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Syntheses and characterisation of *N,N′*-biscarbazolyl azine and *N,N′*-carbazolyl hydrazine derivatives and their antimicrobial studies

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Reaction of 1-oxo-1,2,3,4-tetrahydrocarbazoles **1a-e** with hydrazine hydrate in absolute ethanol afforded *N,N′*-bis--carbazolylazine derivatives **2a-e**. Treatment of compounds **1a-e** with hydroxylamine hydrochloride in ethanol with a catalytic amount of pyridine resulted in the formation of 1-hydroxyimino-1,2,3,4-tetrahydrocarbazoles **3a-e**. Reduction of **3** with hydrazine hydrate in the presence of palladized carbon afforded *N,N′*-carbazolyl hydrazine derivatives **4a-e**. The newly formed compounds were characterized by IR, ^{1}H NMR, mass spectra and by elemental analysis. All compounds proved to have great potentialities as antibacterial and antifungal agents due to the presence of the azine or the hydrazine group. Particularly, the chloro substituted derivatives **2e** and **4e** showed excellent antibacterial and antifungal activity.

Keywords: 1-oxo-1,2,3,4-tetrahydrocarbazoles, 1-hydroxyimino-1,2,3,4-tetrahydrocarbazoles, *N,N′*-biscarbazolylazines, *N,N′*-carbazolylhydrazines, antibacterial, antifungal activity

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Carbazoles, an important class of indole alkaloids has gained much importance in recent years due to their diverse biological activities (1–4). The therapeutic prominence of the carbazole derivatives was well established (4–6). Also, pyridocarbazoles were reported to elicit anticancer (4–10) and anti-HIV properties (11) and hence they have gained an important place in medicinal chemistry (12). The discovery of the antineoplastic activity of the naturally occurring alkaloid ellipticine and its isomer olivacine have stimulated considerable research efforts in the field of condensed systems (13). A variety of carbazoles and pyrido-annelated carbazoles represent DNA ligands with pronounced antitumor activity (14). Moreover, azines such as naloxone and naltrexone have shown an ultra-long lasting antagonistic activity for the opioid δ receptor sub type (15). With the aim to construct such condensed systems with the carbazole nucleus, we turned our attention to synthesizing 1-hydrazinocarbazoles that would be an important synthon for the synthesis of fused heterocycles.

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EXPERIMENTAL

Melting points were determined using a Mettler FP 51 apparatus (Mettler Instruments, Switzerland) and were uncorrected. IR spectra were recorded on a Shimadzu FTIR-8201 PC spectrophotometer (Shimadzu, Japan) using potassium bromide. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian AMX 400 FT-NMR spectrometer (Varian Australia, Australia) using tetramethylsilane as internal standard. Mass spectra were recorded on a Jeol-JMS-D-300 mass spectrometer (70 eV) (Jeol, Japan). Microanalyses were done on a Perkin Elmer Model 240 CHN analyzer (Perkin-Elmer, USA). The purity of the products was tested by TLC using glass plates coated with silica gel G (HiMedia Laboratories, India) and petroleum ether and ethyl acetate as developing solvents.

Synthesis of N,N′*-bis(1,2,3,4-tetrahydrocarbazol-1-yl)azine (**2a-e**). General method*

A mixture of 1-oxo-1,2,3,4-tetrahydrocarbazole (**1a-e**, 0.001 mol) and hydrazine hydrate (1 mL, 0.02 mol) in absolute ethanol (20 mL) was heated under reflux for 5 h. The solvent was evaporated under reduced pressure and the residue obtained was poured into ice cold water and extracted with ethyl acetate. The organic layer was thoroughly washed with water and then dried over anhydrous sodium sulphate. Thus obtained crude product was recrystallized from petroleum ether/ethyl acetate 95:5 mixture to yield *N,N′*-bis(1,2,3,4-tetrahydrocarbazol-1-yl)azines (**2a-e**) as yellow crystalline powders (Tables I and II).

