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Synthesis and characterization of carbazole derivatives and their antimicrobial studies

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The reaction of 1-oxo-1,2,3,4-tetrahydrocarbazoles (**1a–e**) with paraformaldehyde and ethylenediamine yielded *N*,*N*′--bis(1,2,3,4-tetrahydrocarbazol-1-ylidene)ethane-1,2-diamines (**2a–e**). Here, like in another similar attempt of replacing ethylenediamine by ethanolamine, ended up in formation of 2-{[1-(2-(2-aminoethoxy)ethylimino)-1,2,3,4--tetrahydrocarbazol-2-yl-methyl]amino} ethanols (**3a–e**). These products were characterized by IR, ^{1}H NMR, mass spectra and by elemental analysis. All end products (**2a–e, 3a–e**) were screened for antibacterial and antifungal activities. The compounds having substituents at C-6 position were found to exhibit pronounced antimicrobial activities.

Keywords: 1-oxo-1,2,3,4-tetrahydrocarbazoles, paraformaldehyde, ethylenediamine, ethanolamine, *N*,*N*′-bis(1,2,3,4-tetrahydrocarbazol-1-ylidene)ethane-1,2-diamine, 2-{[1-(2-(2-aminoethoxy)ethylimino)-1,2,3,4-tetrahydrocarbazol-2-yl-methyl]-amino}ethanol, antibacterial, antifungal activity

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Carbazole derivatives are well known for their pharmacological activities. Several reports have appeared on the syntheses of carbazole derivatives in connection with the search for newer physiologically active compounds. Carbazomycin A and carbazomycin B have been found to be useful antibacterial and antifungal agents (1, 2). It has been reported that pyridocarbazoles show marked anticancer and anti-HIV activities (3–13). The discovery of the antineoplastic activity of the naturally occurring alkaloid ellipticine and its isomer olivacine has stimulated considerable research efforts in the field of condensed systems (14). In the present investigation, the Mannich reactions of 1-oxo-1,2,3,4--tetrahydrocarbazole ended up in the formation of *N*,*N*′-bis(1,2,3,4-tetrahydrocarbazol--1-ylidene) ethane-1,2-diamines (**2**) and 2-[{1-(2-(2-aminoethoxy)ethylimino)-1,2,3,4-tetrahydrocarbazol-2-yl methyl}amino] ethanols (**3**).

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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 using KBr on a Shimadzu FTIR-8201PC spectrophotometer (Shimadzu, Japan). ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian AMX 400 FT-NMR (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 (85:15) as the developing solvents.

Synthesis of N,N′*-bis(1,2,3,4-tetrahydrocarbazol-1-ylidene)ethane-1,2-diamines (**2**). General method*

A mixture of the appropriate 1-oxo-1,2,3,4-tetrahydrocarbazole **1** (0.001 mol), paraformaldehyde (0.001 mol) and ethylenediamine (10 mL) was heated on oil bath at 120 °C for 3 h. The reaction was monitored by TLC and after the completion of the reaction the mixture was poured into crushed ice, filtered, dried and recrystallized using ethanol to yield *N*,*N*′-bis(1,2,3,4-tetrahydrocarbazol-1-ylidene)ethane-1,2-diamine (**2**) (Tables I and II).

*Synthesis of 2-{[1-(2-(2-aminoethoxy)ethylimino)-1,2,3,4-tetrahydrocarbazol-2-yl--methyl]amino}ethanols (**3**). General method*

A mixture of the relevant 1-oxo-1,2,3,4-tetrahydrocarbazole **1** (0.001 mol), paraformaldehyde (0.001 mol) and ethanolamine (10 mL) was heated on oil bath at 120 °C for 3 h. The reaction was monitored by TLC. After the completion of the reaction, the mixture was poured into crushed ice, filtered, dried and recrystallized using ethanol to yield 2-{[1--(2-(2-aminoethoxy)ethylimino)-1,2,3,4-tetrahydrocarbazol-2-yl-methyl]amino}-ethanol (**3**) (Tables I and II).

