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Synthesis and anticonvulsant properties of 2,3,3a,4-tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-one derivatives

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Abstract

A number of novel 1*H*-pyrrolo[1,2-*a*]benzimidazol-1-one derivatives were prepared and their anticonvulsant properties evaluated. The new synthesized compounds proved to possess anticonvulsant effects depending on the nature of substituents at C-6, C-2, and C-3a positions of the polycyclic system. In particular, the 6-chloro-3a-(*p*-tolyl)-2,3,3a,4-tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-one derivative (**22**) displayed potency fivefold higher than unsubstituted compound (**13**).

Keywords: 1*H*-Pyrrolo[1,2-*a*]benzimidazol-1-ones; Anticonvulsant agents

1. Introduction

Epilepsy is a brain function disorder characterized by recurrent seizures that have a sudden onset. It was assumed for many years that epilepsy could be treated with just one drug, but it is now apparent that is not the case as more than one mechanism may be responsible for the various types of seizures. Although most seizures can be treated to some extent, 30% of all patients suffering from epilepsy do not respond to any current drug, either in monotherapy or in combinations.

Drugs clinically active against epilepsy include derivatives with common structural characteristics such as a nitrogen heterocyclic system with a carbonyl group and an aromatic or heteroaromatic nucleus linked to the heterocyclic system.

As part of our program on the chemistry of heteropolycyclic systems as potential anticonvulsant agents, we have previously described a series of 2,3,3a,4-tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-ones [1–5].

Our structure–activity relationship studies investigated the effect of the substituents on the pyrrolobenzimidazole system and the comparison of different analogs allowed us to establish some structural requirements for anticonvulsant activity [3,5]. In addition it was also demonstrated that some 1*H*-pyrrolo[1,2-*a*]benzimidazol-1-ones possessed anticonvulsant effects comparable to that of diphenylhydantoin [6].

In order to gain further insight into the structure–activity relationships and to obtain more potent and less toxic agents, we now report here the synthesis of new 2,3,3a,4-tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-one derivatives with different substituents on 2, 3a, 6 and 7 positions and the evaluation of anticonvulsant activity in DBA/2 mice against sound-induced seizures.

2. Experimental

2.1. Chemistry

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses (C, H, N) were carried out on a Carlo Erba Model 1106

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Elemental Analyzer and the results are within ± 0.4% of the theoretical values. Merck silica gel 60 F_{254} plates were used for analytical TLC; column chromatography was performed on Merck silica gel 60 (70–230 mesh). ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Gemini-300 spectrometer. Chemical shifts are expressed in δ (ppm) relative to TMS as internal standard and coupling constants (J) in Hz. All exchangeable protons were confirmed by addition of D_2O. Mass spectra (MS) were run on a Shimadzu GCMS QP 500 gas chromatography-mass spectrometer. Compounds **8**–**10** and **13**–**15** were prepared according to a procedure previously described [3].

*2.1.1. Synthesis of 4-fluoro-1,2-phenylenediamine (**3**)*

To a mixture of 4-fluoro-2-nitroaniline (10 mmol) and granulated tin, HCl 37% (10 ml) was added dropwise. The reaction mixture was heated on a boiling water bath for 1 h. The mixture was cooled, treated with a solution of NaOH and extracted with $CHCl_3$. The organic phase was dried over Na_2SO_4, the solvent was evaporated and the crude residue was used in subsequent reaction without any further purification.

*2.1.2. General procedure for the synthesis of 2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]-benzimidazol-1-ones **11**, **12** and **16**–**25***

A solution of 1,2-phenylenediamine derivative (**1**–**3**) (10 mmol) in anhydrous toluene (50 ml) and 4-acylpropionic acid (**4**–**7**) (10 mmol) was heated to reflux for 24 h with a Dean–Stark apparatus. The reaction mixture was evaporated to dryness, and the oily residue was recrystallized from suitable solvent or subjected to silica gel column chromatography to afford the desired product.