Synthesis of N,N′*-(carbazol-1-yl-1′,2′,3′,4′-tetrahydrocarbazol-1′-yl)--hydrazine (**4a-e**). General method*

The appropriate 1-hydroxyimino-1,2,3,4-tetrahydrocarbazole (**3**, 0.001 mol) was dissolved in 20 mL of absolute ethanol and 100 mg of palladized carbon (10%) was added. To this mixture, maintained in an ice bath, 2 mL (0.04 mol) of hydrazine hydrate was added. The reaction mixture was refluxed for 5 h. The reaction mixture was filtered and the solvent was distilled under reduced pressure. The crude mixture obtained was extracted with ethyl acetate, washed with water and dried over anhydrous sodium sulphate. Removal of the solvent followed by crystallization from petroleum ether/ethyl acetate mixture (98:2) yielded *N,N′*-(carbazol-1-yl-1′,2′,3′,4′-tetrahydrocarbazol-1′-yl)-hydrazines **4** (Tables I and II).

Antimicrobial studies

Antibacterial activity. – All the newly synthesized compounds (**2a-e** and **4a-e**) were screened for their *in vitro* antibacterial activity against *Escherichia coli* (ATCC 10536), *Staphylococcus aureus* (ATCC 6538), *Pseudomonas aeruginosa* (ATCC 9027) and *Bacillus subtilis* (ATCC 6633) according to the disc diffusion method (19). The minimal inhibitory concentration (*MIC*) was determined by the serial dilution technique using chloroform as a solvent. Furacin was used as a standard drug in antibacterial screening studies. The results are presented in Table III.

Table I. Physical characterization of N,N′*-bis(1,2,3,4-tetrahydrocarbazol-1-yl)azine derivatives (***2***a-e) and* N,N′*-(carbazol-1-yl-1′,2′,3′,4′-tetrahydrocarbazol-1′-yl)-hydrazine derivatives (***4***a-e)*

Compd. No.	Yield (%)	M.p. (°C)	Molecular formula (M_r)	Elemental analysis (%) Calcd./found		
				C	H	N
2a	86	238–240	$C_{26}H_{26}N_4$ (394.26)	79.20 79.15	6.60 6.57	14.20 14.18
2b	85	232–235	$C_{26}H_{26}N_4$ (394.26)	79.20 79.16	6.60 6.69	14.20 14.15
2c	80	242–245	$C_{26}H_{26}N_4$ (394.26)	79.20 79.11	6.60 6.63	14.20 14.26
2d	80	228–230	$C_{24}H_{22}N_4$ (366.24)	78.70 78.72	6.01 6.08	15.29 15.20
2e	79	250–252	$C_{24}H_{20}N_4Cl_2$ (435.14)	66.22 66.28	4.60 4.58	12.87 12.90
4a	65	210–213	$C_{26}H_{26}N_4$ (394.26)	79.20 79.26	6.60 6.51	14.20 14.23
4b	67	184–186	$C_{26}H_{26}N_4$ (394.26)	79.20 79.15	6.60 6.63	14.20 14.23
4c	63	194–196	$C_{26}H_{26}N_4$ (394.26)	79.20 79.28	6.60 6.58	14.20 14.14
4d	61	200–202	$C_{24}H_{22}N_4$ (366.24)	78.70 78.77	6.01 6.05	15.29 15.18
4e	60	225–228	$C_{24}H_{20}N_4Cl_2$ (435.14)	66.22 66.20	4.60 4.67	12.87 12.84

Antifungal activity. – The antifungal screening studies of compounds **2a-e** and **4a-e** were performed by the standard agar disc diffusion method (20). Seven days old cultures of *Aspergillus niger* (ATCC 16404), *Candida albicans* (ATCC 10231), *Altenaria macrospora* and *Fusarium oxysporum* (isolated from rotten fruits) were used as test organisms. They were grown on a potato dextrose agar medium. The *MIC* values were determined by the serial dilution technique using chloroform as a solvent. The growth of the microorganisms was determined visually and the lowest concentration that inhibited the growth of the microorganisms for 24 hours at 37 °C was taken as the *MIC*. The standard drug used for comparison in antifungal screening studies was clotrimazole. The results are presented in Table IV.