*Table I. Analytical data for compounds **2a–e** and **3a–e***

Compd. No.	Yield (%)	M. p. (°C)	Molecular formula (M_r)	Elemental analysis (%) Calcd./found		
				C	H	N
2a	65	116–118	$C_{28}H_{30}N_4$ (422.25)	79.59/79.21	7.16/7.30	13.26/13.20
2b	67	139–142	$C_{28}H_{30}N_4$ (422.25)	79.59/79.97	7.16/7.07	13.26/12.99
2c	60	150–153	$C_{28}H_{30}N_4$ (422.25)	79.59/80.77	7.16/6.98	13.26/12.75
2d	70	165–168	$C_{26}H_{24}Cl_2N_4$ (462.14)	67.39/67.10	5.22/5.37	12.09/12.19
2e	55	120–123	$C_{26}H_{26}N_4$ (394.22)	79.16/78.75	6.64/6.95	14.20/14.43
3a	80	140–143	$C_{20}H_{30}N_4O_2$ (358.24)	67.01/67.97	8.44/8.27	15.63/15.30
3b	72	147–150	$C_{20}H_{30}N_4O_2$ (358.24)	67.01/67.63	8.44/8.17	15.63/15.45
3c	74	140–143	$C_{20}H_{30}N_4O_2$ (358.24)	67.01/67.11	8.44/8.58	15.63/15.71
3d	68	152–155	$C_{19}H_{27}ClN_4O_2$ (378.18)	60.23/59.07	7.18/7.23	14.79/15.06
3e	75	138–141	$C_{19}H_{28}N_4O_2$ (344.22)	66.25/65.60	8.19/8.44	16.27/16.03

Table II. IR, ^{1}H NMR and mass spectral data for compounds ***2a–e*** *and* ***3a–e***

