Acta Pharm. **60** (2010) 73–88
10.2478/v10007-010-0009-8

Original research paper

Synthesis, anti-inflammatory, analgesic and anticonvulsant activities of 1,8-dihydro-1-aryl-8-alkyl pyrazolo(3,4-*b*)indoles

ADEL H. MANDOUR[1]*
ESLAM R. EL-SAWY[1]
KAMEL H. SHAKER[2]
MOHAMED A. MUSTAFA[3]

[1] *Chemistry Department of Natural Compounds National Research Centre, Gizza, Egypt*

[2] *Organic Chemistry NWII,1/2 University of Bayreuth, Bayreuth Germany*

[3] *Research Unit Egypt Pharmacist Co. Cairo, Egypt*

A series of 1,8-dihydro-1-aryl-8-alkyl pyrazolo(3,4-*b*)indoles **4a–j**, **5a–j** and **6a–j** has been synthesized and tested for their anti-inflammatory and anticonvulsant activities. Formation of the pyrazoloindole derivatives was achieved by treating arylhydrazones of *N*-alkyl indole-3-carboxaldehydes **1a–j**, **2a–j** and **3a–j** with ten times their mass of polyphosphoric acid as a condensing agent. The newly synthesized compounds were evaluated for their anti-inflammatory, analgesic and anticonvulsant activities compared to indomethacin, flufenamic acid and diazepam as positive controls. Detailed synthesis, spectroscopic and toxicity data are reported.

Keywords: indole-3-carboxaldehyde, anti-inflammatory activity, anticonvulsant activity, analgesic activity

Accepted January 25, 2010

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) (1). Indole, the potent basic pharmacodynamic nucleus, has been reported to possess a wide variety of biological properties, *viz*. anti-inflammatory (2–4), analgesic (5), anticonvulsant (6, 7) antibacterial and antifungal (8, 9). On the other hand, novel pyrazolo(3,4-*b*)indole nucleoside analogs have been synthesized from the corresponding 3-formyl-2-chloro and 3-cyano-2-chloro indole nucleosides by treatment with hydrazine hydrate (10) and they acted as potent and selective inhibitors of human cytomegalovirus (HCMV) *in vitro* (10). Moreover, when *p*-nitrophenylhydrazones of several acetophenones, benzaldehydes and benzophenones were treated with polyphosphoric acid (PPA) new substances containing the original nitrogen atoms were isolated from the reaction and were characterized as nitrophenylindazoles (11). Encouraged by these observations, we synthesized novel pyrazolo(3,4-*b*) indole derivatives and evaluated their anti-inflammatory, analgesic as well as anticonvulsant activities in the hope of obtaining superior pharmacological agents.

* Correspondence; e-mail: ahmandour_z@yahoo.com

EXPERIMENTAL

Melting points were determined in open capillary tubes on an Electrothermal 9100 digital melting point apparatus (Büchi, Switzerland) and were uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 analyzer (USA) and were found within ± 0.4 % of the theoretical values (Table I). IR spectra were recorded on a Perkin-Elmer 1600 FTIR (USA) in KBr pellets. The ^{1}H NMR spectra were measured with a Bruker Avance digital spectrophtometer (300 MHz) in DMSO-d_6 and chemical shifts were recorded in δ ppm relative to TMS. Mass spectra (EI) were run at 70 eV with a JEOL-JMS-AX500 mass spectrometer (Japan).

The *N*-alkylindole-3-carboxaldehydes were prepared as reported (12). Arylhydrazones **1a**, **1b**, **2a** and **2d** were prepared according to previously reported procedures (13).

*Arylhydrazones of N-alkylindole-3-carboxaldehydes (**1c-j**, **2b-j**, **3a–j**). General procedure*

A mixture of *N*-alkylindole-3-carboxaldehyde (0.001 mol) and the appropriate arylhydrazine (0.001 mol) was refluxed (2–3 h) in absolute ethanol in the presence of a few drops of acetic acid. The solvent was evaporated to half of its volume under *vacuo*. After cooling, water was added and the formed solid was filtered off, air dried and then crystallized from aqueous ethanol (85 %).

*1,8-Dihydro-1-aryl-8-alkyl pyrazolo(3,4-b) indoles (**4a-j**, **5a-j**, **6a-j**). General procedure*

Each of aryl hydrazones **1-3** was heated with 10–15 times its mass of polyphosphoric acid. Heating was continued under stirring, the temperature was slowly increased to 165 °C and the mixture was kept at this temperature for 2–3 min. Marked darkening of the mixture was observed. The reaction mixture was cooled, and then diluted with water and extracted with chloroform. The organic layer was washed with water and then dried over anhydrous sodium sulphate. The solvent was evaporated and the obtained solid product was crystallized from 85 % aqueous ethanol.

Biological assay

Animals. – Animals were obtained from the animal house colony of the National Research Center, Cairo, Egypt. All animals were allowed free access to water and were kept on a constant standard diet. All procedures involving animals were carried out in accordance with the guide for the care and use of laboratory animals and were approved by the Ethics Committee of the National Research Centre (Cairo, Egypt). Adult male albino rats (Harlan Sprague-Dawley, USA), weighing 150–180 g, were fasted for 12 hours and used for determining the anti-inflammatory activity. Adult Swiss Webster mice of both sexes (Harlan Sprague-Dawley), weighing 20–25 g, were fasted for 12–24 hours and used for determining the analgesic and anticonvulsant activities.

