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Synthesis and antidepressant-like activity evaluation of sulphonamides and sulphonyl-hydrazones

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ABSTRACT

In this study a series of sulphonamides and sulphonyl hydrazones of maleimide, naphthalimide and phthalimide derivatives was synthesized. The antidepressant effect of these compounds was evaluated by the forced-swimming test in mice. The behavioural parameter observed in this test is a reduction in the immobility time, which is indicative of antidepressant activity. All compounds, except **8**, **11** and **24**, were active as antidepressants. The most active compound was the sulphonyl-hydrazone **10** which showed an activity of around 72.02% at 60 mg/kg, it thus being more active than imipramine (10 mg/kg, ip), a commercial antidepressant. Other important results were obtained for the benzylnaphthalimide derivatives, the sulphonamides **21** and **22** showing activity of 64% at 10 mg/kg, also being more active than imipramine. These results indicate that the sulphonamides and sulphonyl-hydrazone cyclic imide derivatives are potential compounds for use in the designing of new candidates for the treatment of depression.

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1. Introduction

Depression is one of the most prevalent psychopathologies in the Western world.[1] It is characterized by anhedonia or the loss of interest or pleasure in normal daily activities and feelings of sadness.[2] Additional symptoms may include feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, etc. In its worst form it can lead to suicide.[3] The high prevalence of suicide in depressed patients (up to 15%) coupled with complications arising from stress and its effect on the cardiovascular system have suggested, that it will become the second leading cause of premature death or disability worldwide by the year 2020.[3]

Its therapy relies on classical antidepressant drugs such as monoamine oxidase inhibitors and drugs that inhibit the reuptake of catecholamines.[4] 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.[5] In addition, a significant proportion of these patients will not respond to treatment, or will show only partial response. Clinical limitations and adverse effects of currently used antidepressants consequently, there is a need for faster, more effective, therapeutic treatments with less side effects, in order to limit the impact of depression on patients' lives.[6]

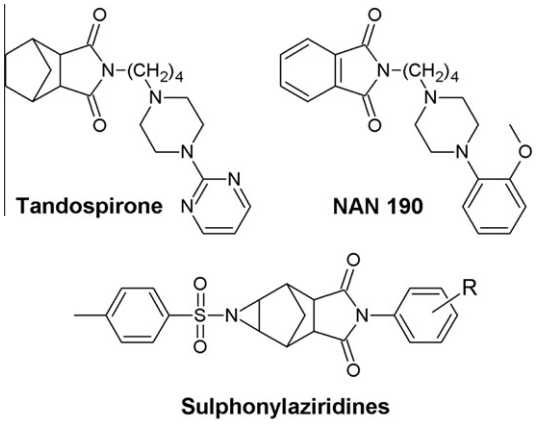

Figure 1. Cyclic imide derivatives active as antidepressants.

In this regard, the cyclic imides and their derivatives have played an important role in the treatment of psychopathologies such as anxiety, schizophrenia, epilepsy and depression.[7–12] The tandospirone[13] and NAN-190 (Fig. 1),[14,15] for example, exert

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antidepressant activity by inhibition of 5-HT_{1A} receptors. Moreover, the promising antidepressant activity of sulphonamides[16] and hydrazones[17] has been reported in the literature, as well as the sulphonylaziridines[10] (Fig. 1). The presence of groups such as, cyclic imides, sulphonyl and amines encouraged us to synthesize and evaluated a series of sulphonamides and sulphonyl-hydrazones cyclic imide derivatives as part of our investigation work. In this study, these compounds were tested in mice using the forced-swimming test (FST) and tail suspension (TST) test two experimental animal models has been extensively used as a screening model for new antidepressant agents.

2. Results

2.1. Chemistry

The seven sulphonamides (**2–4**, **21–24**) and nine sulphonyl-hydrazones (**7–12, 26, 30, 31**) were synthesized as illustrated in Schemes 1–3. In Scheme 1, the sulphonamides (**2–4**) and the sulphonyl-hydrazones (**7–12**) were prepared starting from *N*-(*p*-chlorosulphonyl)phenylmalemide (**1**). The first step involved cycloaddition between the sulphonyl chloride (**1**) and different dienes (furan or 2-methylfuran) in order to observe the influence of the different substitutions on the maleimide. The reactions were carried out at room temperature in diethyl ether, using furan or 2-methylfuran. The sulphonamides (**2–4**) were obtained by condensation of the Diels–Alder adducts with pyrrolidine or morpholine in methanol at approximately 0 °C. The sulphonyl-hydrazones (**7–12**) were obtained by reaction of the adducts with hydrazine hydrate and subsequently with different benzaldehydes (Scheme 1).