Compd. No	IR (ν, cm^{-1})	^{1}H NMR signals (δ, ppm)	MS (*m/z*)
2a	3411, 3275, 2922, 1630, 1614, 1445	11.44, 10.83 (2 b s, 2H, N_9-, N_9'-H), 7.10–7.50 (m, 4H, C_7-, C_8-,C_7'-,C_8'-H), 6.97, 6.95 (2s, 2H, C_5, C_5'-H), 2.39, 2.35 (2 s, 6H, C_6-, C_6'-CH_3), 1.87-3.94 (m, 16H, eight CH_2)	422
2b	3420, 3287, 2924, 1641, 1624, 1464	11.47–10.98 (2 b s, 2H, N_9-, N_9'-H), 7.56, 7.54 (2 s, 2H, C_8, C_8'-H), 6.65–7.43 (m, 4H, C_5-, C_6-,C_5'-,C_6'-H), 2.41, 2.38 (2 s, 6H, C_7-, C_7'-CH_3), 1.90–3.60 (m, 16H, eight CH_2)	422
2c	3414, 3306, 2924, 1630, 1607, 1450	11.44–11.60 (m, 2H, N_9-, N_9'-H), 6.85–7.55 (m, 6H, C_5-, C_6-, C_7-, C_5'-, C_6'-, C_7'-H), 2.50, 2.49 (2 s, 6H, C_8-, C_8'-CH_3), 1.82–4.00 (m, 16H, eight CH_2)	422
2d	3411, 3275, 2922, 1646, 1613, 1462	11.00–11.35 (m, 2H, N_9-, N_9'-H), 7.07–7.79 (m, 4H, C_7-, C_8-, C_7'-, C_8'-H), 6.97, 6.95 (2 s, 2H, C_5, C_5'-H), 1.69–4.17 (m, 16H, eight CH_2)	462
2e	3412, 3240, 2926, 1630, 1607, 1447	11.55,10.96 (2 b s, 2H, N_9-, N_9'-H), 6.93–7.55 (m, 8H, C_5-, C_6-, C_7-, C_8-, C_5'-, C_6'-, C_7'-, C_8'-H), 1.90–3.90 (m, 16H, eight CH_2)	394
3a	3410–3300, 1630, 1600, 1541	11.40 (b s, 1H, N_9-H), 7.44 (s, 1H, C_5-H), 7.25–7.30 (d, 1H, C_8-H, *J* = 8.44 Hz), 7.12–7.17 (d, 1H, C_7-H, *J* = 8.44 Hz), 4.40 (s, 1H, OH), 2.81–3.78 (m, 6H, three CH_2-O), 2.39 (s, 3H, C_6-CH_3), 2.24–2.53 (m, 16H, C_2-H, C_3-H_2, C_4-H_2, four CH_2-N, NH, NH_2)	358
3b	3410–3300, 1630, 1600, 1543	13.42 (b s, 1H, N_9-H), 7.16–7.57 (m, 3H, C_5-, C_6-,C_8-H), 4.05 (s, 1H, OH), 2.22–3.43 (m, 22H, C_2-H, C_3-H_2, C_4-H_2, seven CH_2, NH, NH_2), 2.48 (s, 3H, C_7-CH_3)	358
3c	3408–3300, 1630, 1600, 1543	11.79 (b s, 1H, N_9-H), 7.78–7.87 (d, 1H, C_5-H, *J* = 7.96 Hz), 7.39–7.47 (d, 1H, C_7-H, J=6.88 Hz), 7.29–7.37 (m, 1H, C_6-H), 3.84 (s, 1H, OH), 2.78–3.68 (m, 22H, C_2-H, C_3-H_2, C_4-H_2, seven CH_2, NH, NH_2), 2.82 (s, 3H, C_8-CH_3)	358
3d	3410–3267, 1643, 1600, 1541	11.75 (b s, 1H, N_9-H), 7.43 (s, 1H, C_5-H), 7.31–7.34 (d, 1H, C_8-H, *J* = 8.44 Hz), 7.28–7.30 (d, 1H, C_7-H, *J* = 8.44 Hz), 4.38 (s, 1H, OH), 2.83–4.08 (m, 6H, three CH_2-O), 1.96–2.63 (m, 16H, C_2-H, C_3-H_2, C_4-H_2, four CH_2-N, NH, NH_2)	378
3e	3410–3279 1645, 1600, 1470	11.50 (b s, 1H, N_9-H), 7.64–7.72 (d, 1H, C_8-H, 8.00 Hz), 7.37–7.44 (d, 1H, C_5-H, J=8.28 Hz), 7.27–7.35 (m, 1H, C_7-H), 7.05–7.12 (m, 1H, C_6-H), 4.37 (s, 1H, OH), 3.46–3.79 (m, 6H, three CH_2-O), 2.24–3.02 (m, 16H, C_2-H, C_3-H_2, C_4-H_2, four CH_2-N, NH, NH_2)	344

Antibacterial studies

Newly synthesized compounds **2a–e** and **3a–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 (15). The minimum inhibitory concentration (*MIC*) was determin-

Table III. Antimicrobial activity data of compounds ***2a–e*** *and* ***3a–e***

	Compound No.	**2a**	**2b**	**2c**	**2d**	**2e**	**3a**	**3b**	**3c**	**3d**	**3e**	Ref. st.
MIC (mg mL^{-1}) *Antibacterial data*[a]	*S. aureus*	12.5	100.0	50.0	6.0	50.0	12.5	75.0	25.0	6.0	100.0	6.0
	P. aeruginosa	25.0	150.0	50.0	12.5	100.0	12.5	50.0	50.0	25.0	100.0	12.5
	E. coli	12.5	150.0	50.0	12.5	100.0	25.0	100.0	100.0	12.5	200.0	6.0
	B. subtilis	6.0	100.0	12.5	6.0	150.0	25.0	100.0	100.0	6.0	50.0	6.0
Antifungal data[b]	*A. macrospora*	12.5	100.0	100.0	12.5	100.0	25.0	100.0	150.0	12.5	150.0	6.0
	C. albicans	25.0	150.0	50.0	6.0	200.0	25.0	200.0	100.0	6.0	150.0	6.0
	A. niger	25.0	150.0	100.0	50.0	200.0	100.0	100.0	150.0	25.0	100.0	25.0
	F. oxysporum	25.0	100.0	50.0	12.5	200.0	25.0	50.0	200.0	50.0	150.0	12.5

DMSO – negative control
[a] Referent standard ciprofloxacin
[b] Referent standard carbendazim

ed by the serial dilution technique using dimethylsulphoxide as a solvent. Ciprofloxacin (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid) was used as a standard in these antibacterial screening studies. The results are presented in Table III.

