemistry*,2009:17:1928-1937.
6. Kucukguzel I, Esra T Erik C, Sahin F, Gullucec M. Synthesis, characterization and screening of antimicrobial, antituberculosis, antiviral and anticancer activity of novel 1,3-thiazolidine-4-ones derived

from1-[2-(benzoylamino)-4-(methylthio)butyryl]-4-alkyl/arylalkyl thiosemicarbazides. *ARKIVOC.*,2008:14: 191-210.
7. Setu K, Srivastava T, Gaikwad K, Haq W, Sinha S. Synthesis and biological evaluation of 4-thiazolidinone derivatives as potential antimycobacterial agents. *ARKIVOC*,2005:2:120-130.
8. Kavitha V, Swamy N, Mantelingu K, Oreswamy S, Sridhar A, Shashidhara P *et al*. Synthesis of new bioactive venlafaxine analogs: Novel thiazolidin-4-ones as antimicrobials. *Bioorganic & Medicinal Chemistry*,2006:14:2290-2299.
9. Srivastava K, Nema A, Srivastava D. Conventional as well as microwave assisted synthesis of some new N^9-[hydrazinoacetyl-(2-oxo-3-chloro-4-substituted aryl azetidine)]-carbazoles active as antifungal and antibacterial. *Indian Journal of Chemistry*,2008:47B:606-612.
10. Indian Pharmacopoeia, Govt of India: New Delhi,1996:9:100-124.
11. Shiradkar M, Pandit U, Chakravarthy A, Mahetaa A, Venkata G, Kumarb S. Microwave assisted synthesis and antimicrobial screening of fused Triazoles. *ARKIVOC*,2006:14:141-154.
12. Ajayi A, Jonathan G, Adewuy A, Oderinde A. Antimicrobial Screening of the Essential Oil of Some Herbal Plants from Western Nigeria. *World Applied Sciences Journal*,2008:3(1):79-81.
13. National committee for clinical laboratory standards, 1998.
14. Srivastava K, Nema A, Srivastava D. Conventional as well as microwave assisted synthesis of some new N^9-[hydrazinoacetyl-(2-oxo-3-chloro-4-substituted aryl azetidine)]-carbazoles active as antifungal and antibacterial. *Indian Journal of Chemistry*,2008:47B:606-612.