Solutions of the standards, furacin and clotrimazole, were prepared in chloroform. A control experiment with chloroform alone was also done for both the antibacterial and antifungal activity studies.

Table II. Spectroscopic data for N,N'-bis(1,2,3,4-tetrahydrocarbazol-1-yl)azine derivatives ***2a-e*** *and N,N'-(carbazol-1-yl-1',2',3',4'-tetrahydrocarbazol-1'-yl)-hydrazine derivatives* ***4a-e***

Compd. No.	IR (cm^{-1})	^{1}H NMR signals (δ ppm)	MS (m/z)
2a	3464, 3310 (NH) 1601, 1588 (C=N) 1122 (N-N)	2.10–2.21 (m, 4H, C_3-2H, $C_{3'}$-2H), 2.54 (s, 6H, C_8-CH_3 and $C_{8'}$-CH_3), 2.83–3.10 (m, 8H, C_2-2H, C_4-2H, $C_{2'}$-2H, $C_{4'}$-2H), 7.03–7.64 (m, 6H, C_5-H to C_7-H and $C_{5'}$-H to $C_{7'}$-H), 8.51 (b s, 1H, carbazole-N_9H), 8.58 (b s, 1H, carbazole-$N_{9'}$H)	394
2b	3447, 3282 (NH) 1605, 1598 (C=N) 1132 (N-N)	2.06–2.10 (m, 4H, C_3-2H, $C_{3'}$-2H), 2.47 (s, 6H, C_7-CH_3 and $C_{7'}$-CH_3), 2.86–3.18 (m, 8H, C_2-2H, C_4-2H, $C_{2'}$-2H, $C_{4'}$-2H), 6.80–7.46 (m, 6H, C_5-H, C_6-H, C_8-H and $C_{5'}$-H, $C_{6'}$-H, $C_{8'}$-H), 8.67 (b s, 2H, carbazole-N_9H and carbazole-$N_{9'}$H)	394
2c	3436, 3275 (NH) 1599, 1580 (C=N) 1121 (N-N)	2.05–2.11 (m, 4H, C_3-2H, $C_{3'}$-2H), 2.45 (s, 6H, C_6-CH_3 and $C_{6'}$-CH_3), 2.82–3.02 (m, 8H, C_2-2H, C_4-2H, $C_{2'}$-2H, $C_{4'}$-2H), 7.07–7.39 (m, 6H, C_5-H, C_7-H, C_8-H and $C_{5'}$-H, $C_{7'}$-H, $C_{8'}$-H), 8.69 (b s, 2H, carbazole-N_9H and carbazole-$N_{9'}$H)	394
2d	3435, 3240 (NH) 1600, 1598 (C=N) 1121 (N-N)	2.00–3.06 (m, 12H, C_2-2H, C_3-2H, C_4-2H, $C_{2'}$-2H, $C_{3'}$-2H, $C_{4'}$-2H), 7.06–7.64 (m, 8H, C_5-H, C_6-H, C_7-H, C_8-H, $C_{5'}$-H, $C_{6'}$-H, $C_{7'}$-H, $C_{8'}$-H), 8.80 (b s, 2H, carbazole-N_9H and carbazole-$N_{9'}$H)	366
2e	3425, 3295 (NH) 1602, 1590 (C=N) 1125 (N-N)	2.06–2.12 (m, 4H, C_3-2H, $C_{3'}$-2H), 2.52–2.99 (m, 8H, C_2-2H, C_4-2H, $C_{2'}$-2H, $C_{4'}$-2H), 7.11–7.56 (m, 6H, C_5-H, C_7-H, C_8-H and $C_{5'}$-H, $C_{7'}$-H, $C_{8'}$-H), 8.61 (b s, 1H, carbazole-N_9H), 8.83 (b s, 1H, carbazole-$N_{9'}$H)	435