*2.1.2.1. 6-Fluoro-3a-methyl-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (**11**).* Purified by column chromatography using $CHCl_3$/MeOH (95:5) as eluant. ^{1}H NMR (δ) 1.50 (s, 3H, CH_3), 2.34–2.82 (m, 4H, CH_2CH_2), 4.60 (bs, 1H, NH), 6.37 (dd, 1H, $J = 2.3$ and $J_{HF} = 9.1$ Hz, H-5), 6.43 (dd, 1H, $J = 2.5$ and $J_{HF} = 10.6$ Hz, H-7), 7.29 (dd, 1H, $J_{HF} = 5.0$ and $J = 8.4$ Hz, H-8). MS, m/z: 268 (M^+, 25), 267 (12), 214 (15), 213 (100), 212 (93), 211 (19), 191 (78), 149 (37), 110 (25), 109 (12), 108 (15), 104 (12), 90 (11), 89 (13), 83 (23), 82 (21), 77 (28), 76 (13), 65 (17), 63 (16), 57 (10), 55 (11), 51 (25).

*2.1.2.2. 7-Fluoro-3a-methyl-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (**12**).* Purified by column chromatography using $CHCl_3$/MeOH (95:5) as eluant. ^{1}H NMR (δ) 1.50 (s, 3H, CH_3), 2.34–2.82 (m, 4H, CH_2CH_2), 4.24 (bs, 1H, NH), 6.56 (dd, 1H, $J = 2.3$ and $J_{HF} = 9.1$ Hz, H-5), 6.64 (dd, 1H, $J = 2.5$ and $J_{HF} = 10.6$ Hz, H-6), 7.17 (dd, 1H, $J_{HF} = 2.4$ and $J =$ 8.25 Hz, H-8).

*2.1.2.3. 6-Fluoro-3a-phenyl-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (**16**).* ^{1}H NMR (δ) 2.47–2.82 (m, 4H, CH_2CH_2), 4.66 (bs, 1H, NH), 6.25 (dd, 1H, $J = 1.9$ and $J_{HF} = 9.0$ Hz, H-5), 6.50 (dd, 1H, $J = 2.1$ and $J_{HF} = 9.5$ Hz, H-7), 7.32–7.48 (m, 6H, H-8 and Ar).

*2.1.2.4. 7-Fluoro-3a-phenyl-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (**17**).* ^{1}H NMR (δ) 2.47–2.80 (m, 4H, CH_2CH_2), 4.35 (bs, 1H, NH), 6.56 (dd, 1H, $J = 2.3$ and $J_{HF} = 9.1$ Hz, H-5), 6.64 (dd, 1H, $J = 2.5$ and $J_{HF} = 10.6$ Hz, H-6), 7.30 (dd, 1H, $J = 2.4$ and $J_{HF} = 8.25$ Hz, H-8), 7.32–7.48 (m, 5H, Ar).

*2.1.2.5. 2-Methyl-3a-phenyl-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (cis-**18**).* Purified by column chromatography using diethyl ether/light petroleum (50:50) as eluant. ^{1}H NMR (δ) 1.23 (d, $J = 6.9$ Hz, 3H, CH_3), 2.44 (dd, 1H, $J = 11.5$ and $J = 12.5$ Hz, H-3), 2.70 (m, 1H, H-2) 3.02 (dd, 1H, $J = 6.6$ and $J = 11.5$ Hz, H-3), 4.50 (bs, 1H, NH), 6.61 (d, 1H, $J = 7.5$ Hz, H-5), 6.87 (t, 1H, $J = 7.5$ Hz, H-7), 6.94 (t, 1H, $J = 7.5$ Hz, H-6), 7.30–7.47 (m, 5H, Ar), 7.58 (d, 1H, $J = 7.5$ Hz, H-8). MS, m/z: 264 (M^+, 42), 263 (11), 196 (13), 195 (100), 193 (17), 187 (71), 159 (21), 104 (10), 77 (10).