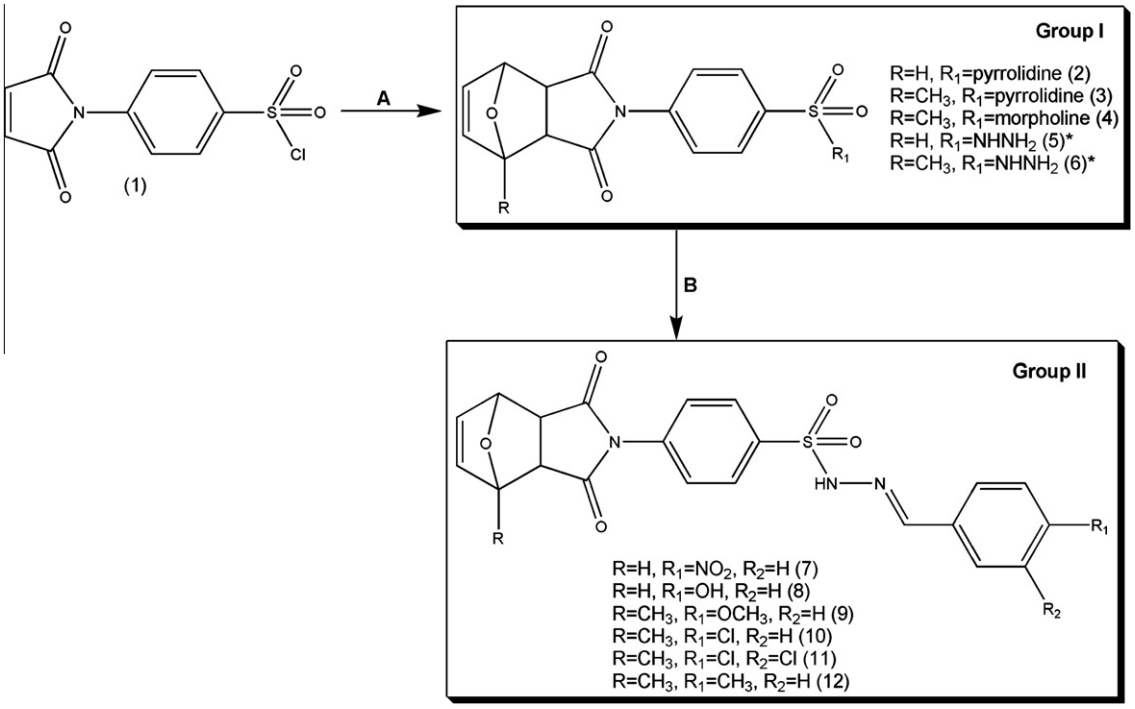
A similar procedure was used to synthesize the compounds **21–24, 26, 30** and **31** (Schemes 2 and 3). In these cases, the sulphonyl chlorides (**18–20** and **28**) were prepared in two steps. The preparation of cyclic imides (**15–17** and **27**) occurred in the first step by reaction between the appropriate cyclic anhydride and different amines. The reaction was refluxed in ethanol for 1–6 h. The cyclic imides were added to 6 equiv of cold chlorosulphonic acid in the second step, followed by heating at 60 °C for around 15 min. The mixture was poured into water/ice and the sulphonyl chlorides were obtained. In the next step, the sulphonyl chlorides (**18–20** and **28**) were condensed with different amines to prepare the sulphonamides (**21–24**) and the sulphonyl hydrazides (when hydrazine hydrate was used) (**25** and **29**). For the synthesis of sulphonyl hydrazones (**26, 30** and **31**), the sulphonyl hydrazides were condensed with benzaldehydes, as described for the *N*-(*p*-chlorosulphonyl)phenylmalemide (**1**) derivatives.

The structures of the compounds were confirmed from chemical identification data obtained by ^{1}H NMR, ^{13}C NMR, IR and elemental analysis.