Table I. Physical and analytical properties of the new compounds

Compd. No.	R	X	Formula (M_r)	M.p. (°C)	Yield (%)	Analysis (%) (calc./found)		
						C	H	N
1c	CH_2CH_3	H	$C_{17}H_{17}N_3$ (263.34)	138–140	82	77.54/ 77.44	6.51/ 6.54	15.96 / 16.00
1d	CH_2Ph	H	$C_{22}H_{19}N_3$ (325.41)	280–282	75	81.20/ 81.00	5.89/ 6.00	12.91/ 12.85
1e	COPh	H	$C_{22}H_{17}N_3O$ (339.39)	180–182	70	77.86/ 77.97	5.05/ 5.21	12.38/ 12.45
1f	COC_6H_4Cl-*p*	H	$C_{22}H_{16}ClN_3O$ (373.83)	191–193	72	70.68/ 70.54	4.31/ 4.44	11.24/ 11.11
1g	COC_6H_4Cl-*o*	H	$C_{22}H_{16}ClN_3O$ (373.83)	181–183	75	70.68/ 70.55	4.31/ 4.39	11.24/ 11.36
1h	SO_2CH_3	H	$C_{16}H_{15}N_3O_2S$ (313.37)	167–179	65	61.32/ 61.21	4.82/ 4.98	13.41/ 13.61
1i	SO_2Ph	H	$C_{21}H_{17}N_3O_2S$ (375.44)	101–103	66	67.18/ 67.42	4.56/ 4.66	11.19/ 11.02
1j	$SO_2C_6H_4Br$-*p*	H	$C_{21}H_{16}BrN_3O_2S$ (454.34)	186–188	55	55.51/ 55.66	3.55/ 3.45	9.25/ 9.44
2b	CH_3	2,4 $(NO_2)_2$	$C_{16}H_{13}N_5O_4$ (339.31)	179–181	92	56.64/ 56.44	3.86/ 3.99	20.64/ 20.84
2c	CH_2CH_3	2,4 $(NO_2)_2$	$C_{17}H_{15}N_5O_4$ (353.11)	271–273	90	57.79/ 57.99	4.28/ 4.10	19.82/ 19.72
2e	COPh	2,4 $(NO_2)_2$	$C_{22}H_{15}N_5O_5$ (429.39)	318–320	90	61.54/ 61.39	3.52/ 3.30	16.31/ 16.55
2f	COC_6H_4Cl-*p*	2,4 $(NO_2)_2$	$C_{22}H_{14}ClN_5O_5$ (463.83)	325–327	88	56.97/ 56.84	3.04/ 3.21	15.10/ 15.28
2g	COC_6H_4Cl-*o*	2,4 $(NO_2)_2$	$C_{22}H_{14}ClN_5O_5$ (463.83)	227 dec.	85	56.97/ 56.79	3.04/ 3.09	15.10/ 15.33
2h	SO_2CH_3	2,4 $(NO_2)_2$	$C_{16}H_{13}N_5O_6S$ (403.06)	244–251	87	47.64/ 47.44	3.25/ 3.44	17.36/ 17.21
2i	SO_2Ph	2,4 $(NO_2)_2$	$C_{21}H_{15}N_5O_6S$ (465.44)	306–308	90	54.19/ 54.32	3.25/ 3.29	15.05/ 15.21
2j	$SO_2C_6H_4Br$-*p*	2,4 $(NO_2)_2$	$C_{21}H_{14}BrN_5O_6S$ (544.33)	243–245	88	46.34/ 46.55	2.59/ 2.77	12.87/ 12.75
3a	H	2,4,6 $(Cl)_3$	$C_{15}H_{10}Cl_3N_3$ (338.62)	98–101	67	53.20/ 53.29	2.98/ 3.00	12.41/ 12.55
3b	CH_3	2,4,6 $(Cl)_3$	$C_{16}H_{12}Cl_3N_3$ (352.65)	87–89	66	54.49/ 54.60	3.43/ 3.52	11.92/ 12.01
3c	CH_2CH_3	2,4,6 $(Cl)_3$	$C_{17}H_{14}Cl_3N_3$ (366.67)	108–111	65	55.69/ 55.88	3.85/ 3.94	11.46/ 11.55
3d	CH_2Ph	2,4,6 $(Cl)_3$	$C_{22}H_{16}Cl_3N_3$ (428.74)	114–116	54	61.63/ 61.49	3.76/ 3.64	9.80/ 9.65
3e	COPh	2,4,6 $(Cl)_3$	$C_{22}H_{14}Cl_3N_3O$ (442.73)	78–80	50	59.68/ 59.81	3.19/ 3.30	9.49/ 9.56

Table I. contd.

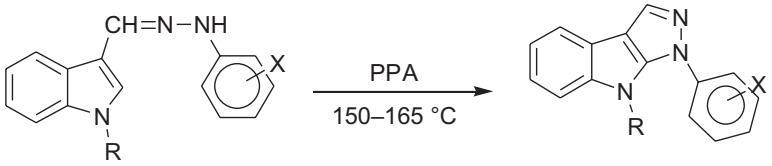
Compd. No.	R	X	Formula (M_r)	M.p. (°C)	Yield (%)	Analysis (%) (calc./found)		
						C	H	N
3f	COC_6H_4Cl-*p*	2,4,6 $(Cl)_3$	$C_{22}H_{13}Cl_4N_3O$ (477.17)	120–122	60	55.38/ 55.11	2.75/ 2.95	8.81/ 8.66
3g	COC_6H_4Cl-*o*	2,4,6 $(Cl)_3$	$C_{22}H_{13}Cl_4N_3O$ (477.17)	93–95	61	55.38/ 55.21	2.75/ 2.87	8.81/ 8.75
3h	SO_2CH_3	2,4,6 $(Cl)_3$	$C_{16}H_{12}Cl_3N_3O_2S$ (416.71)	181–183	55	46.12/ 46.21	2.90/ 2.65	10.08/ 10.21
3i	SO_2Ph	2,4,6 $(Cl)_3$	$C_{21}H_{14}Cl_3N_3O_2S$ (478.78)	66–68	45	52.68/ 52.79	2.95/ 2.80	8.78/ 8.96
3j	$SO_2C_6H_4Br$-*p*	2,4,6 $(Cl)_3$	$C_{21}H_{13}BrCl_3N_3O_2S$ (557.67)	59–61	45	45.23/ 45.44	2.35/ 2.11	7.53/ 7.66
4a	H	H	$C_{15}H_{11}N_3$ (233.27)	187–189	55	77.23/ 77.44	4.75/ 4.89	18.01/ 18.21
4b	CH_3	H	$C_{16}H_{13}N_3$ (247.29)	250 dec.	45	77.71/ 77.85	5.30/ 5.36	16.99/ 17.22
4c	CH_2CH_3	H	$C_{17}H_{15}N_3$ (261.32)	220–222	46	78.13/ 78.32	5.79/ 5.88	16.08/ 16.21
4d	CH_2Ph	H	$C_{22}H_{17}N_3$ (323.39)	200–202	48	81.71/ 81.88	5.30/ 5.55	12.99/ 13.24
4e	COPh	H	$C_{22}H_{15}N_3O$ (337.37)	282–284	61	78.32/ 78.55	4.48/ 4.66	12.46/ 12.66
4f	COC_6H_4Cl-*p*	H	$C_{22}H_{14}ClN_3O$ (371.82)	183–185	65	71.07/ 71.22	3.80/ 3.90	11.30/ 11.66
4g	COC_6H_4Cl-*o*	H	$C_{22}H_{14}ClN_3O$ (371.82)	225–227	45	71.07/ 71.06	3.80/ 3.92	11.30/ 11.32
4h	SO_2CH_3	H	$C_{16}H_{13}N_3O_2S$ (311.36)	282–284	55	61.72/ 61.52	4.21/ 4.21	13.50/ 13.11
4i	SO_2Ph	H	$C_{21}H_{15}N_3O_2S$ (373.43)	248–50	52	67.54/ 67.50	4.05/ 4.00	11.25/ 11.46
4j	$SO_2C_6H_4Br$-*p*	H	$C_{21}H_{14}BrN_3O_2S$ (452.32)	200 dec.	51	55.76/ 55.89	3.12/ 3.21	9.29/ 9.44
5a	H	2,4 $(NO_2)_2$	$C_{15}H_9N_5O_4$ (323.26)	265 dec.	66	55.73/ 55.94	2.81/ 2.88	21.66/ 21.88
5b	CH_3	2,4 $(NO_2)_2$	$C_{16}H_{11}N_5O_4$ (337.29)	380 dec.	56	56.98/ 57.00	3.29/ 3.55	20.76/ 20.55
5c	CH_2CH_3	2,4 $(NO_2)_2$	$C_{17}H_{13}N_5O_4$ (351.32)	225–227	54	58.12/ 58.22	3.73/ 3.55	19.93/ 20.01
5d	CH_2Ph	2,4 $(NO_2)_2$	$C_{22}H_{15}N_5O_4$ (413.39)	212 dec.	44	63.92/ 63.88	3.66/ 3.88	15.48/ 15.88
5e	COPh	2,4 $(NO_2)_2$	$C_{22}H_{13}N_5O_5$ (427.37)	> 300 dec.	45	61.83/ 61.94	3.07/ 3.21	16.39/ 16.55
5f	COC_6H_4Cl-*p*	2,4 $(NO_2)_2$	$C_{22}H_{12}ClN_5O_5$ (461.81)	> 400 dec.	48	57.22/ 57.32	2.62/ 2.79	15.16/ 15.56

Table I. contd.