*2.1.2.6. 2-Methyl-3a-phenyl-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (trans-**18**).* Purified by column chromatography using diethyl ether/light petroleum (50:50) as eluant. ^{1}H NMR (δ) 1.11 (d, $J = 7.6$ Hz, 3H, CH_3), 2.57 (dd, 1H, $J = 1.4$ and $J = 12.6$ Hz, H-3), 2.87 (m, 1H, H-2), 3.04 (dd, 1H, $J = 9.3$ and $J = 12.6$ Hz, H-3), 4.47 (bs, 1H, NH), 6.59 (d, 1H, $J = 7.6$ Hz, H-5), 6.87 (t, $J = 7.5$ Hz, 1H, H-7), 6.95 (t, $J = 7.6$ Hz, 1H, H-6), 7.28–7.46 (m, 5H, Ar), 7.58 (d, $J = 7.5$ Hz, 1H, H-8). MS, m/z: 264 (M^+, 38), 263 (11), 196 (13), 195 (97), 194 (100), 193 (16), 187 (66), 159 (18), 104 (9.8), 77 (12).

*2.1.2.7. 6-Chloro-2-methyl-3a-phenyl-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (cis-**19**).* Purified by column chromatography using diethyl ether/light petroleum (80:20) as eluant. ^{1}H NMR (δ) 1.21 (d, 3H, $J = 6.9$ Hz, CH_3), 2.44 (dd, 1H, $J = 11.7$ and $J = 12.3$ Hz, H-3), 2.69 (m, 1H, H-2), 3.01 (dd, 1H, $J = 6.7$ and $J = 11.7$ Hz, H-3), 4.70 (bs, 1H, NH), 6.57 (d, 1H, $J = 2.0$ Hz, H-5), 6.80 (dd, 1H, $J = 2$ and $J = 8.2$ Hz, H-7), 7.31–7.43 (m, 5H, Ar), 7.45 (d, 1H, $J = 8.2$ Hz, H-8). MS, m/z: 298 (M^+, 31), 231 (33), 230 (44), 229 (100), 228 (90), 223 (17), 221 (61), 193 (24), 192 (11), 115 (10), 90 (14), 77 (18), 63 (18).

*2.1.2.8. 6-Chloro-2-methyl-3a-phenyl-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (trans-**19**).* Purified by column chromatography using diethyl

ether/light petroleum (80:20) as eluant. ^{1}H NMR (δ) 1.11 (d, 3H, $J = 6.9$ Hz, CH_3), 2.56 (dd, 1H, $J = 1.4$ and $J = 12.6$ Hz, H-3), 2.87 (m, 1H, H-2), 3.04 (dd, 1H, $J = 9.4$ and $J = 12.6$ Hz, H-3), 4.55 (bs, 1H, NH), 6.55 (d, 1H, $J = 1.8$ Hz, H-5), 6.82 (dd, 1H, $J = 1.8$ and $J = 8.2$ Hz, H-7), 7.29–7.42 (m, 5H, Ar), 7.47 (d, 1H, $J = 8.2$ Hz, H-8).

*2.1.2.9. 7-Chloro-2-methyl-3a-phenyl-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (cis-**20**).* Purified by column chromatography using diethyl ether/light petroleum (80:20) as eluant. ^{1}H NMR (δ) 1.22 (d, 3H, $J = 7.0$ Hz, CH_3), 2.43 (dd, 1H, $J = 11.5$ and $J = 12.5$ Hz, H-3), 2.69 (m, 1H, H-2), 3.02 (dd, 1H, $J = 6.6$ and $J = 11.5$ Hz, H-3), 4.74 (bs, 1H, NH), 6.50 (d, 1H, $J = 8.2$ Hz, H-5), 6.89 (dd, 1H, $J = 2$ and $J = 8.2$ Hz, H-6), 7.31–7.47 (m, 5H, Ar), 7.56 (d, 1H, $J = 2.0$ Hz, H-8).

*2.1.2.10. 7-Chloro-2-methyl-3a-phenyl-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (trans-**20**).* Purified by column chromatography using diethyl ether/light petroleum (80:20) as eluant. ^{1}H NMR (δ) 1.09 (d, 3H, $J = 7.5$ Hz, CH_3), 2.57 (dd, 1H, $J = 1.2$ and $J = 12.6$ Hz, H-3), 2.87 (m, 1H, H-2), 3.03 (dd, 1H, $J = 9.4$ and $J = 12.6$ Hz, H-3), 4.43 (bs, 1H, NH), 6.48 (d, 1H, $J = 8.2$ Hz, H-5), 6.90 (dd, 1H, $J = 2.0$ and $J = 8.2$ Hz, H-6), 7.29–7.41 (m, 5H, Ar), 7.56 (d, 1H, $J = 2.0$ Hz, H-8).