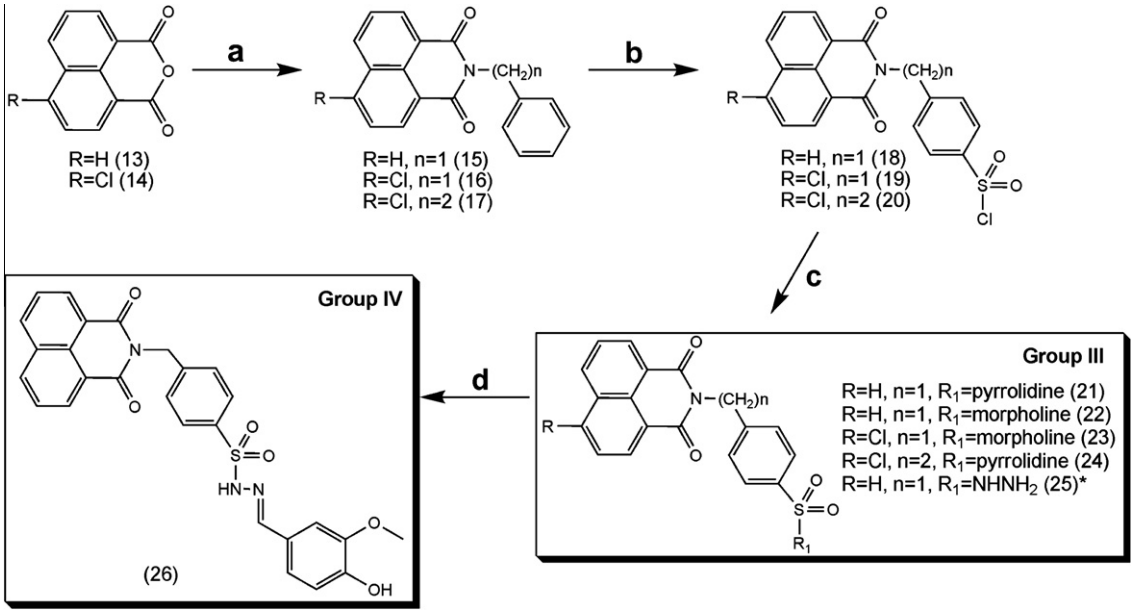
2.2. Evaluation of the antidepressant-like activity of the compounds

When compared with their respective controls, the acute treatment with all compounds of group I, comprising compounds **2** (30 and 60 mg/kg), **3** (10 mg/kg) and **4** (6 and 10 mg/kg), promoted a decrease in the immobility time in the FST, as shown in Figure 2. The values for the percentage reduction (IM) in the immobility time with the highest dose used in this experiment for the three compounds were, respectively, 28.80% [$F_{(23,07)} = 23.03$, $P < 0.01$], 85% [$F_{(3,28)} = 9.07$, $P < 0.01$], and 28.80% [$F_{(3,28)} = 35.73$, $P < 0.01$].

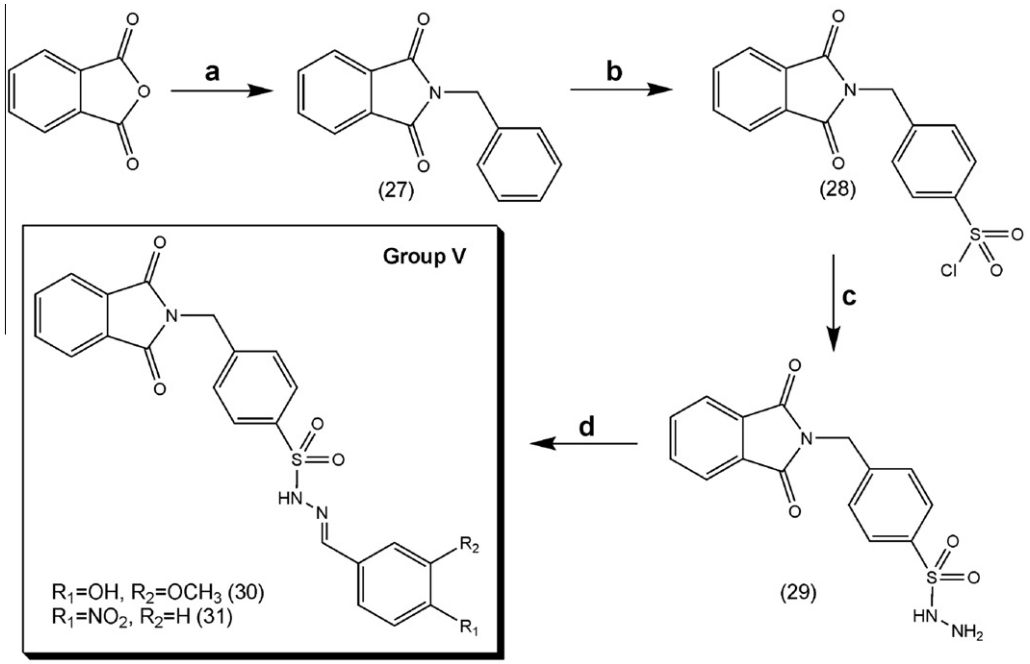
On analyzing the treatment with the compounds of group II (Fig. 3) it was observed that the pre-treatment of animals with compounds **8** and **11** did not produce a decrease in the immobility time of the animals when compared with the control group. However, this effect was observed in animals treated with compounds **7** (6 and 10 mg/kg), **9** (6 and 10 mg/kg) **10** (10–60 mg/kg) and **12** (6 and 10 mg/kg). The IM values for the immobility time calculated in relation to these compounds (with the highest dose used) were, respectively, 65.44% [$F_{(3,28)} = 35.73$, $P < 0.001$], 58.53% [$F_{(3,28)} = 7.56$, $P < 0.01$], 62.83% [$F_{(3,28)} = 46.55$, $P < 0.01$], and 62.83% [$F_{(3,27)} = 41.97$, $P < 0.01$]. In this group, compounds **10** and **12** had the same