Compd. No.	R	X	Formula (M_r)	M.p. (°C)	Yield (%)	Analysis (%) (calc./found)		
						C	H	N
5g	COC_6H_4Cl-*o*	2,4 $(NO_2)_2$	$C_{22}H_{12}ClN_5O_5$ (461.81)	276 dec.	52	57.22/ 57.01	2.62/ 2.51	15.16/ 15.33
5h	SO_2CH_3	2,4 $(NO_2)_2$	$C_{16}H_{11}N_5O_6S$ (401.35)	350 dec.	55	47.88/ 47.65	2.76/ 2.54	17.45/ 17.21
5i	SO_2Ph	2,4 $(NO_2)_2$	$C_{21}H_{13}N_5O_6S$ (463.42)	337 dec.	53	54.43/ 54.33	2.83/ 2.62	15.11/ 15.3
5j	$SO_2C_6H_4Br$-*p*	2,4 $(NO_2)_2$	$C_{21}H_{12}BrN_5O_6S$ (542.32)	246–248	50	46.51/ 46.66	2.23/ 2.42	12.91/ 13.10
6a	H	2,4,6 $(Cl)_3$	$C_{15}H_8Cl_3N_3$ (336.60)	186 dec.	55	53.52/ 53.51	2.40/ 2.55	12.48/ 12.60
6b	CH_3	2,4,6 $(Cl)_3$	$C_{16}H_{10}Cl_3N_3$ (350.63)	> 300 dec.	61	54.81/ 54.99	2.87/ 3.00	11.98/ 12.02
6c	CH_2CH_3	2,4,6 $(Cl)_3$	$C_{17}H_{12}Cl_3N_3$ (364.66)	138–140	52	55.99/ 56.02	3.32/ 3.55	11.52/ 11.77
6d	CH_2Ph	2,4,6 $(Cl)_3$	$C_{22}H_{14}Cl_3N_3$ (426.73)	266–268	44	61.92/ 62.03	3.31/ 3.44	9.85/ 9.90
6e	COPh	2,4,6 $(Cl)_3$	$C_{22}H_{12}Cl_3N_3O$ (440.71)	> 300 dec.	45	59.96/ 60.02	2.74/ 2.81	9.53/ 9.66
6f	COC_6H_4Cl-*p*	2,4,6 $(Cl)_3$	$C_{22}H_{11}Cl_4N_3O$ (475.15)	191–193	44	55.61/ 46.55	2.33/ 2.66	8.84/ 8.62
6g	COC_6H_4Cl-*o*	2,4,6 $(Cl)_3$	$C_{22}H_{11}Cl_4N_3O$ (475.15)	163–165	47	55.61/ 53.00	2.33/ 2.44	8.84/ 9.00
6h	SO_2CH_3	2,4,6 $(Cl)_3$	$C_{16}H_{10}Cl_3N_3O_2S$ (414.69)	230 dec.	55	46.34/ 46.25	2.43/ 2.13	10.13/ 10.04
6i	SO_2Ph	2,4,6 $(Cl)_3$	$C_{21}H_{12}Cl_3N_3O_2S$ (476.76)	74–76	56	52.90/ 52.72	2.54/ 2.44	8.81/ 8.89
6j	$SO_2C_6H_4Br$-*p*	2,4,6 $(Cl)_3$	$C_{21}H_{11}BrCl_3N_3O_2S$ (555.66)	Oil	44	45.39/ 45.55	2.00/ 2.02	7.56/ 7.88

Anti-inflammatory activity. – The inhibitory activity of the studied compounds on carrageenean-induced rat's paw edema was determined according to the method of Obkowicz *et al*. (14). Groups of adult male albino rats, 8 animals each, were orally dosed with tested compounds at doses of 100, 50, 25 and 5 mg kg^{-1} one hour before carrageenean challenge. Foot paw edema was induced by subplantar injection of 0.05 mL of 1 % suspension of carrageenean in saline into the plantar tissue of one hind paw. An equal volume of saline was injected into the other hind paw and served as a control. The animals were decapitated four hours after drug administration.

The average mass of edema was estimated for the treated as well as for the control group and the percentage inhibition of edema was evaluated (15). Indomethacin (5.0 mg kg^{-1}), suspended in saline, was employed as a reference drug against the test compounds.



1–3 **4–6**

1 and **4**	R	X	**2** and **5**	R	X	**3** and **6**	R	X
a	H	H	**a**	H	2,4 $(NO_2)_2$	**a**	H	2,4,6 $(Cl)_3$
b	CH_3	H	**b**	CH_3	2,4 $(NO_2)_2$	**b**	CH_3	2,4,6 $(Cl)_3$
c	CH_2CH_3	H	**c**	CH_2CH_3	2,4 $(NO_2)_2$	**c**	CH_2CH_3	2,4,6 $(Cl)_3$
d	CH_2Ph	H	**d**	CH_2Ph	2,4 $(NO_2)_2$	**d**	CH_2Ph	2,4,6 $(Cl)_3$
e	COPh	H	**e**	COPh	2,4 $(NO_2)_2$	**e**	COPh	2,4,6 $(Cl)_3$
f	COC_6H_4Cl-*p*	H	**f**	COC_6H_4Cl-*p*	2,4 $(NO_2)_2$	**f**	COC_6H_4Cl-*p*	2,4,6 $(Cl)_3$
g	COC_6H_4Cl-*o*	H	**g**	COC_6H_4Cl-*o*	2,4 $(NO_2)_2$	**g**	COC_6H_4Cl-*o*	2,4,6 $(Cl)_3$
h	SO_2CH_3	H	**h**	SO_2CH_3	2,4 $(NO_2)_2$	**h**	SO_2CH_3	2,4,6 $(Cl)_3$
i	SO_2Ph	H	**i**	SO_2Ph	2,4 $(NO_2)_2$	**i**	SO_2Ph	2,4,6 $(Cl)_3$
j	$SO_2C_6H_4Br$-*p*	H	**j**	$SO_2C_6H_4Br$-*p*	2,4 $(NO_2)_2$	**j**	$SO_2C_6H_4Br$-*p*	2,4,6 $(Cl)_3$

Scheme 1

Data are expressed as mean ± SEM. The results of carrageenean-induced paw edema are expressed as percentage of change from the control (pre-drug) values. Differences between the vehicle control and treatment groups were tested using one-way ANOVA followed by multiple comparisons by Duncan's multiple range tests.