*2.1.2.11. 2,3,3a,4-Tetrahydro-3a-(p-tolyl)-1H-pyrrolo-[1,2-a]benzimidazol-1-one (**21**).* ^{1}H NMR (δ) 2.34 (s, 3H, CH_3), 2.50–2.82 (m, 4H, CH_2CH_2), 4.52 (bs, 1H, NH), 6.62 (dd, 1H, $J = 1.2$ and $J = 7.6$ Hz, H-5), 6.86 (dt, 1H, $J = 1.2$ and $J = 7.6$ Hz, H-7), 6.95 (dd, 1H, $J = 1.2$ and $J = 7.6$ Hz, H-6), 7.20 and 7.33 (2d, 4H, $J = 8.1$ Hz, Ar), 7.57 (dd, 1H, $J = 1.2$ and $J = 7.6$ Hz, H-8). MS, m/z: 264 (M^+, 60), 263 (40), 210 (14), 209 (93), 208 (100), 207 (20), 206 (12), 173 (84), 131 (19), 92 (15), 91 (11), 65 (17).

*2.1.2.12. 6-Chloro-2,3,3a,4-tetrahydro-3a-(p-tolyl)-1H-pyrrolo[1,2-a]benzimidazol-1-one (**22**).* Purified by column chromatography using CCl_4/AcOEt (80:20) as eluant. ^{1}H NMR (δ) 2.34 (s, 3H, CH_3), 2.47–2.81 (m, 4H, CH_2CH_2), 4.60 (bs, 1H, NH), 6.56 (d, 1H, $J = 1.9$ Hz, H-5), 6.79 (dd, 1H, $J = 1.9$ and $J = 8.09$ Hz, H-7), 7.19 and 7.30 (2d, 4H, $J = 8.1$ Hz, Ar), 8.01 (d, 1H, $J = 8.09$ Hz, H-8). MS, m/z: 298 (M^+, 46), 297 (26), 245 (33), 244 (38), 243 (100), 242 (79), 241 (13), 209 (22), 208 (15), 207 (78), 206 (10), 165 (19), 91 (12), 90 (12), 63 (15).

*2.1.2.13. 7-Chloro-2,3,3a,4-tetrahydro-3a-(p-tolyl)-1H-pyrrolo[1,2-a]benzimidazol-1-one (**23**).* Purified by column chromatography using CCl_4/AcOEt (80:20) as eluant. ^{1}H NMR (δ) 2.34 (s,3H,CH_3), 2.50–2.85 (m, 4H, CH_2CH_2), 4.47 (bs, 1H, NH), 6.50 (d, 1H, $J = 8.24$ Hz, H-5), 6.89 (dd, 1H, $J = 2.0$ and $J = 8.24$ Hz, H-6), 7.20 and 7.30 (2d, 4H, $J = 8.1$ Hz, Ar), 7.56 (d, 1H, $J = 2.0$ Hz, H-8).

*2.1.2.14. 6-Fluoro-2,3,3a,4-tetrahydro-3a-(p-tolyl)-1H-pyrrolo[1,2-a]benzimidazol-1-one (**24**).* Purified by column chromatography using $CHCl_3$/MeOH (95:5) as eluant. ^{1}H NMR (δ) 2.34 (s, 3H, CH_3), 2.50–2.80 (m, 4H, CH_2CH_2), 4.58 (bs, 1H, NH), 6.31 (dd, 1H, $J = 2.4$ and $J_{HF} = 9.0$ Hz, H-5), 6.50 (dd, 1H, $J = 2.5$ and $J_{HF} = 10.6$ Hz, H-7), 7.20 and 7.28 (2d, 4H, $J = 8.1$ Hz, Ar), 7.44 (dd, 1H, $J_{HF} = 5.03$ and $J = 8.4$ Hz, H-8). MS, m/z: 282 (M^+, 28), 281 (17), 228 (13), 227 (90), 226 (100), 225 (28), 224 (16), 191 (61), 149 (30), 116 (10), 115 (10), 110 (22), 108 (12), 91 (19), 89 (12), 83 (19), 65 (18), 63 (14).

