Synthesis and Evaluation of the CNS Activity of New 4-Alkoxyphenylimidazolidin-2-ones

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Various 4-alkoxyphenylimidazolidin-2-ones were prepared from benzaldehydes *via* a Curtius rearrangement and were evaluated for their anticonvulsant activities.

Key words 4-alkoxyphenylimidazolidin-2-one; anticonvulsant activity; synthesis

Within the framework of our work aiming at the synthesis of a new heterocyclic system, we have already described several examples of those obtained starting from β-aminopropionic acids, and in particular, the access to arylhexahydropyrimidinediones which exhibited benzodiazepinic affinity and anticonvulsant activity *in vivo*.[1] Phenylimidazolidinones, lower homologues of arylhexahydropyrimidinediones, represent a category of compounds known for their central pharmacological properties.[2,3] This system is now accessible from the same amino acids, and we recently described the access to some thienyl and phenylimidazolidinones.[4,5] Herein, we present the synthesis of new imidazolidinones substituted by various alkoxy groups and the results of their preliminary pharmacological screening in the field of the central nervous system.

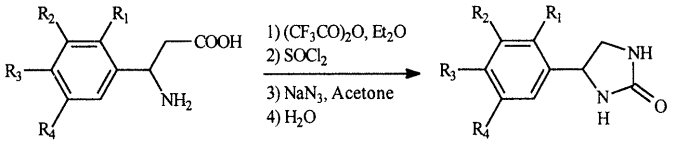
Chemistry

We have already reported the synthesis of 4-thienyl and 4-phenylimidazolidin-2-ones substituted on the phenyl ring by a nitro group or various halogen atoms. Their preparation was achieved in 4 steps starting from arylaldehydes.[4,5] The new title derivatives **1a—h**, which we describe herein, were prepared in a similar manner starting from alkoxybenzaldehydes *via* the aminophenylpropionic acids **2a—h**.[6,7]

Commercially unavailable 3-butoxy-4-methoxybenzaldehyde **3e**, involved in the synthesis of **1e**, was prepared in good yield (87%) by the alkylation of isovanillin with *n*-butylbromide in refluxing acetone and in the presence of potassium carbonate.[8,9]

Results and Discussion

All of the compounds **1a—h** presented in this paper were originally submitted for acute toxicity and behavioural studies in mice, using the method of Morpugo.[10] Antagonism to pentylenetetrazole-induced lethal convulsions, potentiation of secobarbital sleeping time, exploratory behaviour and effects on spontaneous motility and muscle relaxation were studied in female mice at doses not greater than approximately 0.50 LD_{50}. Moreover, the anxiolytic activity of the three compounds of this series



2 a-h **1 a-h**

	R_1	R_2	R_3	R_4
a[17]	H	H	H	H
b	H	CH_3O	H	H
c	H	CH_3O	H	H
d	H	CH_3O	CH_3O	H
e	H	n-C_4H_9O	CH_3O	H
f	H	OCH_2O		H
g	H	OCH_2CH_2O		H
h	H	CH_3O	CH_3O	CH_3O

Chart 1

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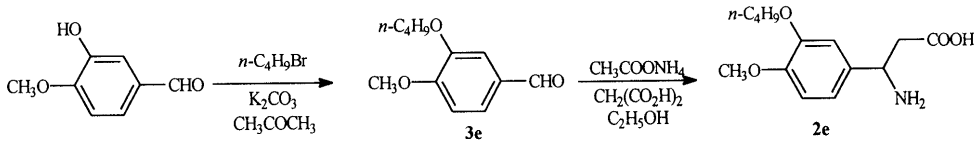

Chart 2

Table 1. Potentiation of Secobarbital Sleeping Time Caused by Tested Compounds

No.	Dose (mg/kg) i.p.	Ns/Nt[a]	t1[b]	t2[c]
[1% PEG/H_2O]	—	23/26	8.9 ±0.94	40.86± 6.38
1a	50	6/6	3.66±0.52*	114.8 ±23.0***
1b	100	10/10	5.75±0.56	103.63±16.02***
1c	100	6/6	6.83±0.77	83.5 ±21.50*
1d	100	10/10	7.43±0.85	91.86±13.50***
1e	100	10/10	3.70±0.61**	115.71± 5.07***
1f	ND[d]	ND	ND	ND
1g	100	6/6	10.17±1.39	50.17±22.30
1h	100	6/6	12.33±2.75	35.33±17.97
Clobazam	5	10/10	5.33±0.68***	138.33±12.80***

a) Ns = number of sleeping mice, Nt = total number of mice. *b*) t1 = sleep induction time (min). *c*) t2 = sleeping time (min). *d*) Not determined. Sodium secobarbital i.p. = 40 mg/kg. $*p<0.05$, $**p<0.01$, $***p<0.001$.

