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Synthesis and antidepressant-like action of stereoisomers of imidobenzenesulfonylaziridines in mice evaluated in the forced swimming test

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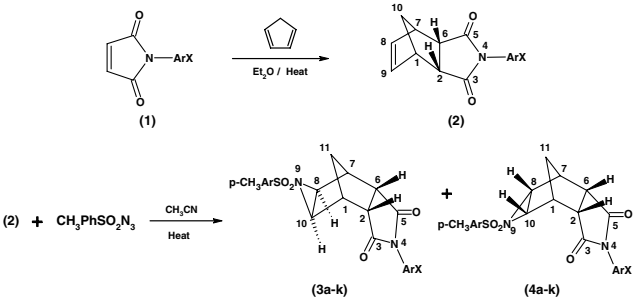
Abstract—The present study describes the chemical synthesis and pharmacological evaluation of a new series of eleven compounds stereoisomers of imidobenzenesulfonylaziridines in the forced-swimming test (FST) in mice. The pharmacological results of these compounds show that six of them, given intraperitoneally, reduced the immobility time of mice evaluated in the FST, an antidepressant-like profile of action similar to imipramine, a well-known standard antidepressant drug used for comparison, without compromising the animals' motor performance. The putative antidepressant-like action demonstrated here indicates their viability for the development of new therapeutic options for the treatment of depression.

1. Introduction

Depression is one of the most prevalent psychopathologies in the Western world and its therapy relies on classical antidepressant drugs such as monoamine oxidase inhibitors and drugs that inhibit the reuptake of catecholamines.[1] A common problem with the current antidepressant therapies is the several side effects (e.g., anti-cholinergic, gastrointestinal distress, anxiety, insomnia and sexual dysfunction) produced by these drugs besides their slow onset of action since there is a delay of about 4 weeks to alleviate the symptoms of depression.[2] Consequently, several research efforts are pursuing the discovery of new antidepressants with less side-effects, a faster onset of action and a better efficacy. In order to accomplish these goals of obtaining new compounds with antidepressant properties, we have studied the chemical and biological aspects of cyclic imides compounds.

In the present work, a series of imidobenzenesulfonylaziridine compounds was synthesized that brought together in a single molecule the chemical functions of imide and aziridine (**3** and **4**; Scheme 1), both known for their pharmacological properties including antitumoral activity. Among the compounds possessing an aziridine ring, mitomycin C has been used to treat stomach and lung cancer.[3–6] Moreover, the cyclic imide derivatives have been known for several decades and have been widely used in popular medicine in the treatment of several



X = H (a); 4-Cl (b); 3,4-Cl_2 (c); 4-CH_3 (d); 4-OCH_3 (e); 4-Br (f); 4-NO_2 (g); 3-ethyl (h); 3-NO_2 (i); 4-F (j) and 4-OH (k).

Scheme 1.

Keywords: Imidobenzenesulfonylaziridines; Antidepressant-like action; Forced-swimming test.
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psychopathologies such as anxiety, schizophrenia, and epilepsy.[7–10]

The pharmaceutical interest in these drugs was strengthened by the isolation of imides from natural sources[7]. In this regard, in the present study several analogue compounds of the cyclic imides were synthesized using phyllantimide (an alkaloid extracted from *Phyllantus sellowianus*) as the basic structure, and these compounds were tested in mice evaluated in the forced-swimming test, an animal model that has been extensively used as a screening model for new antidepressant agents.