4a	3494, 3396, 3294 (NH) 1137 (N-N)	2.01–2.18 (m, 4H, $C_{2'}$-2H, $C_{4'}$-2H), 2.49 (s, 3H, C_8-CH_3), 2.57 (s, 3H, $C_{8'}$-CH_3), 2.78–3.00 (m, 3H, $C_{1'}$-H, $C_{3'}$-2H), 6.92–7.50 (m, 9H, C_2-H to C_7-H and $C_{5'}$-H to $C_{7'}$-H), 10.80 (b s, 1H, carbazole-N_9H), 10.90 (b s, 1H, carbazole-$N_{9'}$H), 11.45 (b s, 1H, C_1-NH), 11.51 (b s, 1H, $C_{1'}$-NH)	394
4b	3450, 3385, 3251 (NH) 1132 (N-N)	2.47 (s, 3H, C_7-CH_3), 2.50 (s, 3H, $C_{7'}$-CH_3), 2.63–3.19 (m, 7H, $C_{1'}$-H, $C_{2'}$-2H, $C_{3'}$-2H, $C_{4'}$-2H), 6.81–7.51 (m, 9H, C_2-H to C_6-H, C_8-H and $C_{5'}$-H, $C_{6'}$-H, $C_{8'}$-H), 8.77 (b s, 1H, carbazole-N_9H), 8.99 (b s, 1H, carbazole-$N_{9'}$H), 9.92 (b s, 1H, C_1-NH), 9.97 (b s, 1H, $C_{1'}$-NH)	394
4c	3464, 3350, 3271 (NH) 1134 (N-N)	2.37 (s, 3H, C_6-CH_3), 2.40 (s, 3H, $C_{6'}$-CH_3), 2.48–2.97 (m, 7H, $C_{1'}$-H, $C_{2'}$-2H, $C_{3'}$-2H, $C_{4'}$-2H), 6.99–7.43 (m, 9H, C_2-H to C_5-H, C_7-H, C_8-H and $C_{5'}$-H, $C_{7'}$-H, $C_{8'}$-H), 11.03 (b s, 2H, carbazole-N_9H and carbazole-$N_{9'}$H), 11.43 (b s, 1H, C_1-NH), 11.71 (b s, 1H, $C_{1'}$-NH)	394
4d	3454, 3414, 3310 (NH) 1124 (N-N)	2.07–3.06 (m, 7H, $C_{1'}$-H, $C_{2'}$-2H, $C_{3'}$-H, $C_{4'}$-2H), 7.10–7.62 (m, 11H, C_2-H to C_8-H and $C_{5'}$-H to $C_{8'}$-H), 8.85 (b s, 1H, carbazole-N_9H), 9.04 (b s, 1H, carbazole-$N_{9'}$H), 10.07 (b s, 2H, C_1-NH and $C_{1'}$-NH)	366
4e	3424, 3390, 3255 (NH) 1127 (N-N)	2.08–3.00 (m, 7H, $C_{1'}$-H, $C_{2'}$-2H, $C_{3'}$-H, $C_{4'}$-2H), 6.98–7.66 (m, 9H, C_2-H to C_5-H, C_7-H, C_8-H and $C_{5'}$-H, $C_{7'}$-H, $C_{8'}$-H), 10.96 (b s, 1H, carbazole-N_9H), 11.17 (b s, 1H, carbazole-$N_{9'}$H), 11.85 (b s, 2H, C_1-NH and $C_{1'}$-NH)	435

Table III. Antibacterial activity of N,N′*-biscarbazolylazine (**2a-e**) and* N,N′*-carbazolyl hydrazine derivatives (**4a-e**)*