Table 2. Pharmacological Data for Tested Compounds

No.	Approximate i.p. LD_{50} in mice (mg/kg)	Spontaneous mobility i.p. ED_{50} values (±approximate standard error)	Relaxant activity (mg/kg) minimal dose active	Anticonvulsant activity in mice i.p. ED_{50} and 95% confidence interval (mg/kg)
1a	500	235±80	100	89 (69—115)
1b	600	98±37	100	77 (59—99)
1c	>600	>200	200	124 (91—169)
1d	500	72± 1	100	Inactive at 300
1e	>600	29± 9	25	192 (107—344)
1f	>600	ND[a]	ND	ND
1g	>700	ND	500	Inactive at 400
1h	>700	270±98	400	Inactive at 400
Diazepam	175	10.2± 6.5	10	0.55 (0.49—0.62)

a) ND = not determined.

were evaluated using a Black and White test box.[11]

The compounds were administered i.p. and the results obtained in this study are recorded in Tables 1 and 2. Some reference standards, such as diazepam, clobazam and chlorazepate, were included in the tests for comparison purposes.

It was found that this series provided moderate to low toxicity with an approximate LD_{50} of near or superior to 500 mg/kg. At the highest doses assayed (700 mg/kg for the less toxic compound), the major signs were hypoactivity, muscular relaxation, ataxia, and tremors, which were prolonged after 3 h. Among this series, four compounds, **1a**—**c** and **1e**, exhibited anticonvulsant activity in terms of protective effects against pentylenetetrazole-induced lethal convulsion (see protocol), with approximate ED_{50} values ranging from 77 to 192 mg/kg. Concerning the potentiation of secobarbital narcoses, derivatives **1a**—**e** significantly increased the sleeping time of animals. The more active compound in this experience was **1a**, which at the dose of 50 mg/kg increased the sleeping time to 285% in comparison with control group. Moreover, **1a** (at the dose of 50 mg/kg) and **1e** (at the dose of 100 mg/kg) reduced the sleeping induction of the animal.

Study of the behavioural effects of compounds **1b**, **1d**, **1e** were also investigated in a Black and White test box. Crawley and co-workers have used the number of transitions made by mice between the two experimental chambers as an index of anxiety.[12-14] In our study, compounds **1b**, **1d** and **1e** were tested at doses inferior to the minimal dose, inducing significative diminution of spontaneous activity in the photoactimeter test (doses ≤ 50 mg/kg for **1a**, and ≤25 mg/kg for **1d** and **1e**). In these conditions, **1b**, **1d** and **1e** failed to demonstrate either anxiolytic or anxiogenic effects (no increase or diminution of transition number with control lot), whereas chlorazepate at 5 mg/kg significantly improved the transition number.

In conclusion, this study intends to make obvious the sedative and anticonvulsant activities of new imidazolidinones. Concerning the mechanism of action of these molecules, secondary studies will have to be carried out. However, it is clear that, contrary to the arylhexahydropyrimidinedione series,[1] which includes the higher homologues of phenylimidazolidinones, their action is not modulated by an interaction with the benzodiazepinic receptor, since studies of displacement of the specific binding of the 3H-flunitrazepam showed that these derivatives do not interest the receptor benzodiazepine (results not given). Concerning the relation structure activity, it is difficult to draw up unquestionable conclusions from this first study.

Experimental

Chemistry Melting points were determinated on a Kofler block and are uncorrected. IR spectra were recorded on a Philips PU-9716 spectrophotometer. NMR spectra (^1H, ^{13}C, ^1H-COSY) were recorded at 400 MHz or 100 MHz with tetramethylsilane as an internal standard using a JEOL JNM-LA 400 spectrometer. Splitting patterns have been designated as follows: s = singlet; bs = broad singlet; d = doublet; t = triplet; dd = double doublet; m = mutiplet. Analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values.

3-(3-Butoxy-4-methoxyphenyl)-3-aminopropionic Acid (2e) To a solution of 3-butoxy-4-methoxybenzaldehyde **3e** (14.7 g, 0.071 mol) in 150 ml of ethanol were added ammonium acetate (10.9 g, 0.141 mol) then malonic acid (7.35 g, 0.071 mol). The reaction mixture was refluxed for 40 h, and the precipitate that formed was collected by filtration, washed with ethanol and dried to give white crystals (18%). mp >260 °C. IR (KBr) cm^{-1}: 3300—2400 (NH_2 and OH), 1670 (C=O). ^1H-NMR (DMSO-d_6) δ: 0.95 (3H, t, J=7.1 Hz, CH_3), 1.45 (2H, m, J=7.1 Hz, CH_2), 1.70 (2H, m, J=7.1 Hz, CH_2), 2.41 (2H, m, CH_2COOH), 3.59 (3H, br s, NH_2 and COOH), 3.75 (3H, s, CH_3O), 3.97 (3H, t, J=7.1 Hz, CH_2), 4.15 (1H, m, 3-H), 6.89 (2H, m, arom-H), 7.01 (1H, m, arom-H). *Anal.* Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.11; H, 7.88; N, 5.27.