Analgesic activity. – The method of Okun *et al.* (16) was used to induce writhing. The test compounds and the reference drugs flufenamic acid and indomethacine were prepared as a suspension in 2 % Tween 80. A sensitivity test was carried out one day before drug administration when the animals were injected (*i.p.*) with 0.2–0.25 mL of 0.02 % freshly prepared solution of *p*-benzoquinone in distilled water. Animals showing writhing to *p*-benzoquinone within 30 minutes were chosen for studying the analgesic activity. On the following day, mice were divided into 13 groups of 6 animals each. The drugs were administered orally according to the following protocol: one group received 2 % Tween 80 (solvent and negative control), the second group received flufenamic acid as reference (20 mg kg^{-1}), and the third group received indomethacine (5 mg kg^{-1}), while the other groups received doses of the tested compounds 100, 50, 25 and 5 mg kg^{-1}. One hour latter, 0.02 % solution of *p*-benzoquinone was administered (*i.p.*). The animals were observed for 30 minutes after injection of the irritant, during which time the animals showing writhing were counted (writhing is defined as stretch, torsion to one side, drawing up of hind leg, retraction of the abdomen, so that the belly touches the floor). All writhing is considered as a positive response. The analgesic activity was expressed as the percent protection.

Anticonvulsant activity. – Mice of both sexes weighing 20–25 g were used and injected intraperitoneally with 2 % Tween 80 (control) and 5 mg kg^{-1} diazepam (reference drug). Other groups received tested components at doses 5, 25 and 50 mg kg^{-1}. One hour after the drug administration, animals were stimulated through an ear electrode of 50 mA as a signal stimulator for 0.2 s (17). Characteristic of an electric shock seizure are a tonic limb flexion for 1 to 2 s, followed by a tonic limb extension for roughly 10 to 12 s, and finally generalized clonic movement for 12 s. Only abolishment of the hind limb tonic extensor spasm is recorded as the measure of anticonvulsant potency. The tonic component is considered abolished if the hind leg extension does not exceed a 90° angle with the plane of the body. Animals showing protection against convulsion were counted in each group. The anticonvulsant activity was expressed as the percent protection.

RESULTS AND DISCUSSION

The starting materials, arylhydrazones **1-3** were prepared through the condensation reaction of *N*-alkylindole-3-carboxaldehydes with substituted phenylhydrazines in refluxing absolute ethanol.

The structure of the new arylhydrazones **1-3** was confirmed based on their precise elemental analyses (Table I) and spectroscopic data (Table II). The ^{1}H NMR spectra of the latter compounds revealed singlet signals at 8.5–8.75 ppm for CH=N and singlet signals from 7.9 to 8.2 ppm for H-2 of indole nucleus, besides other signals (Table II). For example, the ^{1}H NMR spectrum of compound **1c** revealed signals at 9.8 (s, 1H, NH, exchangeable with D_2O), 8.75 (s, 1H, CH=N), 8.2 (s, 1H, H-2 indole), 7.2–7.8 (m, 9H, aromatic protons), 4.0 (q, 2H, CH_2) and 1.9 ppm (t, 3H, CH_3). Its IR spectrum showed absorption bands at 3330 (NH), 1680 (C=N) and 1660 cm^{-1} (C=C).

Treatment of compounds **1-3** with polyphosphoric acid as a condensing agent at 150–165 °C for 2–3 min led to the formation of 1,8-dihydro-1-phenyl-8-alkyl-pyrazolo (3,4-*b*) indoles (**4a-j**), 1,8-dihydro-1-(2,4-dinitrophenyl)-8-alkyl-pyrazolo(3,4-*b*) indoles (**5a-j**) and 1,8-dihydro-1-(2,4,6-trichlorophenyl)-8-alkyl-pyrazolo(3,4-*b*) indoles (**6a-j**), respectively, in good yield (44–66 %). The structure of the products was supported by precise element analyses (Table I), IR, ^{1}H NMR and mass spectral data (Table II).

There is no doubt about the proposed structure of the new target compounds pyrazoloindoles **4-6**. First, the absence of NH absorption bands in the IR spectra of compounds **4-6** which appeared in the starting ones **1-3**. Second, their ^{1}H NMR spectra lack the singlet signals at δ 7.9–8.2 ppm of H-2 indole nucleus and singlet signals of the anilic protons, and revealed new singlet signals at δ 7.6–7.8 ppm of the pyrazole ring. This is a good evidence for the proposed structures **4-6**. For example, the IR spectrum of compound **4c** showed absorption bands at 1620 (C=N) and 1600 cm^{-1} (C=C). Its ^{1}H NMR spectrum revealed signals at δ 7.71 (s, 1H, H-pyrazole), 7.0–7.56 (m, 9H, Ar-H), 4.0 (q, 2H, CH_2) and 1.6 ppm (t, 3H, CH_3). Its mass spectrum is in accordance with the proposed structure, which showed a molecular ion peak at m/z = 261 (65 %) and a base peak at m/z = 105 (100 %) besides the other fragments, as illustrated in Table II. The physical and analytical data of the target compounds **4-6** are given in Table I and the spectroscopic data in Table II.