Compd. No.[a]	*MIC* (μg mL^{-1})			
	Escherichia coli	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Bacillus subtilis*
2a	100.0	150.0	150.0	12.5
2b	200.0	50.0	50.0	100.0
2c	50.0	25.0	50.0	12.5
2d	100.0	50.0	100.0	200.0
2e	6.0	12.5	25.0	12.5
4a	200.0	50.0	25.0	100.0
4b	100.0	75.0	50.0	100.0
4c	12.5	25.0	50.0	100.0
4d	200.0	100.0	100.0	50.0
4e	6.0	12.5	50.0	12.5
Furacin (standard)	6.0	12.5	12.5	12.5

[a] $CHCl_3$ solvent – negative control

Table IV. Antifungal screening data of N,N′*-biscarbazolylazine (**2a-e**) and* N,N′*-carbazolyl hydrazine derivatives (**4a-e**)*

Compd. No.[a]	*MIC* (μg mL^{-1})			
	Aspergillus niger	*Candida albicans*	*Altenaria macrospora*	*Fusarium oxysporum*
2a	100	12.5	100	200
2b	100	100	100	150
2c	25	25	100	25
2d	100	200	200	100
2e	25	12.5	50	50
4a	50	12.5	100	200
4b	200	100	100	200
4c	25	100	50	25
4d	100	200	100	100
4e	25	12.5	50	25
Clotrimazole (standard)	25	12.5	25	25

[a] $CHCl_3$ solvent – negative control

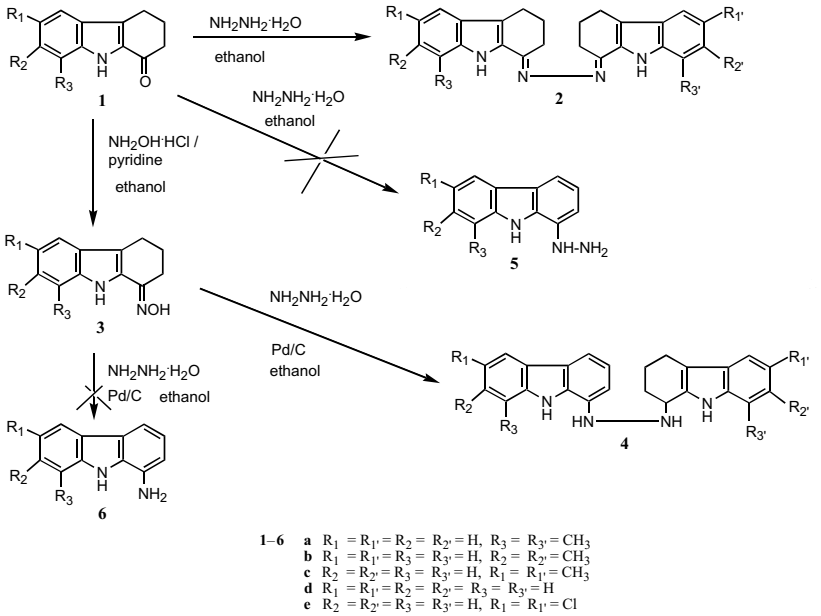
RESULTS AND DISCUSSION

From the aforesaid facts, the reaction of 1-oxo-1,2,3,4-tetrahydrocarbazoles (**1a-e**) (16) with hydrazine hydrate was performed in order to synthesize 1-hydrazinocarbazoles (**5**). However, the reaction afforded the dimerized *N,N′*-biscarbazolylazines **2a-e**. Failing to achieve our targeted 1-hydrazinocarbazoles (**5**), an another attempt was made to reduce 1-hydroxyimino-1,2,3,4-tetrahydrocarbazoles **3** (17, 18) with palladium on 10% carbon in the presence of hydrazine hydrate to obtain 1-aminocarbazoles (**6**), which also failed. The product was again a dimerized product and it was found to be *N,N′*-(carbazol-1-yl--1′,2′,3′,4′-tetrahydrocarbazol-1′-yl)hydrazine (**4a-e**). Thus obtained dimerized carbazole derivatives were tested for their *in vitro* antibacterial and antifungal activity. Some of the compounds have shown significant activities against all the tested bacteria and fungi.

