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Syntheses of 1-Aryl-2-{4-[4-(3-oxobutyl)phenyl]piperazin-1-yl}ethanones

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Syntheses of the biologically active N^1-[4-(3-oxobutyl)phenyl]-N^4-phenacylpiperazines **1a–g** from *N*-phenylpiperazine **(2)** are described.

Synthese von 1-Aryl-2-{4-[4-(3-oxobutyl)phenyl]piperazin-1-yl}ethanonen

Die Darstellung der biologischen aktiven N^1-[4-(3-Oxobutyl)phenyl)-N^4-phenacylpiperazinen **1a–g** aus *N*-phenylpiperazin **(2)** wird beschrieben.

Lindleyin, a glucoside obtained from Aeonium Lindleyi[1], shows analgesic and antipyretic properties[2] but has only a short time action, probably due to a fast metabolism.

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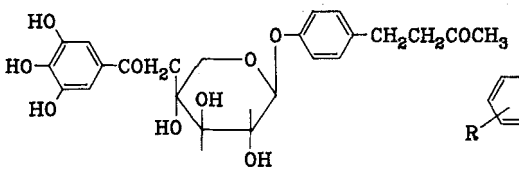
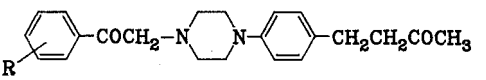
Now, we have undertaken the synthesis of a series of new phenacylpiperazines **1**, related to lindleyin, replacing the original sugar moiety by a piperazine ring, paying attention at the influence of substituents on the phenacyl group.



Lindleyin



1

The selection of test compounds for assessing the contribution of the physicochemical properties such as, hydrophobicity (π)[3,4], electronegativity (σ)[3,5] and steric volume (MR)[3,6] of the substituents on the biological activity can be carried out by manual or computer method[3]. We have applied a 2^{3-1} fractional factorial design[7,8], which allows study of three factors of the substituents by preparing only five compounds, four of them defined by the factorial design and the other one representing the midpoint of experimental domain. (Table 1).

Table 1: *Fractional factorial substituent design for three parameters*

Complund No.	Parameters* π	σ	MR	Substituent
1a	–	–	–	4-NH_2
1b	+	–	+	4-O-n-C_6H_{13}
1c	–	+	+	4-SO_2Et
1d	+	+	–	4-Br
1e	0	0	0	H

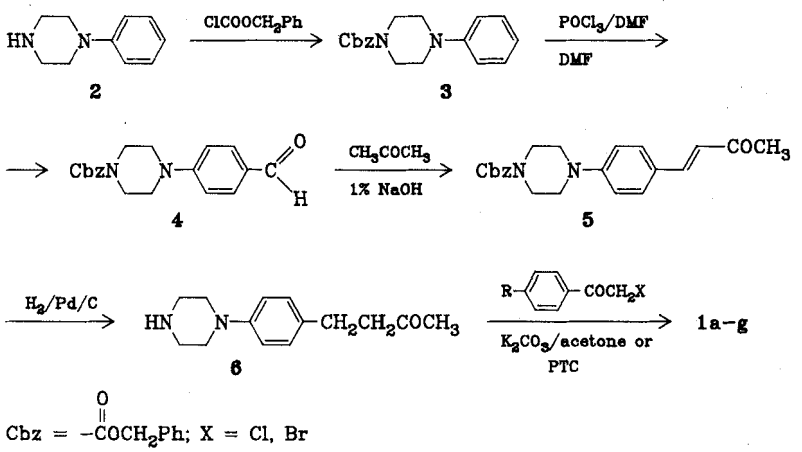
* The signs + and – indicate the high and low levels of each parameter.

Thus, we have prepared the five compounds **1a–1e** which occupy the corners of a tetrahedron and are therefore perfectly equally distributed in parameter space, giving the biggest statistical information.

The syntheses of these test compounds, and also the 4-MeO and 3,4,5-trimethoxy derivatives have been carried out as despicted in scheme 1.