Table II. Spectral characterization of the new compounds

Compd. No.	IR (ν_{max} cm^{-1})	^{1}H NMR (δ, ppm)	Mass (*m/z*, %)
1c	3330 (NH), 1680 (C=N), 1660 (C=C)	9.8 (s, 1H, NH), 8.75 (s, 1H, CH=N), 8.2 (s, 1H, H-2 indole), 7.02–7.87 (m, 9H, Ar-H), 4.0 (q, 2H, CH_2), 1.9 (t, 3H, CH_3)	263 [M$^+$] (51), 156 (32), 144 (20), 105 (100), 77 (60)
1d	3228 (NH), 1620 (C=N), 1601 (C=C)	9.5 (1H, s, NH), 8.75 (1H, s, CH=N), 8.2 (1H, s, H-2 indole), 7.02–7.54 (14H, m, Ar-H), 5.5 (2H, s, CH_2)	325 [M$^+$] (25), 142 (30), 115 (60), 105 (100), 91(60)
1e	3218 (NH), 1670 (C=O), 1620 (C=N), 1577 (C=C)	9.3 (s, 1H, NH), 8.75 (s, 1H, CH=N), 8.1 (s, 1H, H-2 indole), 7.01–7.48 (m, 14H, Ar-H)	
1f	3232 (NH), 1678 (C=O), 1620 (C=N), 1577 (C=C), 740 (Cl)	9.3 (s, 1H, NH), 8.54 (s, 1H, CH=N), 8.1 (s, 1H, H-2 indole), 7.01–7.48 (m, 13H, Ar-H)	373 [M$^+$] (10), 375 [M$^+$+2] (3), 193 (40), 105 (100), 77 (60)
1g	3222 (NH), 1675 (C=O), 1620 (C=N), 1578 (C=C), 740 (Cl)	9.8 (s, 1H, NH), 8.54 (s, 1H, CH=N), 8.1 (s, 1H, H-2 indole), 7.01–7.58 (m, 13H, Ar-H)	
1h	3218 (NH), 1621 (C=N), 1598 (C=C), 1180&1380 (SO_2)	9.8 (s, 1H, NH), 8.55 (s, 1H, CH=N), 8.1 (s, 1H, H-2 indole), 7.02–7.58 (m, 9H, Ar-H), 2.81 (s, 3H, CH_3)	313 [M$^+$] (56), 220 (30), 142 (100), 107 (10), 105 (20)
1i	3225 (NH), 1621 (C=N), 1578 (C=C), 1181&1365 (SO_2)	9.9 (s, 1H, NH), 8.54 (s, 1H, CH=N), 8.12 (s, 1H, H-2 indole), 7.02–7.48 (m, 14H, Ar-H)	
1j	3250 (NH), 1621 (C=N), 1575 (C=C), 1183&1375 (SO_2), 780 (Br)	9.7 (s, 1H, NH), 8.54 (s, 1H, CH=N), 8.12 (s,1H, H-2 indole), 7.01–7.58 (m, 13H, Ar-H)	374 [M$^+$] (20), 376 [M$^+$+2] (18), 141 (40), 105 (100), 76 (50)
2b	3333 (NH), 1654 (C=N), 1601 (C=C)	9.9 (s, 1H, NH), 8.45 (s, 1H, CH=N), 8.21 (s, 1H, H-2 indole), 7.01–7.77 (m, 7H, Ar-H), 3.1 (s, 3H, CH_3)	
2c	3332 (NH), 1645 (C=N), 1578 (C=C)	9.87 (s, 1H, NH), 8.55 (s, 1H, CH=N), 8.21 (s,1H, H-2 indole), 7.01–7.57 (m, 7H, Ar-H), 4.1 (q, 2H, CH_2), 1.6 (t, 3H, CH_3)	339 [M$^+$] (10), 195 (10), 156 (60), 130 (100), 105 (20)
2e	3228 (NH), 1678 (C=O), 1621 (C=N), 1575 (C=C)	9.5 (s, 1H, NH), 8.55 (s, 1H, CH=N), 8.2 (s, 1H, H-2 indole), 7.01–7.55 (m, 12H, Ar-H)	
2f	3330 (NH), 1698 (C=O), 1620 (C=N), 1575 (C=C), 740 (Cl)	9.9 (s, 1H, NH), 8.54 (s, 1H, CH=N), 8.1 (s, 1H, H-2 indole), 7.01–7.48 (m, 11H, Ar-H)	463 [M$^+$](3), 465 [M$^+$+2] (0.7), 195 (20), 117 (100), 105 (70)
2g	3330 (NH), 1670 (C=O), 1622 (C=N), 1545 (C=C), 740 (Cl)	9.9 (s, 1H, NH), 8.75 (s, 1H, CH=N), 8.12 (s, 1H, H-2 indole), 7.01–7.58 (m, 11H, Ar-H)	

Table II. contd.

Compd. No.	IR (ν_{max} cm^{-1})	^{1}H NMR (δ, ppm)	Mass (*m/z*, %)
2h	32181 (NH), 1621 (C=N), 1578 (C=C), 1181&1365 (SO_2)	10.1 (s, 1H, NH), 8.75 (s, 1H, CH=N), 7.99 (s, 1H, H-2 indole), 7.02–7.58 (m, 7H, Ar-H), 2.81 (s, 3H, CH_3)	
2i	3219 (NH), 1628 (C=N), 1548 (C=C), 1185&1375 (SO_2)	9.3 (s, 1H, NH), 8.54 (s, 1H, CH=N), 8.2 (s, 1H, H-2 indole), 7.02–7.48 (m, 12H, Ar-H)	465 [M$^+$] (30), 193 (60), 142 (100), 105 (30), 77 (61)
2j	3220 (NH), 1622 (C=N), 1545 (C=C), 1183&1365 (SO_2), 781 (Br)	9.9 (s, 1H, NH), 8.54 (s, 1H, CH=N), 8.21 (s, 1H, H-2 indole), 7.01–7.48 (m, 11H, Ar-H)	
3a	3350&3218 (NH), 1624 (C=N), 1578 (C=C)	9.3*&9.9* (2s, 2H, 2NH), 8.55 (s, 1H, CH=N), 8.21 (s, 1H, H-2 indole), 7.01–7.47 (m, 6H, Ar-H)	337 [M$^+$](20), 339 [M$^+$+2] (17), 401 [M$^+$+4] (9), 403 [M$^+$+6] (1), 130 (100), 105 (30)
3b	3318 (NH), 1620 (C=N), 1577 (C=C)	9.7 (s, 1H, NH), 8.55 (s, 1H, CH=N), 8.21 (s, 1H, H-2 indole), 7.01–7.47 (m, 6H, Ar-H), 3.1 (s, 3H, CH_3)	
3c	3318 (NH), 1622 (C=N), 1585 (C=C)	9.77 (s, 1H, NH), 8.45 (s, 1H, CH=N), 8.2 (1H s, H-2 indole), 7.01–7.57 (m, 6H, Ar-H), 4.2 (q, 2H, CH_2), 1.9 (t, 3H, CH_3)	
3d	3222 (NH), 1620 (C=N), 1645 (C=C)	9.3 (s, 1H, NH), 8.7 (s, 1H, CH=N), 8.2 (s, 1H, H-2 indole), 7.0–7.55 (m, 11H, Ar-H), 5.56 (s, 2H, CH_2)	427 [M$^+$] (10), 429 [M$^+$+2] (7), 431 [M$^+$+4] (1), 433 [M$^+$+6] (0.2), 232 (30), 105 (40), 91 (100)
3e	3222 (NH), 1699 (C=O), 1621 (C=N), 1545 (C=C)	9.3 (s, 1H, NH), 8.55 (s, 1H, CH=N), 8.2 (s, 1H, H-2 indole), 7.01–7.75 (m, 11H, Ar-H)	
3f	3333 (NH), 1678 (C=O), 1621 (C=N), 1545 (C=C), 741 (Cl)	10.2 (s, 1H, NH), 8.54 (s, 1H, CH=N), 8.1 (s, 1H, H-2 indole), 7.01–7.55 (m, 10H, Ar-H)	475 [M$^+$] (10), 477 [M$^+$+2] (7), 479 [M$^+$+4] (1), 481 [M$^+$+6] (0.2), 232 (30), 117 (100), 105 (20)
3g	3350 (NH), 1679 (C=O), 1622 (C=N), 1575 (C=C), 751 (Cl)	9.99 (s, 1H, NH), 8.45 (s, 1H, CH=N), 8.12 (s, 1H, H-2 indole), 7.01–7.58 (m, 10H, Ar-H)	
3h	3219 (NH), 1622 (C=N), 1535 (C=C), 1181&1357 (SO_2)	10.1 (s, 1H, NH), 8.45 (s, 1H, CH=N), 8.0 (s, 1H, H-2 indole), 7.01–7.48 (m, 7H, Ar-H), 2.81 (s, 3H, CH_3)	414 [M$^+$] (16), 416 [M$^+$+2] (9), 418 [M$^+$+4] (3), 420 [M$^+$+6] (0.7), 231 (30), 142 (100), 105 (20)
3i	3235 (NH), 1622 (C=N), 1554 (C=C), 1181&1385 (SO_2)	9.5 (s, 1H, NH), 8.54 (s, 1H, CH=N), 8.2 (s, 1H, H-2 indole), 7.01–7.58 (m, 11H, Ar-H)	
3j	3218 (NH), 1621 (C=N), 1557 (C=C), 1137& 1375 (SO_2), 758 (Br)	8.9 (s, 1H, NH), 8.50 (s, 1H, CH=N), 7.01–8.21 (m, 10H, Ar-H)	

Table II. contd.