In the present investigation, 8-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**1a**) was treated with hydrazine hydrate (99%) in absolute ethanol at 90 °C for 5 h to afford a new product (**2a**). Its IR spectrum showed bands corresponding to the NH group at 3464 and 3310 cm^{-1}. Strong bands in the region 1601 and 1588 cm^{-1} were due to C=N. The N-N stretching vibration was inferred from a less intense band at 1122 cm^{-1}. Its ^1H NMR spectrum showed the presence of two methyl groups by a singlet with six-proton intensity at δ 2.54 ppm. The appearance of a multiplet in the region δ 2.10–2.21 ppm due to the C_3 and $C_{3'}$ methylene protons and another multiplet between δ 2.83–3.10 ppm due to the C_2, C_4, $C_{2'}$ and $C_{4'}$ methylene protons suggest the formation of **2a** instead of compound **5a**. The aromatic protons at C_5, C_6, C_7 and $C_{5'}$ to $C_{7'}$ resonated as a multiplet of six-proton intensity at δ 7.03–7.64 ppm. The carbazole NH protons at N_9 and $N_{9'}$ appeared as two broad singlets at δ 8.51 ppm and δ 8.58 ppm, respectively. The mass spectrum showed the molecular ion (*m/z*) peak at 394 (100%) with major fragmentation peaks at 379 (11.5%), 365 (7.1%), 337 (11.4%), 323 (5.2%), 262 (5.8%) and 198 (22.2%). The elemental analysis agreed well with the molecular formula $C_{26}H_{26}N_4$. The spectral data and the elemental analysis have proved the formation of a dimerized carbazole derivative, *viz.*, *N,N′*-bis(8-methyl-1,2,3,4-tetrahydrocarbazol-1-yl)azine (**2a**). The series of compounds **2b-e** was prepared by repeating the analogous experiment from **1b**, **1c**, **1d** and **1e**, respectively (Scheme 1).

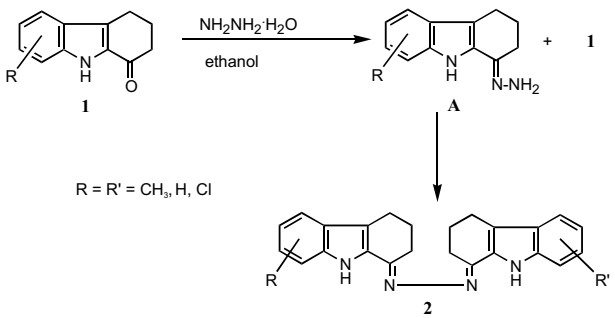
The formation of *N,N′*-bis(1,2,3,4-tetrahydrocarbazole-1-yl)azine (**2**) instead of 1-hydrazinocarbazole (**5**) from 1-oxo-1,2,3,4-tetrahydrocarbazole (**1**) in the reaction with hydrazine hydrate could be explained as follows. In the proposed mechanism it is reasonable to assume that 1-oxo-1,2,3,4-tetrahydrocarbazole (**1**) forms hydrazone **A**, which further reacts with **1** to yield **2**. However, our attempt to isolate hydrazone **A** was unsuccessful. It was supposed to be the *in situ* condensation of **A** with **1**, which resulted in the formation of **2** (Scheme 2).

