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New Quinolines as Potential CNS Agents

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The compounds **1a–1l** and **2a–2m** were synthesized by condensation of various aryl-1-(4-aminophenyl)piperazines and substituted piperidines with substituted 4-chloroquinolines. The compounds were screened for their monoamine oxidase (MAO) inhibitory activities (in vitro) and various CNS activities (in vivo). Some compounds showed promising MAO inhibitory and antidepressant activities. The compounds did not produce acute neurological deficits and have low toxicity. Compound **1b** is the most active member of the series. Structure-activity relationships are discussed.

Neue Chinoline als potentiell CNS-wirksame Verbindungen

Die Verbindungen **1a–1l** und **2a–2m** wurden synthetisiert durch Kondensation von Aryl-1-(4-aminophenyl)piperazinen und substituierten Piperidinen mit substituierten 4-Chlorchinolinen. Die erhaltenen Verbindungen wurden in vitro auf ihre MAO-hemmende Aktivität und in vivo auf ZNS-Aktivität getestet. Einige der geprüften Verbindungen besitzen interessante pharmakologische Eigenschaften. Struktur-Aktivitäts-Beziehungen werden diskutiert.

Quinoline compounds have been found to possess a variety of biological activities such as antimalarial[1] and antihypertensive[2,3]. There are only few reports available on the central nervous system (CNS) properties of quinolines. Recently *Manlee*[4] and *Sathi* et al.[5] reported antidepressant activity in substituted quinolines. In continuation of our interest in the search of new compounds with CNS properties, it appeared of interest to synthesize various quinolines bearing a substituted piperazine or piperidine residue at position-4 of the quinoline nucleus, since a number of compounds acting on CNS possess a piperazine or piperidine residue as an essential structural component.

The synthesized compounds were studied for their effect on monoamine oxidase in vitro and their antidepressant activities.

Results and Discussions

Biochemical Studies

All 25 compounds were assayed for their in vitro MAO inhibitory activity as reported in tables 1 and 2. 15 compounds of series showed more than 80% inhibition at a concentration of $1 \cdot 10^{-4}$M. Therefore, the MAO inhibitory activity of these 15 compounds

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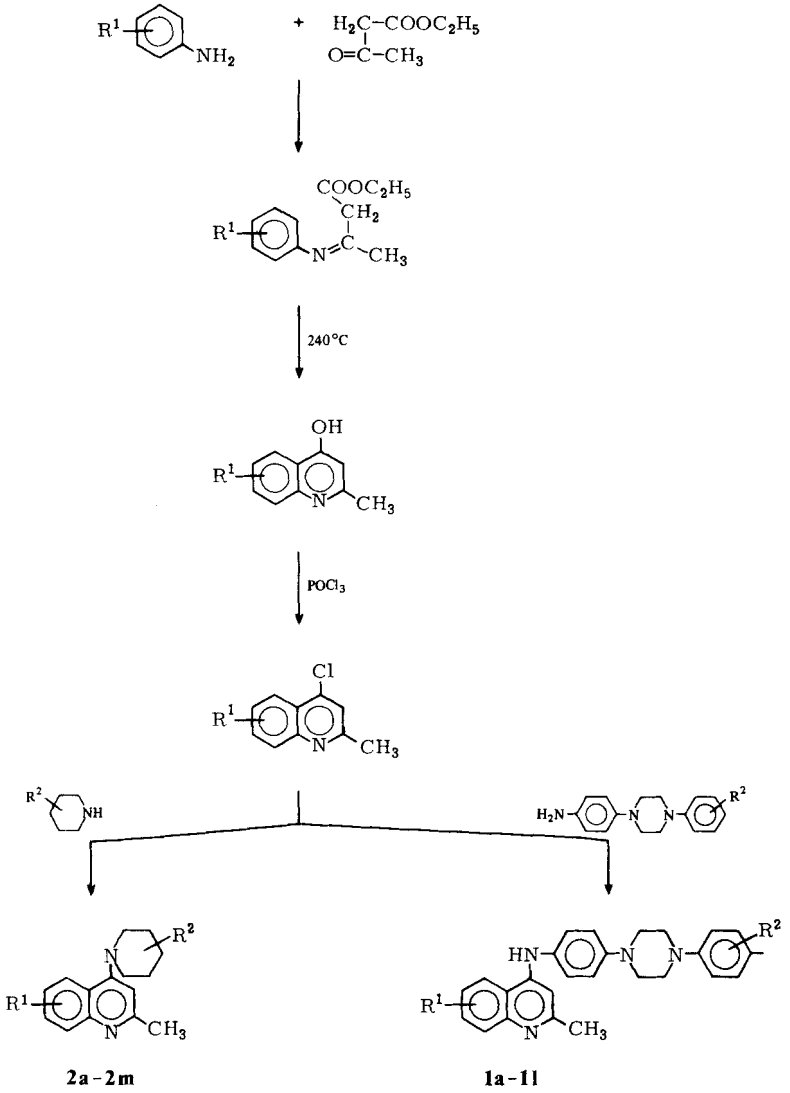