Compd. No.	IR (ν_{max} cm^{-1})	^{1}H NMR (δ, ppm)	Mass (*m/z*, %)
4a	3280 (NH), 1620 (C=N), 1599 (C=C)	9.1 (s, 1H, NH), 7.67 (s, 1H, H-pyrazole), 7.0–7.45 (m, 9H, Ar-H)	233 [M$^+$] (35), 129 (6),105 (100), 93 (10), 77 (50)
4b	1628(C=N), 1601 (C=C)	7.71(s, 1H, H-pyrazole), 7.0–7.47 (m, 9H, Ar-H), 3.2 (s, 3H, CH_3)	247 [M$^+$] (10), 129 (10), 105 (100), 77 (30), 52 (10)
4c	1620 (C=N), 1600 (C=C)	7.71 (s, 1H, H-pyrazole), 7.0–7.56 (m, 9H, Ar-H), 4.0 (q, 2H, CH_2), 1.6 (t, 3H, CH_3)	261 [M$^+$] (65), 157 (10), 105 (100), 77 (80)
4d	1618(C=N), 1578 (C=C)	7.78 (s, 1H, H-pyrazole), 7.0–7.56 (m, 14H, Ar-H), 5.56 (s, 2H, CH_2)	323 [M$^+$] (30), 209 (10), 105 (10), 91 (100), 77 (60), 78 (40)
4e	1678 (C=O), 1620 (C=N), 1578 (C=C)	7.76 (s, 1H, H-pyrazole), 7.0–7.58 (m, 14H, Ar-H)	337 [M$^+$] (20), 309 (2), 140 (10), 139 (100), 77 (40)
4f	1676 (C=O), 1618 (C=N), 1575 (C=C), 740 (Cl)	7.78 (s, 1H, H-pyrazole), 7.0–7.48(m, 13H, Ar-H)	371 [M$^+$] (8), 373 [M$^+$+2] (2), 309 (10), 191 (100), 105 (2), 77(60)
4g	1670 (C=O), 1620 (C=N), 1601 (C=C), 741 (Cl)	7.78 (s, 1H, H-pyrazole), 7.0–7.50(m, 13H, Ar-H)	371 [M$^+$] (10), 373 [M$^+$+2] (3), 336 (30), 231 (100), 105 (10), 77 (40)
4h	1620 (C=N), 1598 (C=C), 1180&1380 (SO_2)	7.81(s, 1H, H-pyrazole), 7.0–7.50(m, 9H, Ar-H), 2.81 (s, 3H, SO_2CH_3)	311 [M$^+$] (25), 207 (20), 129 (30), 105 (100), 77 (50)
4i	1618 (C=N), 1598 (C=C), 1180&1380 (SO_2)	7.80 (s, 1H, H-pyrazole), 7.0–7.58(m, 14H, Ar-H)	373 [M$^+$] (15), 269 (18), 243 (20), 141 (100), 105 (10), 77 (20)
4j	1618 (C=N), 1601 (C=C), 1180&1380 (SO_2), 780 (Br)	7.80 (s, 1H, H-pyrazole), 7.0–7.58(m, 13H, Ar-H)	451 [M$^+$] (40), 453 [M$^+$+2] (3), 241 (100), 105 (10), 77 (50)
5a	3128 (NH), 1635 (C=N), 1578 (C=C)	9.3 (s, 1H, NH), 7.77 (s, 1H, H-pyrazole), 7.0–7.45 (m, 7H, Ar-H)	323 [M$^+$] (45), 195 (30), 167 (40), 129 (20), 117 (100)
5b	1624(C=N), 1600 (C=C)	7.71(s, 1H, H-pyrazole), 7.0–7.47 (m, 7H, Ar-H), 3.2 (s, 3H, CH_3)	337 [M$^+$] (14), 195 (100), 167 (20), 129 (20), 76 (10)
5c	1635 (C=N), 1545 (C=C)	7.78 (s, 1H, H-pyrazole), 7.0–7.58 (m, 7H, Ar-H), 4.1 (q, 2H, CH_2), 1.9 (t, 3H, CH_3)	351 [M$^+$] (5), 195 (100), 167 (30), 76 (40)
5d	1646 (C=N), 1578 (C=C)	7.67 (s, 1H, H-pyrazole), 7.0–7.48 (m, 12H, Ar-H), 5.56 (s, 2H, CH_2)	413 [M$^+$] (35), 195 (40), 129 (20), 91 (100), 76 (10)
5e	1680 (C=O), 1620 (C=N), 1545 (C=C)	7.67 (s, 1H, H-pyrazole), 7.0–7.61 (m, 12H, Ar-H)	427 [M$^+$] (35), 193 (100), 195 (10), 167 (20), 105 (30), 77 (20)
5f	1678 (C=O), 1618 (C=N), 1545 (C=C), 740 (Cl)	7.77 (s, 1H, H-pyrazole), 7.0–7.48 (m, 11H, Ar-H)	461[M$^+$] (15), 463 [M$^+$+2] (4), 167 (20), 117 (100), 111/113 (8/2)

Table II. contd.

Compd. No.	IR (ν_{max} cm^{-1})	^{1}H NMR (δ, ppm)	Mass (*m/z*, %)
5g	1678 (C=O), 1620 (C=N), 1578 (C=C), 741 (Cl)	7.76 (s, 1H, H-pyrazole), 7.0–7.46 (m, 11H, Ar-H)	461 [M$^+$] (35), 463 [M$^+$+2] (17), 265 (100), 167 (20), 76 (40)
5h	1628 (C=N), 1601 (C=C), 1180&1380 (SO_2)	7.78 (s, 1H, H-pyrazole), 7.0–7.56 (m, 7H, Ar-H), 2.81 (3H, s, SO_2CH_3)	
5i	1618 (C=N), 1598 (C=C), 1180&1380 (SO_2)	7.77 (s, 1H, H-pyrazole), 7.0–7.48 (m, 12H, Ar-H)	
5j	1620 (C=N), 1578 (C=C), 1180&1380 (SO_2), 780 (Br)	7.81 (s, 1H, H-pyrazole), 7.0–7.48 (m, 11H, Ar-H)	
6a	3228 (NH), 1620 (C=N), 1601 (C=C), 741 (Cl)	9.3 (s, 1H, NH), 7.78 (s, 1H, H-pyrazole), 7.0–7.46 (m, 6H, Ar-H)	335 [M$^+$] (30), 337 [M$^+$+2] (30), 339 [M$^+$+4] (9), 401 [M$^+$+6] (1), 111/113 (8/2), 117 (100), 77 (60)
6b	1635 (C=N), 1601(C=C), 740 (Cl)	7.78 (s, 1H, H-pyrazole), 7.0–7.45 (m, 6H, Ar-H), 3.1 (s, 3H, CH_3)	
6c	1635 (C=N), 1545 (C=C), 741 (Cl)	7.77 (s, 1H, H-pyrazole), 7.0–7.48 (m, 6H, Ar-H), 4.1 (q, 2H, CH_2), 1.6 (t, 3H, CH_3)	
6d	1646 (C=N), 1578 (C=C), 741 (Cl)	7.77 (s, 1H, H-pyrazole), 7.0–7.48 (m, 11H, Ar-H), 5.56 (s, 2H, CH_2)	
6e	1678 (C=O), 1620 (C=N), 1575 (C=C), 741 (Cl)	7.67 (s, 1H, H-pyrazole), 7.0–7.61 (m, 11H, Ar-H)	
6f	1700 (C=O), 1620 (C=N), 1575 (C=C), 740 (Cl)	7.81 (s, 1H, H-pyrazole), 7.0–7.48 (m, 10H, Ar-H)	
6g	1698 (C=O), 1620 (C=N), 1575 (C=C), 740 (Cl)	7.80 (s, 1H, H-pyrazole), 7.0–7.58 (m, 10H, Ar-H)	473 [M$^+$] (30), 475[M$^+$+2] (24), 477 [M$^+$+4] (18), 479 [M$^+$+6] (3), 111/113 (10/2), 191 (100), 76 (20)
6h	1620 (C=N), 1578 (C=C), 1180&1380 (SO_2), 750 (Cl)	7.77 (s, 1H, H-pyrazole), 7.0–7.56 (m, 6H, Ar-H), 2.81 (s, 3H, SO_2CH_3)	
6i	1621 (C=N), 1575 (C=C), 1180&1380 (SO_2), 748 (Cl)	7.80 (s, 1H, H-pyrazole), 7.0–7.55 (m, 11H, Ar-H)	475 [M$^+$] (45), 477[M$^+$+2] (40), 479 [M$^+$+4] (18), 481 [M$^+$+6] (1), 255 (30), 191 (10),109 (100)
6j	1621 (C=N), 1535 (C=C), 1180&1380 (SO_2), 780 (Br), 741 (Cl)	7.81 (s, 1H, H-pyrazole), 7.0–7.45 (m, 10H, Ar-H)	

