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Short communication

Synthesis and antidepressant activities of some 1,3,5-triphenyl-2-pyrazolines

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Summary — Ten new 1,3,5-triphenyl-2-pyrazoline derivatives were synthesized by reacting 1,3-diphenyl-2-propen-1-one with phenylhydrazine. The chemical structures of the compounds were proved by means of their UV, IR, ^{1}H-NMR spectroscopic data and elementary analyses. The antidepressant activities of these compounds were screened by the Porsolt behavioral despair test. 1-Phenyl-3-(4-methylphenyl)-5-(3,4-dimethoxyphenyl)-2-pyrazoline and 1-phenyl-3-(4-methylphenyl)-5-(2-chloro-3,4-dimethoxyphenyl)-2-pyrazoline showed significant antidepressant activity compared with clomipramine and tranylcypromine. A methyl substituent on the phenyl ring at position 3 of the pyrazoline ring enhances the antidepressant activity; the replacement of this methyl group by chloro or bromo substituents decreases the activity. In addition, introduction of a chloro substituent to the phenyl at the position 5 decreases the antidepressant activity.

triphenyl-2-pyrazoline / antidepressant activity

Introduction

Compounds with a pyrazole structure are known to possess tranquilizing, muscle relaxant, psychoanaleptic, anticonvulsant and monoamine oxidase inhibitor activities [1–4]. In our previous studies, we synthesized some 8-thiocarbamoyl-7,8-diazabicyclo-[4.3.0]non-6-ene, 1-thiocarbamoyl-3,5-diphenyl-2-pyrazoline and 1,3,5-triphenyl-2-pyrazoline derivatives and tested their antidepressant activity [5–7]. On the other hand, 1-phenyl-3-(substituted phenyl)-5-(3,4-dimethoxyphenyl)-2-pyrazoline derivatives exhibit monoamine oxidase inhibitor properties [3]. Since we observed significant potency for these compounds, it was of interest to synthesize some new 1-phenyl-3-(4-substituted phenyl)-5-(3,4-dimethoxy- and/or 2-chloro-3,4-dimethoxyphenyl)-2-pyrazolines and evaluate them for their antidepressant activity using the 'behavioral despair test'.

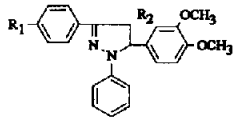
Chemistry

The formula, melting points, percentage yields, crystallization solvents and microanalysis of the compounds are listed in table I. The 1,3,5-triphenyl-2-pyrazolines (**4a–j**) were synthesized by the reaction of appropriate 1,3-diphenyl-2-propen-1-one derivatives and phenylhydrazine in glacial AcOH (scheme 1). The UV spectra of the compounds have two intensive absorption bands at 242–243 nm (log ε: 4.35) and 362–369 nm (log ε: 4.35). The IR spectra of the compounds showed a C=N stretching band at 1590 cm^{-1}. In the ^{1}H-NMR spectra, H_A, H_B and H_X protons of pyrazoline ring were seen as doublets of doublets at 3.05–3.1, 3.85–3.95 and 5.4–5.6 ppm (J_{AB} = 17, J_{AX} = 7, J_{BX} = 10 Hz), respectively. The protons belonging aromatic ring and phenyl substituents were observed at expected chemical shift and integral values. In the ^{13}C-NMR spectra, the C_3, C_4 and C_5 carbons of the pyrazoline ring were observed at 151.4, 43.2 and 64.9 ppm, respectively. The UV, IR and ^{1}H-NMR data of the compounds are presented in table II and ^{13}C-NMR spectra of compound **4a** in table III.

Pharmacology

The 1,3,5-triphenyl-2-pyrazoline derivatives (**4a–j**) were screened for their antidepressant activity using a modified Porsolt forced swimming (behavioral despair) test. The Porsolt behavioral despair test is

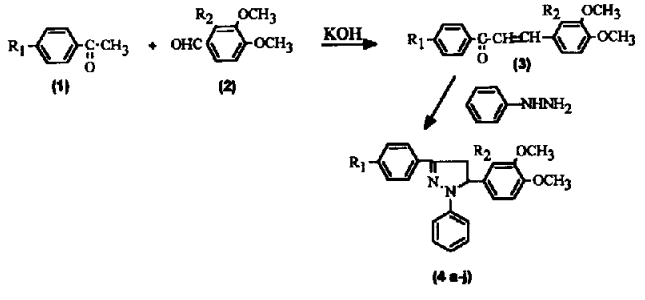
Table I. 1,3,5-Triphenyl-2-pyrazolines.