was determined at $1 \cdot 10^{-5}$M concentration. Six compounds **1a, 1b, 1e, 1i, 2c** and **2i**) showed more than 65 % inhibition at this concentration (table 3).

An examination of enzyme inhibitory activity in relation to chemical structure showed that compounds with a piperazine moiety at position 4 of the quinoline system showed better inhibitory activity than the compounds with a piperidyl moiety at this position. CH_3 or OCH_3 substitution at position 3 of quinoline evoked more inhibitory activity than CH_3 or OCH_3 substitution at position 6. Substitution of the piperidine moiety or the phenyl ring of quinoline moiety with a methyl group caused an increase in inhibitory activity.

Table 1: *Synthesis and MAO inhibitory activity of the compounds* **1**

No.	R^1	R^2	M.P. °C	Yield %	Molecular formula	% MAO inhibitory activity $1 \cdot 10^{-4}$M
1a	6,8-$(CH_3)_2$	H	195	80	$C_{28}H_{30}N_4$	86.9
1b	6,8-$(CH_3)_2$	4-CH_3	220	83	$C_{29}H_{32}N_4$	100.0
1c	6-OCH_3	H	215	75	$C_{27}H_{28}N_4O$	75.9
1d	8-OCH_3	2-CH_3	235	72	$C_{28}H_{30}N_4O$	86.2
1e	8-OCH_3	H	195	90	$C_{27}H_{28}N_4O$	93.7
1f	8-OCH_3	2-Cl	105	65	$C_{27}H_{27}N_4OCl$	96.8
1g	6-Cl	2-Cl	250	70	$C_{26}H_{24}N_4Cl_2$	71.8
1h	6-Cl	4-CH_3	198	55	$C_{27}H_{27}N_4Cl$	90.6
1i	6-Cl	2-CH_3	210	60	$C_{27}H_{27}N_4Cl$	86.4
1j	8-CH_3	2-CH_3	213	82	$C_{28}H_{30}N_4$	67.8
1k	8-CH_3	2-Cl	122	50	$C_{27}H_{27}N_4Cl$	77.8
1l	6-CH_3	2-Cl	170	90	$C_{27}H_{27}N_4Cl$	87.5

[a] Analyses: N within ± 0.4 of theoretical value.

[b] The compounds were dissolved in propylene glycol.

[c] Each experiment was done in duplicate. Values in the table are mean of two separate experiments.