2. Results

2.1. Evaluation of the antidepressant-like effect of the endo–endo stereoisomers of imidobenzenesulfonylaziridines

Acute treatment with the compounds **4a**, **4b**, **4c**, **4f**, **4g**, and **4h** promoted a decrease in the immobility time in the FST, as depicted in Figure 1 (control = 100.00 ± 3.82 %; (**4a**) = 76.62 ± 3.62 %; (**4b**) = 76.84 ± 7.82 %; (**4c**) = 73.33 ± 7.06 %; (**4f**) = 73.77 ± 8.22 %; (**4g**) = 75.64 ± 6.04 %; (**4h**) = 67.73 ± 9.88 %; $\text{Imipramine}_{(15\ mg/kg)}$ = 44.52 ± 7.75 %; ($F_{(7,53)} = 5.46$; $P < 0.0001$). The immobility time of animals treated with the other compounds **4d**, **4e**, **4i**, **4j**, and **4k** did not statistically differ from control values as shown in Figure 2 (control = 100.00 ± 3.82 %; (**4d**) = 74.09 ± 17.29 %; (**4e**) = 89.91 ± 9.13 %; (**4i**) = 86.20 ± 5.81 %; (**4f**) = 111.06 ± 1.70 %; (**4k**) = 90.65 ± 6.64 %; $\text{Imipramine}_{(15\ mg/kg)}$ = 44.52 ± 7.75 %; $F_{(6,46)}$ = 5.53; $P > 0.05$). However, compound **4d** has a trend to present an antidepressant-like profile of action which did not reach statistical significance due to data variation.

2.2. Evaluation of the locomotor effect of the endo–endo stereoisomers of imidobenzenesulfonylaziridines in the open-field test

Acute systemic treatment with the compounds **4a**, **4b**, **4c**, **4f**, **4g**, and **4h** promoted no changes in the locomotor activity registered on the open-field test, as depicted in Figure 3 (A: number of crossings, control = 93.67 ± 5.74 s; (**4a**) = 78.43 ± 6.78 s; (**4b**) = 100.40 ± 13.04 s; (**4c**) = 90.29 ± 18.68 s; (**4f**) = 86.00 ± 10.78 s; (**4 g**) = 77.86 ± 10.57 s; (**4h**) = 80.29 ± 4.84 s; $F_{(6,36)} = 0.55$; $P > 0.05$; B: rearing, control = 38.67 ± 3.42 s; (**4a**) = 36.00 ± 4.36 s; (**4b**) = 48.00 ± 2.34 s; (**4c**) = 35.71 ± 5.97 s; (**4f**) = 41.00 ± 3.42 s; (**4g**) = 33.57 ± 2.83 s; (**4h**) = 45.14 ± 3.40

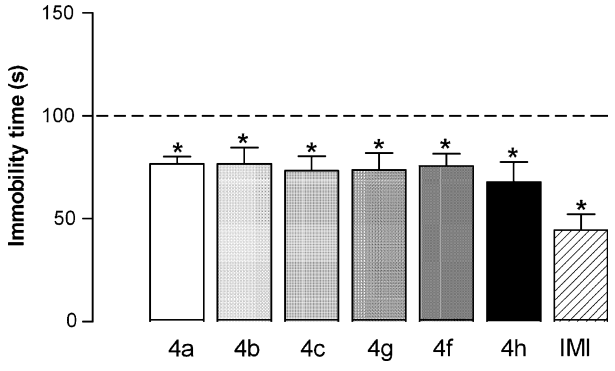

Figure 1. Effects of acute treatment with different endo–endo stereoisomers of imidobenzenesulfonylaziridines (**4a**, **4b**, **4c**, **4f**, **4g**, and **4h**, 1 mg/kg ip) and the standard antidepressant imipramine (IMI, 15 mg/kg, ip) on the immobility time in a 5-min swimming test. Each column represents means ± SEM. The dotted line represents the mean of the values of control animals. $^*P < 0.05$ as compared to control (all comparisons were made by ANOVA followed by Dunnett's test).