*2.1.2.15. 7-Fluoro-2,3,3a,4-tetrahydro-3a-(p-tolyl)-1H-pyrrolo[1,2-a]benzimidazol-1-one (**25**).* Purified by column chromatography using $CHCl_3$/MeOH (95:5) as eluant. ^{1}H NMR (δ) 2.34 (s, 3H, CH_3), 2.50–2.80 (m, 4H, CH_2CH_2), 4.35 (bs, 1H, NH), 6.56 (d, 1H, $J = 2.3$ and $J_{HF} = 9.1$ Hz, H-5), 6.64 (dd, 1H, $J = 2.5$ and $J_{HF} = 10.6$ Hz, H-6), 7.30 (dd, 1H, $J = 2.4$ and $J_{HF} = 8.25$ Hz, H-8).

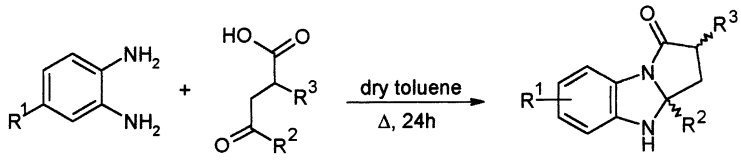
2.2. Lipophilicity measurements

The relative lipophilicity (R_m) of the compounds was measured by reversed-phase high-performance thin-layer chromatography (RP-HPTLC) according to the method previously described [7]. Briefly, Whatman KC18F plates were used as the non-polar stationary phase. The plates were dried at 105 °C for 1 h before use. The polar mobile phase was a 2:1 (v/v) mixture of acetone and water. Each compound was dissolved in $CHCl_3$ (3 mg/ml), and 1 μl of solution was applied onto the plate. The experiments were repeated five times with a different disposition of the compounds on the plate. The R_f values were expressed as the mean values of the five determinations. The R_m values were calculated from the experimental R_f values according to the formula $R_m = \log[(1/R_f) - 1]$. Higher R_m values indicate higher lipophilicity.

2.3. Pharmacology

2.3.1. Test of anticonvulsant activity against audiogenic seizures in DBA/2 mice

All experiments were performed with DBA/2 mice which are genetically susceptible to sound-induced seizures [8]. DBA/2 mice (8–12 g; 22–25 days old) were purchased from Charles River (Calco, Como, Italy). Groups of 10 mice of either sex were exposed to



1 R^1 = H
2 R^1 = Cl
3 R^1 = F

4 R^2 = Me; R^3 = H
5 R^2 = Ph ; R^3 = H
6 R^2 = *p*-tolyl; R^3 = H
7 R^2 = Ph; R^3 = Me

8-25

	R^1	R^2	R^3
8	H	Me	H
9	6-Cl	Me	H
10	7-Cl	Me	H
11	6-F	Me	H
12	7-F	Me	H
13	H	Ph	H
14	6-Cl	Ph	H

	R^1	R^2	R^3
15	7-Cl	Ph	H
16	6-F	Ph	H
17	7-F	Ph	H
***cis*-18**	H	Ph	Me
***trans*-18**	H	Ph	Me
***cis*-19**	6-Cl	Ph	Me
***trans*-19**	6-Cl	Ph	Me

	R^1	R^2	R^3
***cis*-20**	7-Cl	Ph	Me
***trans*-20**	7-Cl	Ph	Me
21	H	*p*-tolyl	H
22	6-Cl	*p*-tolyl	H
23	7-Cl	*p*-tolyl	H
24	6-F	*p*-tolyl	H
25	7-F	*p*-tolyl	H

Scheme 1.