Table 2: *Synthesis and MAO inhibitory activity of the compounds* **2**

No.	R^1	R^2	M.P. °C	Yield %	Molecular formula	% MAO inhibitory activity $1 \cdot 10^{-4}$M
2a	6-CH_3	4-OH, 4-C_6H_5	156	80	$C_{22}H_{24}N_2O$	78.2
2b	8-CH_3	4-OH, 4-C_6H_5	166	72	$C_{22}H_{24}N_2O$	53.1
2c	8-CH_3	2-CH_3	142	85	$C_{17}H_{22}N_2$	86.6
2d	8-CH_3	3-CH_3	110	55	$C_{17}H_{22}N_2$	74.8
2e	6-Cl	2-CH_3	130	60	$C_{16}H_{19}N_2Cl$	64.1
2f	6-Cl	3-CH_3	125	90	$C_{16}H_{19}N_2Cl$	96.8
2g	6-Cl	4-OH, 4-C_6H_5	143	75	$C_{21}H_{21}N_2OCl$	77.1
2h	8-OCH_3	4-OH, 4-C_6H_5	149	60	$C_{22}H_{24}N_2O_2$	95.8
2i	8-OCH_3	2-CH_3	128	80	$C_{17}H_{22}N_2O$	93.6
2j	6-OCH_3	4-OH, 4-C_6H_5	208	75	$C_{22}H_{24}N_2O_2$	87.4
2k	6,8$(CH_3)_2$	4-OH, 4-C_6H_5	165	90	$C_{23}H_{26}N_2O$	90.3
2l	6,8$(CH_3)_2$	2-CH_3	152	85	$C_{18}H_{24}N_2$	56.6
2m	6,8$(CH_3)_2$	3-CH_3	137	80	$C_{18}H_{24}N_2$	74.8

[a] Analyses: N within ± 0.4 of theoretical value.

[b] The compounds were dissolved in propylene glycol.

[c] Each experiment was done in duplicate. Values in the table are mean of two separate experiments.

Table 3: *MAO inhibitory activity of the compounds* **1** *and* **2**

No.	% MAO inhibitory acitivity		No.	% MAO inhibitory activity	
	$1 \cdot 10^{-5}$M	$1 \cdot 10^{-6}$M		$1 \cdot 10^{-5}$M	$1 \cdot 10^{-6}$M
1a	72.1	46.7	**1j**	67.2	42.6
1b	69.2	36.8	**1l**	58.2	–
1c	56.0	–	**2c**	72.9	39.8
1e	65.7	39.4	**2f**	60.0	–
1f	57.7	–	**2i**	70.0	24.6
1h	54.0	–	**2j**	66.5	44.9
1i	55.0	–	**2k**	55.0	–

[a] The compounds were dissolved in propylene glycol.

[b] Each experiment was done in duplicate. Values in the table are mean of two separate experiments.

Pharmacological Studies

The six compounds which showed promising in vitro MAO inhibition were studied for their general behavioural effects, and MAO inhibition in vivo, and the ALD_{50} values were determined (table 4).

Table 4

Test compound 100 mg/kg i.p.	C. N. S. Profile		Anti-depressant activity						ALD_{50} mg/kg i.p.
	Spontaneous locomotor	General awareness	L-Dopa potentiation			Reserpine reversal			
			Locomotor	Stereotype	Piloerection	Locomotor	Ptosis	Diarrhoea	
Control	+	87	107	+	+	(–) 79.4	8	++	–
1a	+	(–) 7.6	(–) 3.9	+	+	(–) 86.9	8	++	> 1000
1b	+	(+) 12.6	(+) 55.7	+++	+++	(–) 54.2*	4.6*	+	> 1000
1e	+	(+) 8.0	(+) 21.5	++	++	(–) 65.4*	6.0	+	> 1000
1j	(+)	(–) 23.9	(+) 0.9	+	+	(–) 77.6	8	++	500
2c	(+)	(–) 10.3	(–) 13.1	+	+	(–) 82.24	8	++	> 1000
2i	+	(–) 1.1	(+) 11.8	+	+	(–) 76.1	8	++	750

General behaviour was not affected to a marked extent by any test compound. Compounds **1b** and **1e** showed significant antidepressant activity. Reserpine per se caused a decrease of 79.4 % in locomotor activity from control (untreated). This reserpine induced hypokinesia was significantly antagonised by compounds **1b** and **1e**. Pretreatment with these two compounds resulted in a decrease in locomotor activity after reserpine of only 54.2 % and 65.4 % resp. Compounds **1b** and **1e** significantly reversed the reserpine induced ptosis. The control ptosis score was reduced by compounds **1b** and **1e** to 4.6 and 6.0, resp. The diarrhoea was also inhibited by these two compounds, whereas all the other compounds did not exhibit any significant reserpine reversal.