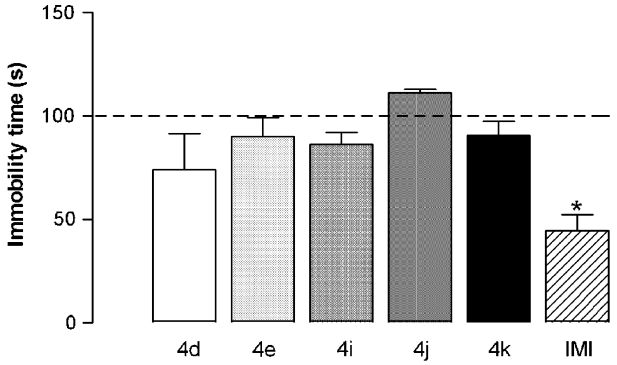

Figure 2. Effects of acute treatment with endo–endo stereoisomers of imidobenzenesulfonylaziridines (**4e**, **4i**, **4j**, and **4k**, 1 mg/kg, ip and the standard antidepressant imipramine (IMI, 15 mg/kg, ip) on the immobility time in a 5-min swimming test. Each column represents means ± SEM. The dotted line represents the mean of the values of control animals. $^*P < 0.05$ as compared to control (all comparisons were made by ANOVA followed by Dunnett's test).

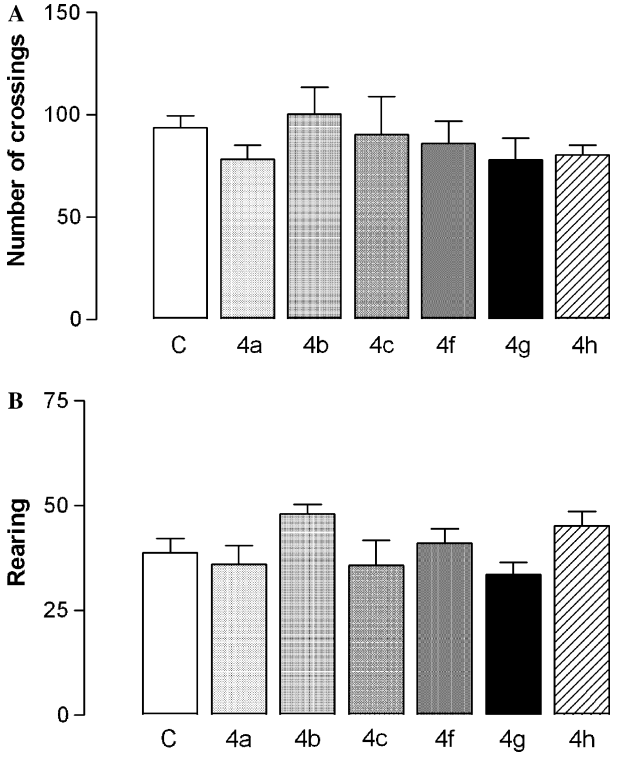

Figure 3. Effects of acute treatment with different endo–endo stereoisomers of imidobenzenesulfonylaziridines (**4a**, **4b**, **4c**, **4f**, **4g**, and **4h**, 1 mg/kg ip) on the behavioral parameters (A, number of crossings and B, rearing) evaluated in the open-field test. Each column represents means ± SEM. $^*P < 0.05$ as compared to control (all comparisons were made by ANOVA followed by Dunnett's test).

s; $F_{(6,36)} = 1.61$; $P > 0.05$), as compared to the values presented by control group.

3. Discussion

To the best of our knowledge, this is the first demonstration that the structural analogues of cyclic imides have an antidepressant-like profile of action after acute treatment in the classical Porsolt's model of forced-swimming test (FST).[11,12] The FST was designed by Porsolt as a primary screening test for antidepressants and it remains one of the best models for this purpose for several reasons. It is a low-cost, fast, and reliable model to test potential antidepressant treatments with a strong predictive validity. Porsolt et al. (1977) and Porsolt et al. (1978), who proposed this behavioral model for the screening of new antidepressant compounds, concluded that the immobility time observed in the test reflected a state of lowered mood or hopelessness in animals; thus, this animal model is the most widely used tool for preclinical screening of putative antidepressant agents.[17–20] The FST shows a strong sensitivity to monoamine alterations and is a very specific cluster of stress-induced behaviors that have no direct, empirical relation to depression symptoms in humans, but which are nonetheless exquisitely sensitive to monoaminergic manipulations.[11,20] It also provides a useful model to study neurobiological and genetic mechanisms underlying stress and antidepressant responses.[21–23]