Compound	R_1	R_2	*Formula*	*Mp (°C)*	*Yield (%)*	*Crystallization solvent*[a]	*Microanalysis (%)*[b]
4a	H	H	$C_{23}H_{22}N_2O_2$	133–134	88.4	A	C, H, N
4b	Cl	H	$C_{23}H_{21}ClN_2O_2$	145–146	92.1	B	C, H, N
4c	Br	H	$C_{23}H_{21}BrN_2O_2$	154	93.6	B	C, H, N
4d	CH_3	H	$C_{24}H_{24}N_2O_2$	118–119	80.9	A	C, H, N
4e	OCH_3	H	$C_{24}H_{24}N_2O_3$	139	82.2	A	C, H, N
4f	H	Cl	$C_{23}H_{21}ClN_2O_2$	161	89.6	B	C, H, N
4g	Cl	Cl	$C_{23}H_{20}Cl_2N_2O_2$	161–162	89.3	B	C, H, N
4h	Br	Cl	$C_{23}H_{20}BrClN_2O_2$	163	90.2	B	C, H, N
4i	CH_3	Cl	$C_{24}H_{23}ClN_2O_2$	142	84.8	B	C, H, N
4j	OCH_3	Cl	$C_{24}H_{23}ClN_2O_3$	163	87.4	B	C, H, N

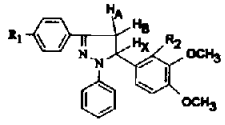
[a]A: Ethanol; B: ethanol/acetone; [b]elemental analyses for C, H, N are within ±0.4% of the theoretical values.

effective at predicting the activity of a wide variety of antidepressants for new molecules [8, 9]. Although the Porsolt forced swimming induced behavioral despair model is capable of predicting a variety of potential antidepressants, it is not devoid of bias. However, the validity of these biases is unclear, because the test gives false-positive results in cylinders with 10 cm diameter, and with central nervous system stimulants, anticholinergics and antihistaminics. For example, mice in 10 cm chambers touch the cylinder wall and bottom with their fore and hind paws and so the data may not reflect the true immobility times. We therefore employed the modified behavioral despair test [10]. In this method, the diameter of the cylinder is increased and the mice lose their ability to touch the sides and the bottom of the cylinder. They are thus forced to swim and the duration of immobility in 30 cm diameter cylinders is significantly lower than in 10 cm cylinders. The most striking result obtained by increasing the diameter of the cylinder was that anticholinergics, antihistaminics and CNS stimulants did not give false-positive results when duration of immobility was used as a criterion. Parmar *et al* [3] investigated the ability of some substituted pyrazolines to inhibit rat brain MAO and indicated that the presence of a 3,4-dimethoxyphenyl substituent at position 5 of the pyrazoline ring produced a maximal inhibition of MAO and an electron-donating substituent on the phenyl at position 5 of pyrazoline ring produced a relatively higher degree of MAO inhibition. Prompted by these findings, we synthesized some new 1,3,5-triphenyl-2-pyrazoline derivatives with chloro, bromo, methyl and methoxy (electron-donating and -withdrawing substituents) substituted phenyl or unsubstituted phenyl at position 3, and 3,4-dimethoxyphenyl and 2-chlorophenyl-3,4-dimethoxyphenyl substituent at position 5 of the pyrazoline ring. While the methyl substituent at phenyl ring at position 3 of the pyrazoline ring enhanced the antidepressant activity, the replacement of the methyl group with chloro and bromo decreased the activity. In addition, the introduction of a chloro substituent on the phenyl at position 5 decreases the antidepressant activity (compounds **4f–j**) (table IV).



Scheme 1. Synthesis of the compounds.

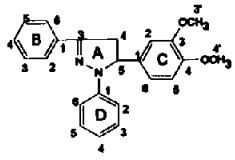
Table II. Spectral data of the compounds.