Antifungal studies

The antifungal screening studies of compounds **2a**–**e** and **3a**–**e** were performed by the standard agar disc diffusion method (16). 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 dimethylsulphoxide as solvent. The growth of 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 used for comparison in antifungal screening studies was carbendazim (1*H*-benzimadazol-2-yl carbamic acid methyl ester). The results are presented in Table III.

Solutions of the standards, ciprofloxacin and carbendazim, were prepared in dimethylsulphoxide. A control experiment with dimethylsulphoxide alone was also done for both the antibacterial and antifungal studies.

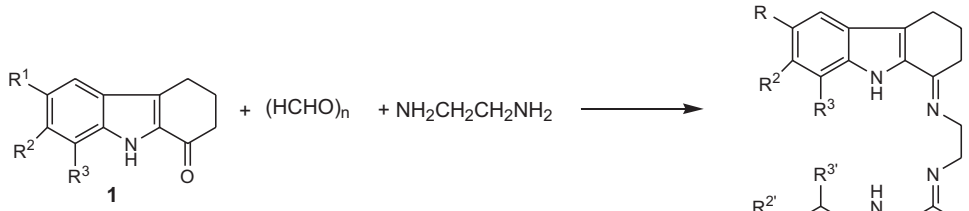
RESULTS AND DISCUSSION

The reaction of 1-oxo-1,2,3,4-tetrahydrocarbazoles (**1a**–**e**) (17) with paraformaldehyde and ethylenediamine ended up in the formation of *N*,*N*′-bis(1,2,3,4-tetrahydrocarbazol--1-ylidene)ethane-1,2-diamines (**2a**–**e**) (Scheme 1). On the other hand, the treatment of

1-oxo-1,2,3,4-tetrahydrocarbazoles (**1a**–**e**) with paraformaldehyde and ethanolamine yielded 2-{[1-(2-(2-aminoethoxy)ethylimino)-1,2,3,4-tetrahydrocarbazol-2-yl-methyl]-amino}-ethanols (**3a**–**e**) (Scheme 2).

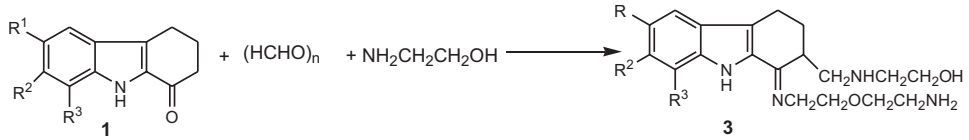
In our present investigation, the mixture of 6-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**1a**), paraformaldehyde and ethylenediamine was heated at 120 °C for 3 h to afford product **2a**. Its IR spectrum (Table II) showed two bands at 3410 and 3275 cm^{-1} for two NH stretching vibrations. Two strong vibrations at 1630 and 1614 cm^{-1} were due to C=N stretchings. Its ^1H NMR spectrum (Table II) showed the presence of two methyl groups as two singlets at δ 2.35 and δ 2.39. The multiplets between δ 1.87–3.94 showed the presence of eight aliphatic protons. Two singlets at δ 6.95 and δ 6.97 were due to C_5 and C_5' protons. The four-proton multiplet between δ 7.11–7.50 was due to C_7, C_7', C_8, C_8' protons. Two broad singlets at δ 10.83 and δ 11.44 were due to indole NH proton at N_9-H and N_9'-H.