The present study describes the pharmacological evaluation of a new series of eleven compound stereoisomers of imidobenzenesulfonylaziridines, six of which showed a clear antidepressant activity in mice evaluated in the FST. On the other hand, our preliminary studies showed that the compounds with exo–endo configuration are inactive, probably due to severe steric restrictions.[15]

Nevertheless, the compounds with endo–endo configurations and four attached electron-withdrawing substituents in the aromatic ring, except for compound **4j** (X = F), were active in the FST, whereas the compounds with four attached electron-donating substituents did not show any biological activity. In this regard, studies involving cyclic imides have demonstrated that their biological activity is related to the opening of the imidic ring due to a nucleophilic attack on one of the carbonyls by a biomolecule.[29] It has been previously shown that succinimide derivatives possess an important anticonvulsant activity, attributed to a –CO–NR–CO– fragment also present in barbiturates and in other drugs with well-known anticonvulsant activity.[7]

On the other hand, many drugs are reported to affect several aspects of motor function, resulting in false assumptions about the drugs' effects, which is specially important in the forced-swimming test that is based on a motor response of the animals. Thus, we cannot discard the possibility that our results with the several compounds are merely due to a general stimulation of the animals' motor activity. For this reason, animals were evaluated in an open-field at the same dose which presented the antidepressant-like profile of action in the FST. We observed that these compounds did not modify the behavioral performance of mice evaluated in the open-field test which essentially depends on their motor function. This observation strongly indicates that the reduction in the immobility time is due to a selective antidepressant-like effect of these aziridine compounds and not merely a result of a general stimulation of the animal's motor activity. Therefore, these compounds deserve to be studied further because, as previously mentioned, there is a need for new and improved antidepressant compounds.

We also intend to carry out biological assays with tumor cell lines since the imidobenzenesulfonylaziridines present potential anticancer activity due to the aziridine ring.[3–6] Nevertheless, as any other new compound, these aziridines have to be tested in toxicological assays, although in our preliminary test with *Artemia salina* Leach they did not present any significant toxicity.[24]

4. Conclusion

In conclusion, the present results showed a clear antidepressant-like effect for the endo–endo stereoisomers of imidobenzenesulfonylaziridines after acute treatment. The exact underlying molecular mechanism of action is presently under investigation but the findings shown here are very significant because they reveal new potential tools for the treatment of depression, an important psychopathology which is one of the most prevalent throughout the world and is still in need of new and perhaps better therapeutic approaches.[25]

5. Materials and methods

5.1. Drugs and solvents

The drugs and solvents used were: imipramine chlorhydrate, from Sigma Chemical Company (St. Louis, USA) and the endo–endo stereoisomers of imidobenzenesulfonylaziridines that were synthesized in-house.[26] Due to the hydrophobic characteristics of these synthetic compounds, they were solubilized in corn oil, while imipramine was dissolved in saline solution (NaCl 0.9%) only.

5.2. Compound synthesis and features

Analytical grade reagents were used and purified according to methods cited in the literature.[27] For the determination of the melting point (mp), a Microquímica™ device model MQRPF-301 was used. For the CHN analysis, a CHN elemental analyzer PERKIN ELMER 2400 was used. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Brucker AC-200F (at 200 and 50 MHz, respectively). $CDCl_3$ was used as the solvent with TMS as the internal standard; chemical shifts (δ) were in parts per million. In the thin-layer chromatography (TLC), aluminum sheets with silica gel 60 F-254 of 0.2 mm thickness were used. All imidobenzenesulfonylaz-

iridines were purified by column chromatography with silica gel 60 (230–400 mesh) purchased from Merck.