First, the free nitrogen of *N*-phenylpiperazine **(2)** is protected by treatment with benzyl chloroformate as usual[9] to yield the carbamate **3** with excellent yield. **3** is formylated by treatment with phosphorus oxychloride and DMF according to *Vilsmeier-Haack*[10] to yield mainly the corresponding 4-formyl derivative **4**. The reaction of **4** with acetone in excess, in presence of 1 % sodium hydroxide, takes place as an aldol condensation, followed by a

dehydration[11] affording the expected α,β-unsaturated ketone **5**. The treatment of **5** with hydrogen at atmospheric pressure in presence of Pd/C accomplishes the reduction of the double bond and cleavage of the benzyloxycarbonyl group to afford the amine **6**. The final compounds **1** are obtained by reaction of amine **6** with the appropriate 2'-phenacyl halide (chloride or bromide) in acetone or methyl isobutylketone, a base, such as, a carbonate or bicarbonate of an alkali metal and a catalytic quantity of potassium iodide (Method A). Alternatively, this condensation can be performed under phase transfer catalysis in milder conditions with comparable yields (Method B).



	a	b	c	d	e	f	g
R	NH_2	O-n-C_6H_{13}	SO_2Et	Br	H	MeO	3,4,5-$(MeO)_3$

Compounds **1** have shown moderated analgesic and antipyretic activities in "*in vivo*" assays. The results of the full biological studies will be reported elsewhere.

Experimental Part

M. P.: open capillaries (uncorr.), Büchi 510 apparatus; *IR spectra*: Perkin-Elmer 257; *^{1}H-NMR spectra*: Varian EM-360 L (60 MHz), TMS int. stand.

1-Carbobenzoxy-4-(4-formylphenyl)piperazine **(4)**

2.3 g (15 mmol) of phosphorus oxychloride was added dropwise to 4 g of cooled and well stirred anhydrous DMF (54.8 mmol), and then the mixture was heated (60 °C) for 2 h. The reaction mixture was cooled and poured into 15 g of crushed ice, treated with aqueous sodium acetate until neutrality and extracted with ethyl acetate. The combined organic layers were washed with aqueous sodium

hydrogen carbonate, dried over sodium sulfate and the solvent was evaporated i. vac. The residue was recrystallized from ethyl acetate/n-hexane to give 2.6 g (53 %) **4**, mp. 92–93 °C. IR (KBr): 1700, 1600, 1220 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm) = 9.73 (s, 1H, CHO), 7.9–7.6 (m, 2H, 3',5'-CH arom), 7.33 (s, 5H, CH arom Cbz), 7.0–6.7 (m, 2H, 2',6'-CH arom), 5.13 (s, 2H, CH_2O), 3.8–3.2 (m, 8H, CH_2N).

1-Carbobenzoxy-4-[4-(3-oxo-1-butenyl)phenyl]piperazine **(5)**

18 ml of aqueous 1 % sodium hydroxide were added to a 50 °C thermostatized solution of **4** (23.7 g, 73.2 mmol) in 9 ml of water and enough acetone for the solution to be homogeneous, with efficient stirring. When the condensation was completed (t. l. c.) 5 % hydrochloric acid was added to pH = 1 and stirred at room temp. for 10 min to achieve the crotonization. The reaction mixture was neutralized with sodium hydrogen carbonate and extracted thoroughly with ethyl ether. The combined organic layers were dried over sodium sulfate and the solvent was evaporated i. vac. The crude product was chromatographied on silica gel using petroleum ether/ethyl acetate (7:3) as eluent to give 19.4 g (73 %) **5**, mp. 156–158 °C. IR (KBr): 1690, 1650, 1605, 1225 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.6–6.4 (m, 6H, CH arom and CH=CH), 7.34 (s, 5H, CH arom Cbz), 5.13 (s, 2H, CH_2O), 3.8–3.5 (m, 4H, CH_2NCO), 3.5–3.1 (m, 4H, CH_2N), 2.33 (s, 3H, CH_3).