auditory stimulation 30 min following administration of vehicle or each dose of drugs studied. The compounds were given ip (0.1 ml/10 g of body weight of the mouse) as a freshly prepared solution in 50% dimethyl sulfoxide (DMSO) and 50% sterile saline (0.9% NaCl). Individual mice were placed under a hemispheric Perspex dome (diameter 58 cm), and 60 s were allowed for habituation and assessment of locomotor activity. Auditory stimulation (12–16 kHz, 109 dB) was applied for 60 s or until tonic extension occurred, and induced a sequential seizure response in control DBA/2 mice, consisting of an early wild running phase, followed by generalized myoclonus and tonic flexion and extension sometimes followed by respiratory arrest. The control and drug-treated mice were scored for latency to and incidence of the different phases of the seizures [9]. The experimental protocol and all the procedures involving animals and their care were conducted in conformity with the institutional guidelines and the European Council Directive of laws and policies.

Table 1
Physicochemical data for compounds **11**, **12** and **16**–**25**

Comp.	Formula	M.p. (°C)	Solvent	Yield (%)
11	$C_{11}H_{12}FN_2O$	108–110	MeOH	69
12	$C_{11}H_{12}FN_2O$	125–127	MeOH	12
16	$C_{16}H_{13}FN_2O$	168–170	EtOH	71
17	$C_{16}H_{13}FN_2O$	179–181	EtOAc	16
cis-**18**	$C_{17}H_{16}N_2O$	148–150	MeOH	35
trans-**18**	$C_{17}H_{16}N_2O$	150–152	Et_2O	29
cis-**19**	$C_{17}H_{15}ClN_2O$	135–138	MeOH	28
trans-**19**	$C_{17}H_{15}ClN_2O$	192–195	Et_2O	21
cis-**20**	$C_{17}H_{15}ClN_2O$	163–165	MeOH	16
trans-**20**	$C_{17}H_{15}ClN_2O$	182–185	EtOH	11
21	$C_{17}H_{16}N_2O$	158–160	EtOH	78
22	$C_{17}H_{15}ClN_2O$	162–165	MeOH	44
23	$C_{17}H_{15}ClN_2O$	150–153	Et_2O	10
24	$C_{17}H_{15}FN_2O$	128–130	MeOH	61
25	$C_{17}H_{15}FN_2O$	134–136	Et_2O	9

2.3.2. Statistical analysis

Statistical comparisons between groups of control and drug-treated animals were made using Fisher's exact probability test (incidence of the seizure phases). The ED_{50} values of each phase of audiogenic seizures were determined for each dose of compound administered, and dose–response curves were fitted using a computer program by the method of Litchfield and Wilcoxon [10].

3. Results and discussion

The synthesis of 2,3,3a,4-tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-ones (**8**–**25**) was performed according to the synthetic approach shown in Scheme 1, by reacting the appropriate 1,2-phenylenediamine (**1**–**3**) with 3-acylpropionic acids (**4**–**7**) in refluxing anhydrous toluene. Derivatives **11**, **12** and **16**–**25** are new compounds, whereas the synthesis of **8**–**10** and **13**–**15** has already been reported [3]. Physicochemical data of compounds **11**, **12** and **16**–**25** are reported in Table 1.

When a 4-substituted 1,2-phenylenediamine derivative (**2** or **3**) was employed as starting material two series of isomeric derivatives, i.e. 6- or 7-substituted, were isolated from the reaction mixture, with a clear prevalence of the first. The regiospecificity may be

Table 2
Anticonvulsant activity against audiogenic seizures in DBA/2 mice and relative lipophilicity (R_m)