All compounds, except for compounds **4i**, **4j**, and **4k**, were obtained using previously described methodologies, with minor modifications, which produced good yields (approximate 65–90%) as recently reported by our group.[26] Compounds **4i**, **4j**, and **4k** have not yet been reported in the literature. The exo–endo (**3**) and endo–endo (**4**) imidobenzenesulfonylaziridines were synthesized through a 1,3-dipolar-type reaction of *p*-toluenesulfonylazide (previously prepared) and different *endo*-norbornenesuccinimides (**2**). The *endo*-norbonenesuccinimides were prepared through the Diels–Alder reaction between substituted *N*-phenylmaleimides (**1**) and cyclopentadiene according to the method described in the literature for similar structures.[28] The *N*-phenylmaleimides were prepared through the reaction of a substituted aniline and maleic anhydride in acetic anhydride.[29]

All compounds were characterized by CHN analysis, ^{1}H NMR and ^{13}C NMR.[29] For exo–endo (**4c**) and endo–endo (**4b**) we also determined the molecular and crystal structures by X-ray diffraction.[30]

5.3. Animals

Male adult Swiss mice (30–45 g) were used in all experiments. They were housed in groups of 20 animals per plastic cage under controlled conditions of light (from 07:00 to 19:00 h) and temperature (23 ± 2 °C). The animals were allowed free access to standard laboratory food and tap water, and to adapt to the laboratory environment for at least one week before the behavioral assessment. For each treatment, a different group of experimental and control animals was used. All tests were carried out according to international standards of animal welfare recommended by the Brazilian Society of Neuroscience and Behavior (Act 1992) and approved by the local Committee for Animal Care in Research (# 081/CEUA and 23080.001156//2001-50/UFSC). The minimum number of animals and duration of observation required to obtain consistent data were employed.

5.4. Forced-swimming test

The forced-swimming procedure was a modification of that described by Porsolt et al.[11,12] Briefly, animals were submitted to a swimming stress session for 15 min, 24 h before being individually returned to the same plastic cylinders (height 18.5 cm, diameter 12.5 cm) containing 13.5 cm of water at 25 °C, for 5 min. On the test day, the behavioral observation was performed for up to 5 min by an experienced observer, who was blind to the treatment condition. Animals were judged to be immobile when they ceased struggling and remained floating motionless in the water, making only those movements necessary to keep the head above water.

5.5. Open-field test

The spontaneous motor activity was measured in an open-field made of transparent Plexiglas (height, 17.0 cm; length, 30.0; width, 30.0 cm) with a black floor marked with white lines in 10 cm^2 areas. Thirty minutes after administration of the compounds, each mouse was placed in the center of the arena and their ambulation was recorded for a 5-min period.[13] The number of grid lines crossed with both hind feet (number of crossings) and the number of rearings were counted as an index of spontaneous ambulation. After each trial, the open-field apparatus was wiped and cleaned with ethanol (10%) solution.

5.6. Experimental procedures

5.6.1. Compound synthesis. 9-(4′-Methylphenylsulfonyl)-4-(3″-nitrophenyl)-(2*R*,6*S*,8*R*,10*S*)-4,9-diazatetracycle[5.3.1.0^{2,6}.0^{8,10}]undecane-3,5-dione (**4i**). *p*-Toluenesulfonylazide (0.96 g, 0.0049 mol) was added to a mixture of 4-(3′-nitrophenyl)-4-aza-tricycle[5.2.1.0$^{2,6\text{-endo}}$]dec-8-ene-3,5-dione (0.92 g, 0.0033 mol) in acetonitrile (20 mL). The reaction was refluxed (26 h) and the solvent was evaporated under vacuum. The solid residue was triturated with methanol/chloroform (3:7) and filtered off by suction to give the mixture of (**3i**) and (**4i**). The endo–endo (**4i**) product was isolated by column chromatography (silica gel, ethyl acetate/acetone/hexane, 6:3:11). Yield: 88 %; mp (dec.) 280.0 °C Anal. Calcd for $C_{22}H_{19}N_3O_6S$: C, 58.27; H, 4.23; N, 9.27; O, 21.16; S, 7.07. Found: C, 58.81; H, 4.58; N, 7.54. ^{1}H NMR δ ppm: CH_2-11 (m: 1.90); CH_2-11 and CH_3–Ph (br s: 2.32); CH-7 (s: 3.16); CH-8 (s: 3.30); CH-6 (s: 3.60); ArH (m: 7.06–8.32). ^{13}C NMR δ ppm: CH_3–Ph (21.56); CH_2-11 (40.22); CH-7 (48.05); CH-8 (49.63); CH-6 (55.09); C Ar (123.87; 126.25; 128.12; 129.47; 132.34; 138.20; 145.24; 146.08); C=O (174.50).