From the aforesaid facts it was concluded that the Schiff base formation was taking place by both amino groups of ethylenediamine with two moles of 6-methyl-1-oxo-1,2,3,4--tetrahydrocarbazole (**1a**) instead of the expected Mannich reaction. The reaction was generalized for other 1-oxo-1,2,3,4-tetrahydrocarbazole derivatives (**1b–e**).



1 and 2 **a:** $R^1 = R^{1'} = CH_3$, $R^2 = R^{2'} = R^3 = R^{3'} = H$
b: $R^2 = R^{2'} = CH_3$, $R^1 = R^{1'} = R^3 = R^{3'} = H$
c: $R^3 = R^{3'} = CH_3$, $R^1 = R^{1'} = R^2 = R^{2'} = H$
d: $R^1 = R^{1'} = Cl$, $R^2 = R^{2'} = R^3 = R^{3'} = H$
e: $R^1 = R^{1'} = R^2 = R^{2'} = R^3 = R^{3'} = H$

Scheme 1



1 and 3 **a:** $R^1 = CH_3$, $R^2 = R^3 = H$
b: $R^2 = CH_3$, $R^1 = R^3 = H$
c: $R^3 = CH_3$, $R^1 = R^2 = H$
d: $R^1 = Cl$, $R^2 = R^3 = H$
e: $R^1 = R^2 = R^3 = H$

Scheme 2

In the second trial, after replacing ethylenediamine by ethanolamine under the same conditions, product **3a** was formed. Its IR spectrum (Table II) showed a band between 3430 and 3300 cm^{-1} for OH and NH stretching vibrations. A strong vibration at 1600 cm^{-1} was due to C=N stretching. Its ^1H NMR spectrum (Table II) showed the presence of a methyl group as a singlet at δ 2.39. The multiplets between δ 2.24–2.53 and δ 2.81–3.78 showed the presence of twenty two protons, including methylene protons and NH protons. A singlet at δ 4.40 was due to the OH proton. Two doublets (J = 8.44 Hz) between δ 7.12–7.17 and δ 7.25–7.30 were due to C_7 and C_8 protons. A singlet at δ 7.44 was due to C_5 proton. A broad singlet at δ 11.40 was due to the indole NH proton at N_9-H. The mass spectrum showed the molecular ion (*m/z*) at 358 (28%). Major fragmentation peaks appeared at 357 (100%), 356 (76%), 212 (44%), 211 (86%), 210 (34%), 182 (33%), 88 (47%), 74 (27%) and 43 (42%). The fragment ions that appeared at 88 (47%) and 74 (27%) showed the presence of =N-$CH_2CH_2OCH_2CH_2NH_2$ and –$CH_2NHCH_2CH_2OH$ groups, respectively. Also, the absence of the fragment ion at 117 confirmed the absence of –$CHNHCH_2CH_2OCH_2CH_2NH_2$.

The formation of compound **3** from 1-oxo-1,2,3,4-tetrahydro carbazole (**1**) upon reaction with paraformaldehyde and ethanolamine is rather surprising. It was considered worthwhile to gain an insight into the mechanistic aspects of this intriguing result. It is reasonable to assume that the Mannich reaction of carbazole derivative **1** with paraformaldehyde and ethanolamine afforded the expected 2-[(2-hydroxyethylamino)-methyl]-1-oxo-1,2,3,4-tetrahydro carbazole. However, our attempt to isolate the compound 2-[(2-hydroxyethylamino)-methyl]-1-oxo-1,2,3,4-tetrahydro carbazole was unsuccessful. Surprisingly, *in situ* condensation between 2-[(2-hydroxyethylamino)-methyl]-1-oxo-1,2,3,4--tetrahydro carbazole and ethanolamine resulted in the formation of product **3**. The generality was tested for other carbazole derivatives (**1b–e**).