Table 3. Yields and Physical Data for the 4-Arylimidazolidin-2-ones (**1b—h**)

Compd.	Yield (%)	mp (°C)	^{1}H-NMR (400 MHz, ppm, DMSO-d_6)	Formula	Analysis (%) Calcd (Found) C	H	N	IR (cm^{-1})
1b	54	106	3.01 (1H, dd, J=8.1, 8.1 Hz, 5b-H), 3.68 (1H, dd, J=8.1, 8.1 Hz, 5a-H), 3.73 (3H, s, CH_3O), 4.70 (1H, dd, J=8.1, 8.1 Hz, 4-H), 6.30 (1H, s, NH), 6.82 (1H, s, NH), 6.84 (1H, m, arom-H), 6.89 (2H, m, arom-H), 7.26 (1H, m, arom-H)	$C_{10}H_{12}N_2O_2$	62.49 (62.62)	6.29 (6.27)	14.57 (14.32)	3240, 1690
1c	61	139	2.99 (1H, dd, J=8.2, 8.2 Hz, 5b-H), 3.64 (1H, dd, J=8.2, 8.2 Hz, 5a-H), 3.73 (3H, s, CH_3O), 4.66 (1H, dd, J=8.2, 8.2 Hz, 4-H), 6.18 (1H, s, NH), 6.68 (1H, s, NH), 6.90 (2H, d, J=8.4 Hz, 3′-H and 5′-H), 7.24 (2H, d, J=8.4 Hz, 2′-H and 6′-H)	$C_{10}H_{12}N_2O_2$	62.49 (62.51)	6.29 (6.45)	14.57 (14.48)	3260, 1710
1d	79	136	3.01 (1H, dd, J=8.3, 8.3 Hz, 5b-H), 3.63 (1H, dd, J=8.3, 8.3 Hz, 5a-H), 3.72 (3H, s, CH_3O), 3.74 (3H, s, CH_3O), 4.65 (1H, dd, J=8.3, 8.3 Hz, 4-H), 6.23 (1H, s, NH), 6.73 (1H, s, NH), 6.84 (1H, dd, J=8.2, 1.5 Hz, 6′-H), 6.91 (1H, d, J=8.2 Hz, 5′-H), 6.92 (1H, d, J=1.5 Hz, 2′-H)	$C_{11}H_{14}N_2O_3$	59.45 (59.65)	6.35 (6.11)	12.60 (12.52)	3240, 1690
1e	58	121	0.92 (3H, t, J=7.1 Hz, CH_3), 1.42 (2H, m, J=7.1 Hz, CH_2), 1.68 (2H, m, J=7.1 Hz, CH_2), 3.00 (1H, dd, J=8.25, 8.25 Hz, 5b-H), 3.62 (1H, dd, J=8.25, 8.25 Hz, 5a-H), 3.72 (3H, s, CH_3O), 3.92 (3H, t, J=7.1 Hz, CH_2), 4.66 (1H, dd, J=8.25, 8.25 Hz, 4-H), 6.20 (1H, s, NH), 6.70 (1H, s, NH), 6.82 (1H, dd, J=8.3, 1.0 Hz, 6′-H), 6.90 (1H, d, J=8.3 Hz, 5′-H), 6.91 (1H, d, J=1.0 Hz, 2′-H)	$C_{14}H_{20}N_2O_3$	63.62 (63.50)	7.63 (7.51)	10.60 (10.49)	3290, 3210, 1720
1f	43	208	2.99 (1H, dd, J=8.2, 8.2 Hz, 5b-H), 3.64 (1H, dd, J=8.2, 8.2 Hz, 5a-H), 4.65 (1H, dd, J=8.2, 8.2 Hz, 4-H), 5.99 (2H, s, CH_2), 6.25 (1H, s, NH), 6.75 (1H, s, NH), 6.81 (1H, s, 2′-H), 6.87 (2H, m, 5′-H and 6′-H)	$C_{10}H_{10}N_2O_3$	58.25 (58.40)	4.89 (4.69)	13.59 (13.75)	3200, 1680
1g	57	124	2.98 (1H, dd, J=8.15, 8.15 Hz, 5b-H), 3.63 (1H, dd, J=8.15, 8.15 Hz, 5a-H), 4.21 (4H, s, CH_2CH_2), 4.60 (1H, dd, J=8.15, 8.15 Hz, 4-H), 6.23 (1H, s, NH), 6.74 (1H, s, NH), 6.82 (3H, m, 2′-H, 5′-H and 6′-H)	$C_{11}H_{12}N_2O_3$	59.99 (59.78)	5.49 (5.48)	12.71 (12.63)	3220, 1690
1h	50	179	3.05 (1H, dd, J=8.3, 8.3 Hz, 5b-H), 3.64 (3H, s, CH_3), 3.66 (1H, dd, J=8.3, 8.3 Hz, 5a-H), 3.77 (6H, s, $2CH_3$), 4.68 (1H, dd, J=8.3, 8.3 Hz, 4-H), 6.28 (1H, s, NH), 6.65 (2H, s, 2′-H and 6′-H), 6.79 (1H, s, NH)	$C_{12}H_{16}N_2O_4$	57.13 (56.97)	6.39 (6.52)	11.11 (10.91)	3200, 1685