1-[4-(3-Oxobutyl)phenyl]piperazine **(6)**

A 1 l flask was charged with 2 g (5.5 mmol) of **5**, a suspension containing 0.5 g of 10 % Pd/C in 650 ml of methanol and 4 or 5 drops of glacial acetic acid, and then a quick stream of hydrogen was passed through the system according to[12]. The effluent gases were tested for carbon dioxide by periodic passage through saturated aqueous barium hydroxide. The reaction was monitored by t. l. c. and by disappearance of the yellow colour of the starting ketone (about 1 h.). The reaction mixture was filtered, the filtrate concentrated to dryness and the crude material was recrystallized from acetone/chloroform/n-hexane to give 430 mg (34 %) **6**, mp. 141–145 °C (desc.). IR (KBr): 3510–2500, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.7–7.5 (broad, 1H, NH, removed by D_2O), 7.2–6.7 (m, 4H, CH arom), 3.43 (s, broad, 8H. CH_2N), 2.9–2.5 (m, 4H, CH_2), 2.13 (s, 3H, CH_3).

2-{4-[4-(3-oxobutyl)phenyl]piperazin-1-yl}ethanone 1-substituted **(1)**

General procedure A: A solution of 18.4 mmol of the corresponding phenacyl bromide in 50 ml of acetone was added dropwise to a stirred mixture of 4.27 g (18.4 mmol) **6**, 3 g (22 mmol) finely anhydrous potassium carbonate in 200 ml of acetone and kept at room temp. for 6 h. The reaction mixture was filtered and the inorganic salts washed with acetone, the organic extracts were concentrated i. vac. and the residue recrystallized from adequate solvent.

General procedure B: A mixture of 20 mmol of the corresponding phenacyl bromide, 4.64 g (20 mmol) of **6**, 11 g (80 mmol) of finely divided anhydrous potassium carbonate and 677 mg (2 mmol) of tetrabutylammonium hydrogen sulfate in 25 ml of methylene chloride was vigorously stirred at room temp. When the reaction was completed (t. l. c.), the inorganic salts were filtered and washed with 20 ml of methylene chloride. The organic solution was washed with 4 × 20 ml water, dried and concentrated to dryness. The crude product was recrystallized from adequate solvent.

Table 2: *Data of compounds* **1**

No.	Yield[a] %	M.P. (°C) (recryst. solv.)	Formula (mol. weight)	Calculated / Found C	H	N	IR[b] ν_{max}(cm^{-1})	^{1}H-NMR[c] δ-(ppm)
1a	58	138–141° (isopropanol)	$C_{22}H_{27}N_3O_2$ (365.48)	72.3 / 71.9	7.45 / 7.48	11.5 / 11.1	3350, 1700 1590	8.1–7.7 (m,2H, 2,6–CH arom.), 7.2–6.5 (m,6H,3,5–CH arom., CH′arom), 4.4–3.8 (broad, 2H, NH_2 removed by D_2O), 3.74 (s,2H, CH_2CO), 3.4–3.0 (m,4H, CH_2N–Ar), 3.0–2.5 (m,8H,CH_2N, CH_2CH_2CO), 2.11 (s,3H, CH_3CO).
1b	80	120–122° (methanol)	$C_{28}H_{38}N_2O_3$ (450.63)	74.6 / 74.5	8.50 / 8.62	6.2 / 6.4	1705, 1675 1600	8.2–7.8 (m,2H, 2,6–CH arom), 7.2–7.6 (m, 6H, 3,5–CH, CH′ arom), 4.2–3.8 (m,4H,CH_2O, CH_2CO), 3.4–3.0 (m,4H, CH_2N–Ar), 3.0–2.6 (m,8H, CH_2N, CH_2CH_2CO), 2.10 (s,3H,CH_3CO), 2.0–1.1 (m,8H, CH_2), 1.1–0.7 (m,3H, CH_3).
1c	63	146–147° (methanol)	$C_{24}H_{30}N_2O_4S$ (442.58)	65.1 / 64.8	6.83 / 6.85	6.3 / 6.2	1700, 1305, 1145	8.3–7.8 (m,4H, CH arom), 7.2–6.7 (m,4H, CH′ arom), 4.15 (s,2H, CH_2CO), 3.5–2.8 (m, 10H, CH_2N, CH_2SO_2), 2.8–2.6 (m,4H, CH_2CH_2CO), 2.10 (s,3H, CH_3CO), 1.5–1.1 (m,3H, $CH_2\underline{CH_3}$).
1d	74	135–136° (ethanol)	$C_{22}H_{25}BrN_2O_2$ (429.37)	61.5 / 61.7	5.87 / 5.92	6.5 / 6.5	1685, 1580, 1510	8.9–7.5 (m,4H, CH arom), 7.2–6.7 (m,4H, CH′ arom), 3.85 (s,2H,CH_2CO), 3.4–3.0 (m, 4H, CH_2–NAr), 3.0–2.7 (m,8H, CH_2N, CH_2CH_2CO), 2.10 (s,3H, CH_3CO).
1e	83	130–132° (ethanol)	$C_{22}H_{26}N_2O_2$ (350.46)	75.4 / 75.0	7.48 / 7.49	8.0 / 8.1	1710, 1690, 1520	8.1–7.9 (m,2H, 2,6–CH arom), 7.6–7.3 (m, 3H, 3,4,5-CH arom), 7.2–6.7 (m,4H,CH′ arom), 3.83 (s,2H, CH_2CO), 3.4–3.0 (m,4H,CH_2NAr), 3.0–2.5 (m,8H, CH_2N, CH_2CH_2CO), 2.10 (s, 3H, CH_3CO).