Table III. Effect of the most active pyrazoloindoles on carrageenean induced paw oedema in rat

Compd.[a]	Dose (mg kg^{-1})	Inhibition (%)	Compd.[a]	Dose (mg kg^{-1})	Inhibition (%)
4d	100	24	**5g**	100	54
	50	19		50	39
4e	100	54	**5j**	100	54
	50	50		50	39
4f	100	62	**6d**	100	64
	50	57		50	65
4g	100	78	**6e**	100	24
	50	63		50	19
4j	100	54	**6f**	100	69
	50	50		50	57
5d	100	69	**6g**	100	84
	50	65		50	69
5e	100	54	**6j**	100	54
	50	39		50	50
5f	100	54	Negative control[a]	0	0
	50	39	Indomethacin	5	51

[a] Negative control: saline; also solvent for test compounds and indomethacin.

Table IV. Analgesic activity of the most active compounds[a]

Compd.[b]	Dose (mg kg^{-1})	Protection (%)	Compd.[b]	Dose (mg kg^{-1})	Protection (%)
4e	100	66	**5i**	100	33
	50	50		50	16
4f	100	66	**6d**	100	66
	50	66		50	33
4g	100	83	**6f**	100	100
	50	50		50	66
4j	100	83	**6g**	100	100
	50	50		50	50
5d	100	50	**6j**	100	100
	50	16		50	33
5f	100	33	Negative control[b]	0	0
	50	16	Indomethacin	5	63
5g	100	33	Flufenamic acid	20	66
	50	16			

[a] *p*-Benzoquinone was used for inducing writhing in mice.
[b] Negative control: 2 % Tween 80; also solvent test compounds and reference drugs.

The newly synthesized compounds **4-6** were evaluated for their anti-inflammatory activity against carrageenean induced rat's paw oedema by administration of 100, 50, 25 and 5 mg kg^{-1} (*p.o.*) using indomethacin as a reference drug (5 mg kg^{-1}). None of the tested compounds showed antiinflammatory activity at doses of 3 and 5 mg kg^{-1}, whereas compounds **4e, 4f, 4g, 4j, 5d, 5g, 6d, 6f, 6g** and **6j** exhibited remarkable anti-inflammatory activity ranging from 30 to 65 % at a dose of 50 mg kg^{-1} and from 54 to 78 % at a

*Table V. Anticonvulsant activity of compounds **4a–j**, **5a–j** and **6a–j***

Compd.[a]	Dose (mg kg^{-1})	Protection (%)	Compd.[a]	Dose mg kg^{-1}	Protection (%)
4a	50	33	**5f**	50	66
	25	0		25	50
4b	50	33	**5g**	50	66
	25	0		25	50
4c	50	33	**5h**	50	50
	25	0		25	33
4d	50	33	**5i**	50	33
	25	0		25	16
4e	50	33	**5j**	50	66
	25	0		25	33
4f	50	66	**6a**	50	50
	25	50		25	33
4g	50	66	**6b**	50	33
	25	50		25	16
4h	50	16	**6c**	50	33
	25	16		25	16
4i	50	16	**6d**	50	33
	25	16		25	33
4j	50	50	**6e**	50	33
	25	33		25	33
5a	50	33	**6f**	50	66
	25	16		25	50
5b	50	33	**6g**	50	83
	25	16		25	50
5c	50	33	**6h**	50	16
	25	16		25	0
5d	50	33	**6i**	50	16
	25	16		25	0
5e	50	66	**6j**	50	66
	25	33		25	33
Negative control[a]	0	0			
Diazepam	5	50			

[a] Negative control: 2 % Tween 80; also solvent for test compounds and diazepam.

dose of 100 mg kg^{-1}. The results of the tested compounds are given in (Table III). Higher anti-inflammatory activity of the previously mentioned compounds compared to the others may be due to the presence of the halo atoms in their skeletons. The most potent compounds were **6g** and **4g** with anti-inflammatory activity of 85 and 79 % at a dose of 100 mg kg^{-1} and 70 and 64 % at a dose of 50 mg kg^{-1}, respectively.

None of the tested components showed analgesic activity at doses of 25 and 5 mg kg^{-1}, but the chosen compounds showed remarkable analgesic activity at a dose of 100 mg kg^{-1} (Table IV). Compounds **4e, 4f, 4g, 4j, 6d, 6f, 6g** and **6j** showed higher activity at a dose of 100 mg kg^{-1} than the reference drug flufenamic acid at a dose of 20 mg kg^{-1}. The protection of these compounds ranged from 66 to 100 %, while compounds **4f** and **6f**, at a dose of 50 mg kg^{-1}, showed the same analgesic activity as the reference drug flufenamic acid. From the data in Table IV it is clear that only compounds **6f** and **6g** showed high analgesic activity at a dose of 50 mg kg^{-1} of 67 and 83 %, while at a dose of 25 mg kg^{-1} they showed 33 and 50 % protection.

Compounds **4-6** exhibited remarkable anticonvulsant activity (Table V). Compounds **4f, 4g, 5f, 5g, 5j, 6f, 6g** and **6j** at a dose of 50 mg kg^{-1} showed anticonvulsant activity higher than that of diazepam at 5 mg kg^{-1}. On the other hand, compounds **4f, 4g, 5f, 5g, 6f** and **6g** at a dose of 25 mg kg^{-1} showed 50 % anticonvulsant protection as did the reference drug diazepam at 5 mg kg^{-1}. None among the tested compounds showed anticonvulsant activity at a dose of 5 mg kg^{-1}.