The reduction of **3** with hydrazine hydrate in the presence of palladium on 10% carbon yielded a dimerized product, namely, *N,N′*-(carbazol-1-yl-1′,2′,3′,4′-tetrahydrocarbazol-1′-yl)hydrazine (**4**) instead of 1-aminocarbazole **6**. In this regard, the reduction of 8-methyl-1-hydroxyimino-1,2,3,4-tetrahydrocarbazole (**3a**) with hydrazine hydrate in the presence of palladium on 10% carbon afforded a new product. The IR spectrum of the compound showed intense bands at 3494, 3396 and 3294 cm^{-1} for NH stretching vibrations. A weak band at 1137 cm^{-1} was due to the N-N stretching vibration. The ^1H NMR spectrum revealed the presence of two methyl groups (C_8-CH_3 and $C_{8'}$-CH_3) by



1–6 **a** $R_1 = R_{1'} = R_2 = R_{2'} = H$, $R_3 = R_{3'} = CH_3$
b $R_1 = R_{1'} = R_3 = R_{3'} = H$, $R_2 = R_{2'} = CH_3$
c $R_2 = R_{2'} = R_3 = R_{3'} = H$, $R_1 = R_{1'} = CH_3$
d $R_1 = R_{1'} = R_2 = R_{2'} = R_3 = R_{3'} = H$
e $R_2 = R_{2'} = R_3 = R_{3'} = H$, $R_1 = R_{1'} = Cl$

Scheme 1

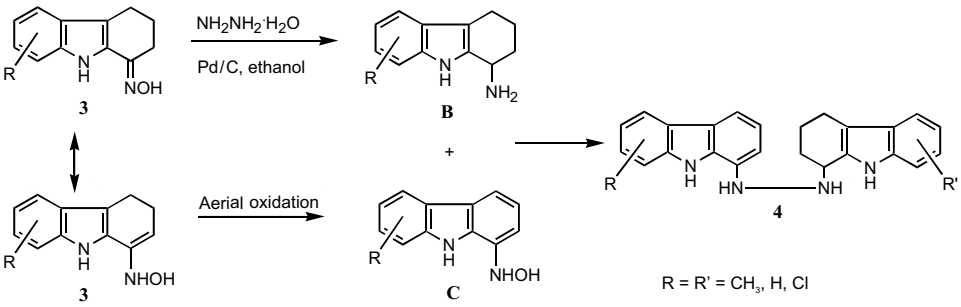


Scheme 2

two singlets at δ 2.49 ppm and δ 2.57 ppm. The methylene protons at $C_{2'}$ and $C_{4'}$ resonated as a multiplet at δ 2.01–2.18 ppm. The methylene protons at $C_{1'}$-H and $C_{3'}$-2H appeared as a multiplet between δ 2.78–3.00 ppm. The aromatic protons at C_2 to C_7 and $C_{5'}$ to $C_{7'}$ resonated as a multiplet between δ 6.92–7.50 ppm. The carbazole NH protons at N_9 and $N_{9'}$ showed two broad singlets at δ 10.80 ppm and at δ 10.90 ppm, respectively. The two broad singlets at δ 11.45 ppm and at δ 11.51 ppm were due to the C_1-NH and

$C_{1'}$-NH protons, respectively. The intensity of the peaks present in the aliphatic and aromatic region in the ^{1}H NMR spectrum has clearly revealed that only a part of the product was aromatized and differed from compound **2a**. The mass spectra showed the molecular ion peak at m/z 394 (100%) with fragmentation peaks at 380 (48%), 366 (18.8%), 351 (5.8%), 337 (4.5%), 323 (3.3%), 224 (15%) and 199 (68%). The elemental analysis agreed well with the molecular formula $C_{26}H_{26}N_4$. From the spectral and elemental data, the structure of the product was found to be *N,N′*-8,8′-dimethyl-(carbazol-1-yl-1′,2′,3′,4′-tetrahydrocarbazol-1′-yl)-hydrazine (**4a**). The repeatability of the experiment was tested on **3b**, **3c**, **3d** and **3e** to afford **4b**, **4c**, **4d** and **4e**, respectively (Scheme 1).

The formation of **4** might be as follows. Hydrazine hydrate in the presence of palladized carbon in ethanol reduced as expected the C=N-OH to the amino derivative to yield **B**. On dehydration with **C** (which was formed *in situ* from **3** by tautomerization and areial oxidation) this resulted in the formation of **4**. However, our attempts to isolate compounds **B** and **C** were unsuccessful (Scheme 3).