In L-dopa pretreated animals the locomotor activity stereotype and piloerection were potentiated by compounds **1a** and **1e**. The remaining compounds did not potentiate L-dopa

induced symptoms. Acute neurological toxicity did not occur with these two active compounds and the ALD_{50} values were 10 times higher than the test doses.

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Experimental Part

MP: open capillary tubes, uncorr. All the compounds were routinely checked by TLC on silica gel G for their homogeneity (benzene/methanol 8:2). *I.R. Spectra*: Perkin-Elmer 177 in KBr. *NMR Spectra*: Varian A-600 (T.M.S.). 4-Hydroxyquinolines[6], 4-chloroquinolines[7] and 4-substituted phenyl-1-(4'-aminophenyl)piperazines[8] were synthesized by known methods.

Synthesis of compounds **1a–1l** *and* **2a–2m**

0.01 mole substituted 2-methyl-4-chloroquinolines and 0.01 mole of substituted aminophenyl-aryl-piperazine or substituted piperidine in absol. ethanol were refluxed for 6–8 h with few drops of pyridine. The ethanol was distilled off. The residue was washed several times with dilute HCl and water, recrystallized from ethanol. The compounds thus synthesized are listed in tables 1 and 2 along with their analytical data.

Compound **1a** and **2b** IR (KBr): 3200 (NH), 1610 (C=N), 2860 cm^{-1} (CH_3). Compound **1a** ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.2 (s; 9H, aromatic); 7.0 (s, 3H, H-3, H-5 and H-6, aromatic); 2.9 (s, 1H, NH), 2.23 (s, 9H, Ar-$C\underline{H}_3$); 1.5 (m, 8H, 4 methylene units of piperazine).

Biochemical Studies
Determination of Monoamine Oxidase (MAO) Inhibition

MAO activity was determined by the spectrophotofluorometric method of *Krajl*[9] using partially purified rat brain preparation (16,000 · g sedimented particles) as an enzyme source and kynuramine as a substrate at a final concentration of $4 \cdot 10^{-6}$ M at pH 8. Compounds were tested at 10^{-4}, 10^{-5} and 10^{-6} M conc. After suitable dilution, optical density was recorded at 315 nm and fluorescence at 380 nm in a fluorometer.

Pharmacological Studies (In vivo)

The present study was carried out on mice of either sex weighing 20–30 g. The animals were allowed food and water ad libitum. Test compounds were administered in a dose of 100 mg/kg i.p. in the form of aqueous suspension with gum acacia.

1. *General Behavioural Profile*

Spontaneous locomotor activity, awareness, posture, gait, reflexes, autonomic symptoms (respiration, lacrimation, salivation, urination and defaecation) were observed before and 3 h after administration of the test compounds.

2. *Anti-depressant Activity*

Antidepressant effect (in vivo MAO inhibition) was observed by testing the compound for reserpine reversal and L-dopa potentiation test (*Chessin* et al.[10], *Everett* et al.[11]). Reserpine was injected in a dose of 5 mg/kg i.p. 3 h after administration of test compounds. 2 h later locomotor activity, ptosis and

diarrhoea were observed. Ptosis was scored from 0 to 4/eye according to the method of *Rubin* et al.[12]. Locomotor activity and diarrhoea were observed visually and graded in comparison to control. L-Dopa in a dose of 100 mg/kg i.p. was administered 3 h after test compounds. 1 h later locomotor activity, piloerection, stereotypy and fighting behavior were observed visually and scored in comparison to control.

3. *Toxicity Studies*

Acute neurological Toxicities

The mice were subjected to neurological tests, before and 30 min, 1, 2, 3 and 4 h after administration of test compounds for the determination of acute neurological toxicity, (*Swinyard* et al.[13]).

Approximate 50 % lethal dose (ALD_{50}) of the synthesized compounds was determined in albino mice of either sex according to the method of *Smith*[14].

4. *Statistical Analysis*

Mean scores were calculated for the groups and significance of differences from control was determined by the *Mann-Whitney* U test. The chi square method (with Yates correction) was applied to determine the significance of differences between percent changes.

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