General Procedure for 4-Arylimidazolidin-2-ones (1) To a stirred ice-cold solution of 3-aryl-3-trifluoroacetylaminopropionic acid chloride (0.01 mol) in 50 ml of acetone was added sodium azide (0.015 mol). The reaction mixture was stirred at 0—5 °C for 30 min, then 100 ml of water was added and the well-stirred resulting mixture was heated at reflux temperature for 4 h. After cooling, the mixture was extracted twice with chloroform. The organic layers were collected, dried over calcium chloride and evaporated to dryness. The residue was triturated in ether and the precipitate that formed was filtered, washed with ether and recrystallized from water to yield **1a—h**. The physical properties, elemental analysis and ^{1}H-NMR and IR spectral data of the compounds are listed in Table 3.

Pharmacology

Pharmacological Evaluation Female OF-1 mice (France, Iffa Credo) weighing 18—22 g were used for pharmacological studies. The animals were allowed free access to food and water and were housed at room temperature (20—22 °C). All the test compounds were administered *via* intraperitoneal injection (i.p.) in a 1% PEG solution.

Gross Behavioral Effects and Acute Toxicity in Mice Morpugo's modification[10] of Irwin's multidimensional screening procedure was used on groups of four mice to evaluate drug-induced behavioral alterations. The test compounds were administered in log-spaced doses, and detailed observations of the mice were made 1, 3 and 24 h after treatment. The approximate LD_{50} was obtained from the mortality observed during a 48 h period.

Spontaneous Motor Activity Locomotor activity was recorded with a photocell activity meter for 10 min, beginning 30 min after i.p. administration of each test drug. The approximate LD_{50} and standard error were estimated by the method of Miller and Tainter.[14]

Muscle Relaxant Activity Traction test: experiments were performed by the method of Courvoisier *et al.*[15] Mice were forced to hang with their forelegs on a wire of 1 mm in diameter, which was stretched horizontally at a height of 17 cm. When they fell off the wire within 5 s, or they failed to grasp the wire with their legs within 10 s, muscle relaxation was juged to be positive.

Anticonvulsant Activity Test compounds were given to groups of four mice 30 min before the i.p. injection of 160 mg/kg pentylenetetrazole.[10] The protection against pentylenetetrazole-induced lethal convulsions was evaluated for a 15 min observation period (100% of controls die within 10 min). For the test compound, the initial dose was 1/3 or 1/6 LD_{50}. If such a dose was found to have an active effect, successive log-spaced doses were tested, and the ED_{50} and 95% confidence intervals were estimated by the method of Spearman and Karber.[16] Diazepam 5 mg/kg was used as a reference drug.

Interaction with Barbiturate Induced Sleep in Mice Sodium secobarbital at a (sub)hypnotic dose of 40 mg/kg was injected i.p. to groups of 6 or 10 mice simultaneously with an i.p. injection of the drug. The number of mice which lost the righting reflex, as well as latency and duration of sleep (loss and recovery of the righting reflex), were recorded. Clobazam 5 mg/kg was used as a reference drug.

Light/dark Exploration Test[11] The test boxes, entirely constructed of perpex, consist of two compartments with walls 270 mm high. The first of these, colored matte black, measures 270 × 180 mm; the other, matte white, measures 270 × 270 mm, with an opening in its base. The box does not have a top cover. Each compartment is independently illuminated: the white one with a 100 W bulb (white) and the black one with a 40 W bulb (red). Both bulbs are 370 mm from the floor of the box. Each mouse (10 mice for each dose treatment) was placed in the center of the light compartment of the light-dark box and, over a 5 min period, 30 min after i.p. administration of test compounds, measurements were made of the number of transitions between the light and dark

compartments.

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