CONCLUSIONS

The newly synthesized compounds 1,8-dihydro-1-aryl-8-alkyl pyrazolo(3,4-*b*)indoles **4**, **5** and **6a–j** showed remarkable anti-inflammatory, analgesic and anticonvulsant activities. The presence of the halogen atoms in their skeletons seem to be essential for these activities.

Acknowledgments. – The authors are thankful to Prof. Dr. Kartheinz Seifert, Organic Chemistry NWII, 1/2, University of Bayreuth, Bayreuth, Germany, for providing the facilities for carrying out the measurement of NMR spectra. Also, the authors are grateful to Microanalytical Unit, National Research Center, Cairo, Egypt, for carrying out elemental analyses, IR and mass spectra.

REFERENCES

1. *Goodman and Gilman's the Pharmacological Basis of Therapeutics*, 7th ed. (Eds. R. J. Flower, S. Moncada and J. R. Vane), MacMillan, New York 1985, p. 695.
2. P. Rani, V. K. Srivastava and A. Kumar, Synthesis and anti-inflammatory activity of heterocyclic indole derivatives, *Eur. J. Med. Chem.* **39** (2004) 449–452; DOI: 10.1016j.egmech 2003.11.002.
3. S. M. Sondhi, M. Dinodia and A. Kumar, Synthesis, anti-inflammatory and analgesic activity evaluation of some amidine and hydrazone derivatives, *Bioorg Med. Chem.* **14** (2006) 4657–4663; DOI: 10.1016/j.bmc.2006.02.014.

4. S. S. Panada and P. Chowdary, Synthesis of novel indolyl-pyrimidine anti-inflammatory, antioxidant and antibacterial agents, *Indian J. Pharm. Sci.* **70** (2008) 208–15; DOI: 10.4103/0252-474x.41457.
5. M. A. A. Radwan, E. A. Ragab, N. M. Sabrya and S. M. El-Shenawy, Synthesis and biological evaluation of new 3-substituted indole derivatives as potential anti-inflammatory and analgesic agents, *Bioorg. Med. Chem.* **15** (2007) 3832–3841; DOI: 10.1016/j.bmc.2007.03.024.
6. F. D. Popp, Potential anticonvulsants. VIII. Some hydrazones of indole-3-carboxaldehyde, *J. Heterocycl. Chem.* **21** (1984) 617–620.
7. A. El-Gendy Adel, A. Abdou Naida, Z. Sarhan El-Taher, A. El-Banna Hosny, Synthesis and biological activity of functionalized indole-2-carboxyates, triazino and pyridazino indoles, *Alexandria J. Pharm. Sci.* **7** (1993) 99–103.
8. R. K. Tiwari, D. Singh, J. Singh, V. Yadav, A. K. Pathak, R. Dabur, A. K. Chillar, R. Singh, G. L. Sharma, R. Chandra and A. K. Verma, Synthesis and antibacterial activity of substituted 1,2,3,4-tetrahydropyrazino [1,2-*a*] indoles, *Bioorg. Med. Chem. Lett.* **16** (2006) 413–416; DOI: 10.1016/j.bmcl.2005.09.066.
9. C. Ryu, J. Y. Lee, R. Park, M. Ma and J. Nho, Synthesis and antifungal activity of 1H-indole-4,7-diones, *Bioorg. Med. Chem. Lett.* **17** (2007) 127–131; DOI: 10.1016/j.bmcl.2006.09.076.
10. J. D. Williams, J. C. Darach and L. B. Townsend, Synthesis and evaluation of some novel tricyclic pyrazolo(3,4-*b*)indole nucleosides, *J. Med. Chem.* **23** (2004) 5766–5772; DOI: 10.1021/jm 040032n.
11. E. B. Dennler and A. R. Frasca, Synthesis of indazoles using polyphosphoric acid-I, *Tetrahedron* **22** (1966) 3131–3141; DOI: 10.1016/50040-4020(01)82291-2.
12. A. L. Mndzhoyan, G. L. Papayan, L. D. Zhuruli, S. G. Karagezyan, L. S. Galstyan and V. G. Sarafyan, Synthesis and biological study of hydrazinohydrazones of indole aldehydes and ketons series, *Arm. Khim. Zh. (USSR)* **22** (1969) 707–713; ref. *Chem. Abst*. **72** (1970) 11189f.
13. A. Kalir and S. Szara, 1-Benzyl tryptamine and its α-Me homolog were prepared from 3-indolealdehyde, *J. Med. Chem.* **9** (1966) 793–794.
14. M. G. Obukowicz, D. J. Welsch, W. J. Salsgiver, M. Berger, K. S. Chinn and K. L. Duffin, Novel, selective delta6 or delta5 fatty acid desaturase inhibitors as antiinflammatory agents in mice, *J. Pharmacol. Exp. Ther.* **287** (1998) 157–162.
15. C. A. Winter, E. A. Risely and G. W. Nuss, Anti-infalmmatory and antipyretic activities of indomethacin, 1-(*p*-chlorobenzyl)-5-methoxy-2-methyl-indole-3-acetic acid, *J. Pharmacol. Exp. Ther.* **141** (1963) 369–376.
16. R. Okun, S. C. Liddon and L. Lasagna, Effect of reserpine pre-treatment on the protective action of amphetamine and phenoxy propazine in the phenylbenzoquinone-induced writhing syndrome in mice, *J. Pharm. Exp. Ther.* **139** (1963) 107–110; DOI: 10.1038/201306a0.
17. H. G. Vogel and W. H. Vogel, *Drug Discovery and Evaluation*, *Pharmacological* Assay, Springer-Verlag, Berlin 1997, pp. 260–261.

S A Ž E T A K

Sinteza, protuupalno, analgetsko i antikonvulzivno djelovanje 1,8-dihidro-1-aril-8-alkil pirazolo(3,4-*b*)indola

ADEL H. MANDOUR, ESLAM R. EL-SAWY, KAMEL H. SHAKER i MOHAMED A. MUSTAFA

Serija 1,8-dihidro-1-aril-8-alkil pirazolo(3,4-*b*)indola **4a-j, 5a-j** i **6a-j** sintetizirana je i testirana na protuupalno i antikonvulzivno djelovanje. Pirazolindol derivati pripravljeni su reakcijom arilhidrazona *N*-alkil indol-3-karboksaldehida **1a-j**, **2a-j** i **3a-j** s deset puta većom masom polifosforne kiseline kao sredstva za kondenzaciju. Novosintetizirani spojevi testirani su na protuupalno, analgetsko i antikonvulzivno djelovanje i uspoređeni s djelovanjem indometacina, flufenaminske kiseline i diazepama. U radu su dati detaljni sintetski, spektroskopski i toksikološki podaci.

Ključne riječi: indol-3-karboksaldehid, protuupalno djelovanje, antikonvulzivno djelovanje, analgetsko djelovanje

Chemistry Department of Natural Compounds, National Research Centre, Gizza, Egypt

Organic Chemistry NWII,1/2, University of Bayreuth, Bayreuth, Germany

Research Unit, Egypt Pharmacist Co., Cairo, Egypt