Compound	*UV (λ_{max}, nm)*	*IR (KBr, cm^{-1})*	*^{1}H-NMR ($CDCl_3$, ppm)*
4a	238, 288, 356	1598, 1519 (C=C, C=N), 1238, 1154 (C-O), 1068 (C-N)	3.15 (1H, dd, H_A), 3.80 (1H, dd, H_B), 3.83 (3H, s, -OCH_3), 3.86 (3H, s, -OCH_3), 5.19 (1H, dd, H_X), 6.76–7.90 (11H, m, aromatic proton), (J_{AB} = 17.04, J_{AX} = 7.66, J_{BX} = 9.71 Hz)
4b	241, 284 sh, 365	1600, 1522 (C=C, C=N), 1238, 1163 (C-O), 1068 (C-N)	3.07 (1H, dd, H_A), 3.81 (3H, s, -OCH_3), 3.86 (3H, s, -OCH_3), 3.90 (1H, dd, H_B), 5.37 (1H, dd, H_X), 6.73–7.84 (12H, m, aromatic proton), (J_{AB} = 17.23, J_{AX} = 7.64, J_{BX} = 10.08 Hz)
4c	241, 283 sh, 366	1599, 1500 (C=C, C=N), 1238, 1162 (C-O), 1067 (C-N)	3.10 (1H, dd, H_A), 3.80 (3H, s, -OCH_3), 3.85 (3H, s, -OCH_3), 390 (1H, dd, H_B), 5.42 (1H, dd, H_X), 6.75–7.93 (12H, m, aromatic proton), (J_{AB} = 17.05, J_{AX} = 7.52, J_{BX} = 9.89 Hz)
4d	243, 287, 358	1598, 1500 (C=C, C=N), 1233, 1159 (C-O), 1074 (C-N)	2.20 (3H, s, -CH_3), 3.06 (1H, dd, H_A), 3.83 (3H, s, -OCH_3), 3.85 (3H, s, -OCH_3), 3.86 (1H, dd, H_B), 5.40 (1H, dd, H_X), 6.65–7.85 (12H, m, aromatic proton), (J_{AB} = 17.06, J_{AX} = 7.04, J_{BX} = 10.06 Hz)
4e	240, 287 sh, 314 sh, 354	1595, 1499 (C=C, C=N), 1231, 1177 (C-O), 1068 (C-N)	3.15 (1H, dd, H_A), 3.75 (3H, s, -OCH_3), 3.82 (3H, s, -OCH_3), 3.85 (3H, s, -OCH_3), 3.94 (1H, dd, H_B), 5.40 (1H, dd, H_X), 6.62–7.84 (12H, m, aromatic proton), (J_{AB} = 16.98, J_{AX} = 7.08, J_{BX} = 9.72 Hz)
4f	245, 284 sh, 315 sh, 359, 363	1597, 1504 (C=C, C=N), 1265, 1139 (C-O), 1047 (C-N)	3.12 (1H, dd, H_A), 3.82 (3H, s, -OCH_3), 3.85 (3H, s, -OCH_3), 3.90 (1H, dd, H_B), 5.44 (1H, dd, H_X), 6.60–8.85 (12H, m, aromatic proton), (J_{AB} = 17.03, J_{AX} = 6.99, J_{BX} = 10.05 Hz)
4g	244, 284 sh, 363	1598, 1504 (C=C, C=N), 1265, 1143 (C-O), 1047 (C-N)	3.11 (1H, dd, H_A), 3.83 (3H, s, -OCH_3), 3.86 (3H, s, OCH_3), 3.88 (1H, dd, H_B), 5.42 (1H, dd, H_X), 6.76–7.90 (11H, m, aromatic proton), (J_{AB} = 17.04, J_{AX} = 7.11, J_{BX} = 10.06 Hz)
4h	249, 287 sh, 314 sh, 366	1598, 1504 (C=C, C=N), 1264, 1143 (C-O), 1046 (C-N)	3.08 (1H, dd, H_A), 3.82 (3H, s, -OCH_3), 3.86 (3H, s, -OCH_3), 3.90 (1H, dd, H_B), 5.48 (1H, dd, H_X), 6.65–7.84 (11H, m, aromatic proton), (J_{AB} = 17.12, J_{AX} = 7.06, J_{BX} = 10.01 Hz)
4i	248, 287 sh, 314 sh, 362	1598, 1499 (C=C, C=N), 1259, 1131 (C-O), 1047 (C-N)	2.23 (3H, s, CH_3), 3.07 (1H, dd, H_A), 3.82 (3H, s, -OCH_3), 3.85 (3H, s, -OCH_3), 3.88 (1H, dd, H_B), 5.45 (1H, dd, H_X), 6.82–7.90 (11H, m, aromatic proton), (J_{AB} = 17.07, J_{AX} = 6.94, J_{BX} = 9.98 Hz)
4j	249, 286 sh, 315 sh, 353	1595, 1489 (C=C, C=N), 1254, 1126 (C-O), 1042 (C-N)	3.05 (1H, dd, H_A), 3.72 (3H, s, -OCH_3), 3.83 (3H, s, -OCH_3), 3.84 (3H, s, -OCH_3), 3.92 (1H, dd, H_B), 5.49 (1H, dd, H_X), 6.62–7.87 (11H, m, aromatic proton), (J_{AB} = 17.53, J_{AX} = 7.06, J_{BX} = 10.15 Hz)

sh: shoulder, s: singlet, dd: doublet of doublets, m: multiplet.