Forts. **Table 2:**

No.	Yield[a] %	M.P. (°C) (recryst. solv.)	Formula (mol. weight)	Calculated / Found C	H	N	IR[b] $\nu_{max}(cm^{-1})$	^{1}H-NMR[c] δ-(ppm)
1f	69	143–144° (methanol)	$C_{23}H_{28}N_2O_3$ (380.49)	72.6 / 72.4	7.42 / 7.57	7.4 / 7.6	1700, 1675, 1595	8.1–7.9 (m,2H, 2,6–CH arom), 7.2–6.7 (m, 6H, 3,5–CH, CH' arom), 3.83 (s,3H,CH_3O), 3.81 (s,2H, CH_2CO), 3.4–3.1 (m,4H, CH_2NAr), 3.0–2.4 (m,6H, CH_2N, CH_2CH_2CO), 2.10 (s, 3H, CH_3CO).
1g	81	92–96° (benzene/ cyclohexane)	$C_{25}H_{32}N_2O_5$ (440.54)	68.2 / 67.9	7.32 / 7.41	6.4 / 6.5	1710, 1690, 1585	7.4–7.2 (m,2H, 2,6–CH arom), 7.1–6.7 (m, 4H, CH' arom), 3.94 (s,9H, CH_3O), 3.81 (s,2H, CH_2CO), 3.4–3.1 (m,4H, CH_2NAr), 2.9–2.6 (m,8H, CH_2N, CH_2CH_2CO), 2.12 (s,3H, CH_3CO).

[a] Yields of pure products obtained by method A. Method B affords similar results.

[b] In KBr disc.

[c] In $DCDl_3$ solutions.

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Untersuchung des Zerfalls von HGG 12 in wäßriger Lösung

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Zur Beurteilung möglicher Risiken bei der Applikation des Soman-Antidots HGG 12 wurden Zerfallsprodukte in HGG 12-Lösungen von pH 2 und 7.4 untersucht. Bei pH 7.4 erfolgt die Umwandlung von HGG12 an der Oximgruppe, wobei über eine Nitril-Zwischenstufe das entsprechende verbrückte Pyridon entsteht. Dieses wurde anhand seines ^{1}H- und ^{13}C-NMR-Spektrums als 1-(((3-Benzoylpyridinio)methoxy)methyl)2-pyridon-acetat identifiziert. Die zu erwartende Menge an freier Blausäure wurde nicht gefunden, da Cyanid an den in 3-Stellung substituierten Pyridiniumring von HGG12 addiert wird. Daneben zerfällt HGG12 auch durch Spaltung der Aminal-acetalbrücke, wobei 3-Benzoylpyridin, Pyridin-2-aldoxim, 2-Cyanpyridin und Formaldehyd entstehen. Ein anderer Teil der intermediär gebildeten Blausäure reagiert mit Formaldehyd zu Hydroxyacetonitril.

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