Scheme 3

The antibacterial screening studies indicated that the compound having $R_1 = R_{1'} =$ Cl, $R_2 = R_{2'} = R_3 = R_{3'} =$ H (**2e**) and $R_1 = R_{1'} =$ Cl, $R_2 = R_{2'} = R_3 = R_{3'} =$ H (**4e**) showed excellent antibacterial activity against *E. coli*, *B. subtilis* and *S. aureus*, namely it was as active as furacin, but slightly less active against *P. aeruginosa* (Table III). Among the other compounds, **2c** with the methyl group at C-6 and C-6′ showed significant activity against *B. subtilis* at 12.5 μg mL^{-1}. Moreover, **4c** possessed good activity towards *E. coli*. The activity of the other compounds was markedly lower than that of the standard furacin.

The antifungal activity screening studies (Table IV) showed that the chloro substituted compounds **2e** and **4e** showed also excellent activity against *Aspergillus niger* and *Candida albicans* with *MIC* values of 25 and 12.5 μg mL^{-1}, respectively, when compared to the conventional fungicide clotrimazole. Among the other compounds, **2a** and **4a** exhibited good activity against *C. albicans* while **2c** and **4c** were active against *F. oxysporum* at concentration of 25 μg mL^{-1}. The activities of other compounds were markedly lower than that of clotrimazole.

Our earlier report (19) indicated that the chloro substituted carbazole derivatives showed enhanced pharmacological properties. Hence it was supposed that the presence of either the azine or the hydrazine group along with that of the chloro group might be

the reason for the enhanced activity of compound **2e** or **4e** compared to other methyl substituted compounds. The activity of the compounds was directly proportional to the concentration of the test solution. The solvent used as the control was found to be inactive against all the microorganisms chosen for antibacterial and antifungal activity studies.

CONCLUSIONS

A plausible mechanism has been proposed for the synthesis of *N,N′*-bis(1,2,3,4-tetrahydrocarbazol-1-yl)azines and *N,N′*-(carbazol-1-yl-1′,2′,3′,4′-tetrahydrocarbazol-1′-yl)-hydrazines. They were tested for their *in vitro* antibacterial and antifungal activity and the chloro substituted compounds showed significant activity, comparable with that of both the conventional antibacterial and antifungal standards. Efforts are continuing to alkylate the carbazole nitrogen so that the derived compounds may have enhanced pharmacological activity.

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S A Ž E T A K

Sinteza i karakterizacija derivata *N,N′*-biskarbazolil azina i *N,N′*-karbazolil hidrazina i antimikrobni učinak

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Reakcijom 1-okso-1,2,3,4-tetrahidrokarbazola **1a-e** s hidrazin hidratom u apsolutnom etanolu dobiveni su derivati *N,N′*-biskarbazolilazina **2a-e**, a s hidroksilamin hidrokloridom u etanolu, uz katalitičke količine piridina, 1-hidroksiimino-1,2,3,4-tetrahidrokarbazoli **3a-e**. Redukcijom **3** s hidrazin hidratom u prisutnosti paladija na ugljenu nastali su derivati *N,N′*-karbazolil hidrazina **4a-e**. Novosintetizirani spojevi su karakterizirani IR, ^{1}H NMR i masenom spektroskopijom te elementarnom analizom. Spojevi **2**, **3** i **4** su potencijalna antibakterijska i antimikotska sredstva. Najjače djelovanje pokazali su derivati **2e** i **4e** koji sadrže klor.

Ključne riječi: 1-okso-1,2,3,4-tetrahidrokarbazoli, 1-hidroksiimino-1,2,3,4-tetrahidrokarbazoli, *N,N′*-biskarbazolilazini, *N,N′*-karbazolilhidrazini, antibakterijsko djelovanje, antimikotsko djelovanje

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