By this procedure the following imidobenzenesulfonylaziridines were prepared:

9-(4′-Methylphenylsulfonyl)-4-(4″-fluorophenyl)-(2*R*, 6*S*, 8*R*,10*S*)-4,9-diazatetracycle[5.3.1.0^{2,6}.0^{8,10}]undecane-3,5-dione (**4j**). Yield: 73%; mp 242.3–242.7 °C. Anal. Calcd for $C_{22}H_{19}FN_2O_4S$: C, 60.39; H, 4.90; F, 3.18; N, 4.69; O, 16.09; S, 10.75. Found: C, 60.45; H, 4.82; N, 5.02. ^{1}H NMR δ ppm: CH_2-11 (d: 1.93, J = 10 Hz); CH_2-11 and CH_3–Ph (m: 2.34); CH-7 (s: 3.09); CH-8 (m: 3.23); CH-6 (s: 3.56); ArH (m: 7.05 – 7.59). ^{13}C NMR δ ppm: CH_3–Ph (22.31); CH_2-11 (40.75); CH-7 (48.73); CH-8 (50.38); CH-6 (55.09); C Ar (115.99; 116.44; 128.54; 128.71; 129.05; 130.15; 133.29; 145.80; 164.73); C=O (175.74).

9-(4′-Methylphenylsulfonyl)-4-(4″-hidroxyphenyl)-(2*R*, 6*S*,8*R*,10*S*)-4,9-diazatetracycle[5.3.1.0^{2,6}.0^{8,10}]undecane-3,5-dione (**4k**). Yield: 81%; mp 128.8–129.4 °C. Anal. Calcd for $C_{22}H_{20}N_2O_5S$: C, 62.25; H, 4.75; N, 6.60; O, 18.85; S, 7.55. Found: C, 61.92; H, 4.84; N, 6.52. ^{1}H NMR δ ppm: CH_2-11 (m: 1.97); CH_2-11 and CH_3–Ph (s: 2.33); CH-7 (s: 3.11); CH-8 (s: 3.23); CH-6 (s: 3.60); ArH (m: 7.58).^{13}C NMR δ ppm: CH_3–Ph (21.64); CH_2-11 (40.09); CH-7 (47.99); CH-8 (49.64); CH-6 (55.25); C Ar (121.82; 126.90; 128.36; 129.51; 130.15; 132.61; 145.12; 149.57); C=O (174.96).

5.6.2. Evaluation of the antidepressant-like effect in forced-swimming test. Our preliminary dose–response studies provided evidence that these compounds exerted central depressant effects at 1 mg/kg in mice.[14–16] Thus, the compounds were administered ip, at this dose, 30 min before the forced-swimming test (5 min). Imipramine (IMI, 15 mg/kg ip) was employed as the standard antidepressant drug using the same administration schedule. The control group received corn oil plus NaCl 0.9% in the same proportion and in a constant volume, by the same route, and under a similar schedule of administration.

5.6.3. Evaluation of the spontaneous motor effect in the open-field test. The compounds were administered at the same dose (1 mg/kg ip) 30 min before the open-field test (5 min). Control animals received corn oil plus NaCl 0.9% in the same proportion and in a constant volume, by the same route, and under a similar schedule of administration.

5.7. Statistical analysis

Values are presented as group means and SEM. The data were analyzed by one-way analysis of variance (ANOVA), and the post hoc comparison of means was carried out with Dunnett's test, using the software GraphPad Prism® version 3.0, with $P < 0.05$ being considered statistically significant.

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