Scheme 1. Synthesis of sulphonamides and sulphonyl-hydrazones *N*-(*p*-chlorosulphonyl)phenylmalemide derivatives. Reagents and conditions: (A) (i) furan or 2-methylfuran, Et_2O, rt; (ii) amine or N_2H_4, MeOH, ~0 °C; (B) EtOH, rt, 1 h, benzaldehydes. *Compounds not evaluated in biological test.



Scheme 2. Synthesis of naphthalimide derivatives. Reagents and conditions: (a) EtOH/AcOH, reflux, 1–6 h, appropriate amine; (b) $HClSO_3$, 0–50 °C; (c) amine, MeOH, ca. 0 °C; (d) EtOH, 2 or 3 drops concd HCl, rt, 1–3 h, benzaldehydes. *Compound not evaluated in biological test.



Scheme 3. Synthesis of phthalimide derivatives. Reagents and conditions: (a) EtOH, reflux, 2 h, benzylamine; (b) $HClSO_3$, 0–50 °C; (c) N_2H_4, MeOH, ca. 0 °C; (d) EtOH, 2 or 3 drops concd HCl, rt, 1–3 h, benzaldehydes.

pharmacological profile, differing only in the dose used to produce the antidepressant-like effect in the animals.

The compounds comprising group III are listed in Figure 4. Compounds **21** (6 and 10 mg/kg), **22** (6 and 10 mg/kg) and **23** (6 and 10 mg/kg), respectively, promoted reductions in the immobility time (with the highest dose used) of 52.26% [$F_{(3,28)} = 17.50$, $P < 0.01$], 60.3% [$F_{(3,27)} = 24.64$, $P < 0.01$] and 52.63% [$F_{(3,28)} = 7.89$, $P < 0.01$] compared with the control group. However, compound **24** (60 mg/kg) demonstrated no action, a result which was not of statistical significance due to the high degree of variation in the data.

The activity of compound **26** (10 mg/kg) (group IV) was 60.30% [$F_{(3,28)} = 25.14$], as observed in Figure 5.

Finally, the results obtained with the compounds of group V can be seen in Figure 6. This group is represented by compounds **30** (6–30 mg/kg) and **31** (10–60 mg/kg), which were able to reduce with statistical significance, the immobility time in the FST by 63.9% [$F_{(3,28)} = 43.08$, $P < 0.01$] and 68.64% [$F_{(3,28)} = 30.43$, $P < 0.01$], respectively.

In a second experiment to confirm the antidepressant-like effect of the compounds only those which showed activity in the FST were tested again in the TST (Fig. 7). The results showed that all tested compounds exhibited statistically anti-immobility effect when compared with their respective controls, and the values for the percentage reduction (IM) in the immobility time were: group