Antibacterial and antifungal activities of all the newly prepared compounds against four bacteria and four fungi are presented in Table III. The antibacterial activity of compound **2d** is quite good. Out of the four tested bacteria it is as active as the standard, ciprofloxacin, against *S. aureus*, *P. aeruginosa* and *B. subtilis*. It also exhibited moderate activity against *E. coli*. Similarly, compound **3d** exhibited good results against *S. aureus* and *B. subtilis*, moderate activity against *E. coli* and *P. aeruginosa*. In the case of compound **2a**, it is active against *B. subtilis*. Its activity against the other three bacteria is also considerable. Compound **3a** elicited moderate activity against all the tested bacteria. The other compounds were found to have lower activity than ciprofloxacin.

In an earlier report (15) it was found that the C-6 substituted carbazole derivatives showed enhanced pharmacological properties. Similarly, compounds **2a** and **3a**, having the methyl group as substituent at C-6 position, exhibit better activities than their C-7 and C-8 counterparts. Also compounds **2d** and **3d** having the chloro group as substituent at C-6 position exhibited more pronounced activities than other compounds.

The antifungal activity studies showed that the activity of compound **2d** against *C. albicans* and *F. oxysporum* is on a par with the standard, carbendazim. It is also moderately active against *A. macrospora*. Compound **3d** is as active as the standard against *C. albicans* and *A. niger* and moderately active against *A. macrospora*. The activity of **2a** against *A. niger* is quite good and considerable against *A. macrospora*. The other compounds showed lower activity towards all the fungal species tested.

From the above observations, the antimicrobial activities of compounds **2d** and **3d** are rather good against all the tested bacteria and fungi. As far as the chemical structure of active compounds is concerned, it is pertinent to mention here that compounds **2a** and **3a** having the methyl group as substituent at the C-6 position exhibit better activities against their C-7 (**2b** and **3b**) and C-8 (**2c** and **3c**) counterparts. On replacing the C-6 methyl group by the C-6 chloro group (compounds **2d** and **3d**) even more pronounced activity against all the tested microbial than that of their methyl analogs was achieved.

CONCLUSIONS

All the prepared compounds were well characterized using their spectral results. Perusal of the antibacterial and antifungal results revealed that the compounds having the methyl group as substituent at the C-6 position are active against the tested bacteria and fungi. Also, compounds having the chloro group as substituent at C-6 position exhibited better activity than their methyl counterparts. Considering the structures of the standard ciprofloxacin and carbendazim, it was concluded that, to further enhance the activity of thus synthesized compounds **2a**, **3a**, **2d** and **3d**, attempts to introduce groups like fluoro, carboxylic acid, cyclopropyl and piperazine should be carried out.

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S A Ž E T A K

Sinteza, karakterizacija i antimikrobni učinak derivata karbazola

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Reakcijom 1-okso-1,2,3,4-tetrahidrokarbazola (**1a**–**e**) s paraformaldehidom i etilendiaminom dobiveni su *N*,*N*′-bis(1,2,3,4-tetrahidrokarbazol-1-iliden)etan-1,2-diamini (**2a**–**e**). Ovdje su, kao i u drugim sličnim pokušajima zamjene etilendiamina etanolaminom, nastali derivati 2-{[1-(2-(2-aminoetoksi)etilimino)-1,2,3,4-tetrahidrokarbazol-2-il-metil]amino}-etanola (**3a**–**e**). Spojevi su karakterizirani pomoću IR, ^{1}H NMR i masenom spektrometrijom, te elementarnom analizom. Ispitano je antibakterijsko i antimikotsko djelovanje produkata **2a**–**e** i **3a**–**e**. Spojevi sa supstituentima na položaju C-6 imaju izraženo antimikrobno djelovanje.

Ključne riječi: 1-okso-1,2,3,4-tetrahidrokarbazoli, paraformaldehid, etilendiamin, etanolamin, *N*,*N*′-bis(1,2,3,4-tetrahidrokarbazol-1-iliden)etan-1,2-diamin, 2-{[1-(2-(2-aminoetoksi)etilimino)-1,2,3,4-tetrahidrokarbazol-2-il-metil]-amino}etanol, antibakterijsko i antimikotsko djelovanje

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