Table III. ^{13}C-NMR data for compound **4a**.



Carbon	*A*	*B*	*C*	*D*
1	–	146.0 s	133.3 s	136.1 s
2	–	125.4 d	108.2 d	113.1 d
3	151.4 s	128.3 d	148.9 s	128.2 d
3'	–	–	56.1 d	–
4	43.2 t	128.2 d	147.5 s	117.8 d
4'	–	–	56.1 d	–
5	64.9 d	128.3 d	111.2 d	128.2 d
6	–	125.4 d	119.0 d	113.1 d

$CDCl_3$; ppm; s: singlet, d: doublet, t: triplet.

Experimental protocols

Chemistry

With the exception of 2-chloro-3,4-dimethoxybenzaldehyde (SKF/BRL45151, London, UK) all chemicals were supplied from E Merck (Darmstadt, Germany). Melting points were determined in a Thomas Hoover capillary melting point apparatus and uncorrected. UV spectra were recorded on a Shimadzu 160 A UV spectrophotometer (2.5 x 10^{-5} M, CH_3OH). IR spectra were obtained on a Perkin Elmer 1720X FT-IR spectrometer (KBr pellets). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC200, 200 MHz spectrometer in using TMS as an internal standard in $CDCl_3$. Microanalysis of the compounds were performed at the Scientific and Technical Research Council of Turkey with a Perkin Elmer Model 240C.

1,3-Diphenyl-2-propen-1-ones 3

1,3-Diphenyl-2-propen-1-ones derivatives were synthesized by condensing appropriate acetophenones **1** with 3,4-dimethoxy- and/or 2-chloro-3,4-dimethoxybenzaldehyde **2** according to the Claisen-Schmidt condensation given in the literature [11–13].

*1,3,5-Triphenyl-2-pyrazolines **4a–j***

To the solution of 0.01 mol/l of the appropriate derivative **3** in 15 ml glacial acetic acid, 1.11 g (0.01 mol/l) phenyl hydrazine was added. The mixture was refluxed for 4 h and left overnight. The reaction mixture was poured onto crushed ice and the solid mass that separated out was filtered, washed with cold ethanol, dried and crystallized from a suitable solvent.

Pharmacology

The Porsolt forced swimming test (behavioral despair test) was employed. Local breed, male (20 ± 2 g) mice were used with free access to food and water. They were housed in groups of six. On the test day the mice were dropped one at a time into a plexiglass cylinder (25 cm height, 30 cm diameter) containing 20 cm height of water at 21–23°C.

Test procedure

The synthesized compounds, clomipramine and tranylcypromine suspended in aqueous Tween 80 (0.2% w/v, 0.9% NaCl) were injected as ip (n = 6) at a 100 mg/kg (clomipramine, tranylcypromine: 10 and 20 mg/kg) dose level in a constant volume 5 ml/kg. One hour later, the mouse was dropped into the cylinder and left for 6 min. At the end of the first 2 min, the animals showing initial vigorous struggling were immobile. The immobility times of each mouse was measured over the period of 4 min.

Statistical analysis

Dunnet's test was used to evaluate the results, employing Pharmacological Calculation System, Version 4.1.

Table IV. Antidepressant activities of the compounds.

Compound		*Duration of immobility (s)*	*Change from control (%)*[a]
4a[b]		30.4 ± 4.7	–26.21
4b		37.8 ± 5.9	– 8.25
4c		34.3 ± 3.7	–16.75
4d		20.8 ± 3.6	–49.51
4e		28.1 ± 4.2	–31.80
4f		36.7 ± 5.3	–10.92
4g		36.4 ± 6.0	–11.65
4h		35.9 ± 5.8	–12.86
4i		24.5 ± 4.3	–40.53
4j		29.8 ± 6.4	–27.67
Clomipramine	10 mg/kg	27.3 ± 5.1	–33.74
Clomipramine	20 mg/kg	12.1 ± 3.1	–70.63
Tranylcypromine	10 mg/kg	22.8 ± 2.6	–44.66
Tranylcypromine	20 mg/kg	9.1 ± 2.4	–77.91
Control		41.2 ± 12.4	–

[a]95% confidence limits (Dunnet test), n = 6; [b]compounds were tested at 100 mg/kg dose level, ip.

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