Comp.	ED_{50} (μmol/kg) [a] (± 95% confidence limits)		
	Clonic phase	Tonic phase	R_m
8	24.1 (12.7–45.5)	17.9 (8.34–38.6)	−0.357
9	52.7 (33.3–83.2)	27.4 (12.0–62.3)	−0.158
11	23.9 (14.9–38.5)	17.0 (9.19–31.6)	−0.288
13	104 (78.4–138)	79.0 (59.5–105)	−0.122
14	46.4 (26.8–80.5)	31.7 (18.3–54.9)	0.043
16	63.8 (45.5–89.7)	54.4 (37.5–78.8)	−0.065
cis-**18**	63.8 (45.1–90.2)	56.9 (40.9–89.2)	−0.061
trans-**18**	39.1 (22.7–67.5)	25.6 (15.5–45.5)	−0.061
cis-**19**	80.3 (47.9–134)	63.8 (45.1–90.2)	0.131
trans-**19**	43.2 (27.9–66.9)	29.1 (15.0–56.4)	0.122
21	29.2 (17.2–49.3)	27.0 (15.6–46.7)	−0.070
22	18.2 (7.02–47.2)	9.26 (2.35–36.5)	0.105
24	27.7 (17.5–44.1)	18.5 (12.5–27.5)	0.030

[a] All data were calculated according to the method of Litchfield and Wilcoxon [10]. At least 32 animals were used to calculate each ED_{50} value.

explained on the basis of the proposed mechanism of formation of these derivatives [3] which implies the formation of an intermediate benzimidazole derivative which successively undergoes cyclization controlled by the electronic characteristics of the substituent present on the benzimidazole moiety.

The structures of the 6- and 7-substituted isomers were assigned on the basis of ^{1}H NMR spectra, taking into account the shielding effect that the 4-amino group exerts on the proximal hydrogen at C-5. The resonance pattern of this proton depends on the position of the substituent, so the attribution is straightforward.

When **1** or **2** reacted with 3-benzoyl-2-methylpropionic acid (**7**), owing to the presence of a chiral center in the structure of γ-ketoacid **7**, the reaction furnished an approximate 1:1 mixture of *cis* and *trans* isomers which were identified on the basis of ^{1}H NMR spectroscopy assisted by NOE measurements: upon irradiation of the C-2 methyl resonance it is possible to observe a weak NOE effect for the aromatic protons of the C-3a-substituent only in *cis* derivatives.

Among 2,3,3a,4-tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-ones reported in Table 1, only 6-substituted derivatives were tested against audiogenic seizures in DBA/2 mice because our previous studies had suggested that 7-substituted ones did not show anticonvulsant effects. The employed audiogenic stimulation test in DBA/2 mice has been considered an excellent animal model for generalized epilepsy and for screening new anticonvulsant drugs.

As can be seen from the results obtained, these compounds displayed a broad range of anticonvulsant potency, and it is apparent that significant substituent effects occur (Table 2).

Within 3a-methyl-substituted compounds (**8**, **9**, and **11**), the introduction of fluorine atom at C-6 position on benzene fused ring (**11**) does not affect anticonvulsant properties of 6-unsubstituted one (**8**) whereas if this position bears a chlorine atom (**9**) the potency decreases.

A different trend was observed for 3a-phenylsubstituted derivatives (**13**, **14**, and **16**) among which the most active was 6-chloro derivative **14**. The anticonvulsant effects were also generally increased by the introduction of a methyl group at C-2 position (**18** and **19**). It is interesting to note that also the stereochemistry influences the biological properties, the *trans* isomers being more active than the corresponding *cis* ones.

Finally, the potency was strongly enhanced by the presence of a *p*-tolyl moiety at C-3a (**21**, **22**, and **24**). In particular, the combination of 6-chloro and *p*-tolyl substituents afforded the most active derivative of our series (**22**) which displayed an anticonvulsant potency fivefold higher than that of unsubstituted compound (**13**).

The relative lipophilicity (R_m) of the tested compounds is summarized in Table 2. Although the most active compound is also one of the most lipophilic derivatives, a direct correlation between lipophilicity and anticonvulsant activity cannot be pointed out. In fact, compounds with similar R_m values (i.e. **16** and **18**, **19** and **22**) show different potency, thus suggesting the importance of other parameters.

In conclusion, the synthesis and the evaluation of anticonvulsant activity of new 2,3,3a,4-tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-one derivatives have been reported. The obtained results demonstrate that the presence of halogen atom at C-6 of the benzene-fused ring and the *p*-tolyl group at C-3a position as well as the stereochemical features of the system contribute to the anticonvulsant activity.

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