PHARMACOLOGICAL ACTIVITY IN AN ACUTE ANIMAL MODEL OF SEIZURES OF NOVEL ANTICONVULSANTS IDENTIFIED THROUGH COMPUTATIONAL CHEMISTRY

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INTRODUCTION
Epilepsy is the most prevalent chronic brain disorder, affecting about 50 million people worldwide, 90% of which come from developing countries. (1) Current available chemotherapies fail to control epilepsy seizures in around 30-40% of the patients, (2) and even the new generation of anticonvulsant drugs present significant and frequent side-effects, e.g. drowsiness, sedation, ataxia, nausea and other gastrointestinal symptoms and liver toxicity. (3,4)
Recently we have reported the discovery of anticonvulsant activity in the Maximal Electroshock (MES) test of abietic acid, propylparaben (PPB) and methylparaben (MPB), through the application of a discriminant function based in topological molecular descriptors in the virtual screening of Merck Index 13th database (5,6). The three drugs have shown activity at 30 mg/kg (mice, ip), which is the lowest dose tested in phase I of the NIH Anticonvulsant Drug Development Program. MES test is an acute animal model of epilepsy that identifies phenytoin-like anticonvulsants, whose mechanism of action involves blockade of sodium and/or calcium channels.
Here we report the effects of abietic acid, PPB and MPB (AT4, AT2 and AT5, respectively) on another species and another acute animal model of epilepsy, the Pentylenetetrazol (PTZ)-induced seizures, which identifies anticonvulsant drugs that enhance the GABAergic pathway.

MATERIALS AND METHODS
Male Wistar rats of 250-300g received a single administration of PTZ (100 mg/kg, i.p.) 30 min after the injection of saline solution (1 ml/kg, i.p.) or AT2, AT4 or AT5 (30 mg/kg, i.p.). Latencies to the first myoclonus, clonic and tonic seizures as well as the mortality rate were evaluated during 1 h after PTZ administration.

RESULTS
The three drugs tested increased the latency to the myoclonic, clonic and tonic components of PTZ induced seizures in Wistar rats (See table 1). All the experimental groups as well as controls showed 100% of mortality. The AT2 drug presented the higher efficacy to enhance the latency to the different components of PTZ-induced seizures.

CONCLUSIONS
Based on the results in the PTZ-induced seizures, we may conclude that the three drugs tested induce inhibitory effects that result in an enhanced latency to present the PTZ-induced seizures. Further experiments using experimental models such as kindling, are necessary to determine if these drugs are able to modify the epileptogenesis process.

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REFERENCES

Tables

Table 1. Increase of the latency time to different components of PTZ-induced seizures by the three tested drugs (related to the control group).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Myoclonus</th>
<th>Clonus</th>
<th>Tonic Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT2</td>
<td>216%</td>
<td>238%</td>
<td>228%</td>
</tr>
<tr>
<td>AT4</td>
<td>65%</td>
<td>103%</td>
<td>56%</td>
</tr>
<tr>
<td>AT5</td>
<td>68%</td>
<td>78%</td>
<td>206%</td>
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