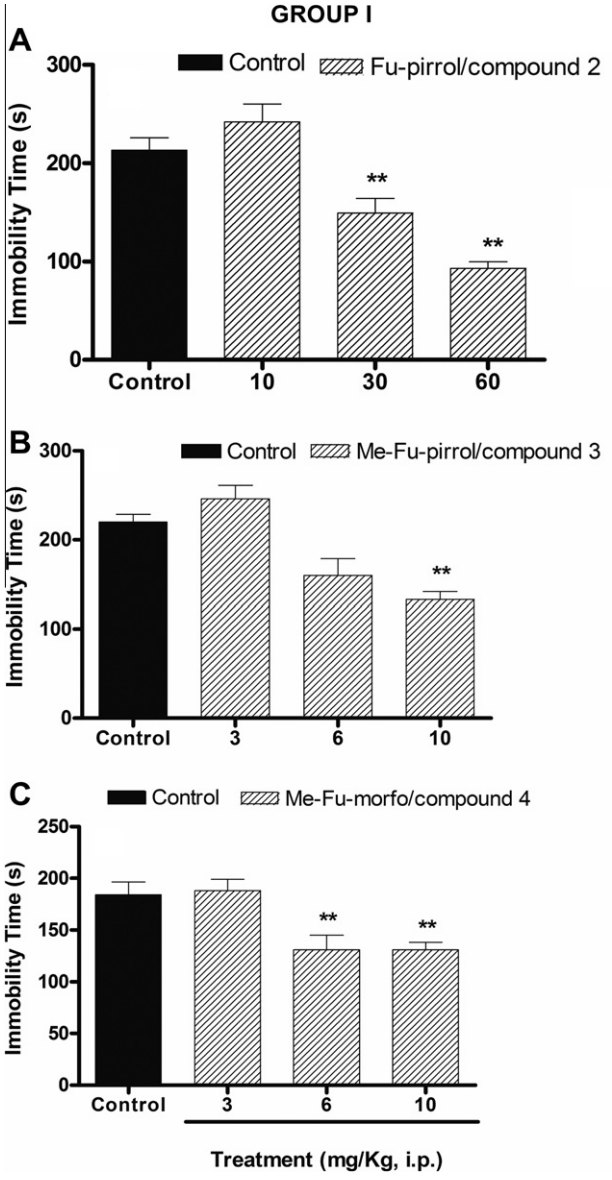


Figure 2. Effect of compounds included in group I (A—Fu-pirrol, B—Fu-o-NO2, C—C-fu-p-OH/3–10 mg/kg or 10–60 mg/kg, ip), with acute administration in mice, on immobility time when evaluated in the forced swimming model. Data are reported as means ± SEM. $N = 8–10$ mice. $^{**}P < 0.01$, compared to the control group (ANOVA followed by Dunnett's analysis).

I [**2** (58.85%), **3** (31.17%), **4** (23.69%)]; group II [**7** (57.50%), **9** (41.64%), **10** (62.87%), **12** (55.05%)]; group III [**21** (45.57%), **22** (57.14%), **23** (30.61)]; group IV [**26** (74.65%)], group V [**30** (69.21%), **31** (64.88%)].

In another experiment, the studied compounds were again tested in the FST, and their activities were also compared with classic agents antidepressives imipramine and fluoxetine (Table 1). The results show that for group I the order of effectiveness was: fluoxetine > imipramine > **2** > **4** > **3**. In group II, the antidepressant-like activity of **10** was superior to that of imipramine but not to that of fluoxetine. In group III, **21** and **22** had efficacies similar to imipramine but lower than fluoxetine. In group IV, **26** had an effect similar to imipramine but weaker than fluoxetine. Finally, in group V, the order of efficacy observed in the experiments was fluoxetine > imipramine > **31** > **30.** In general the results show that compounds in studies may show an antidepressant-like activity but none of them showed a superior effect to conventional antidepressants.

2.3. Evaluation of the locomotor effect of the compounds in the open-field test

In this experiment it was observed that acute systemic treatment with all compounds tested promoted no changes in the locomotor activity, as seen in Table 2. There was no statistical significance for the behavioural parameters of rearing and crossing observed in this test.

3. Discussion

Depression is a frequently seen psychiatric illness resulting from the loss of psychosocial ability. It is a serious public health problem with high morbidity and mortality and it also increases the risk of comorbidity.

The average prevalence of depression among humans is 17–19% and of suicide during depression is 15%.[3,17] An important theory for the formation of depression is the monoamine hypothesis, which proposes that there is a decreasing effect of biological amines like serotonin (5-HT), noradrenaline and dopamine during depression.[18] It is well known that the serotonin system plays an important role in the neural regulation of mood[19] and enhancement of 5-HT neurotransmission is the basis of the therapeutic response to different classes of antidepressant treatment.

In studies using drugs affecting the serotonergic system, the inhibition of serotonin reuptake in the synaptic terminal or inhibition of its metabolism (monoaminooxidase inhibitors) has been investigated. Also, antidepressants affecting 5-HT receptor subtypes have been studied, since this class of antidepressants has been frequently used in the therapy of depression[20,21] and antidepressants used in clinical trials affect these mechanisms.

Given the number of drugs available on the market a question arises: why study new compounds and assess their potential antidepressant activity? In fact, there are several reasons: (i) there is still no drug on the market that offers a 100% cure rate for affective disorders; (ii) the drugs available alter the behaviour of the users; (iii) the drugs available exhibit various side-effects on adherence to the treatment; (iv) there are few drugs available that affect the causative agents of this disease and most are palliative; and (v) some available medications are refractory.

For several years, natural or synthetic compounds with potential antidepressant action have been studied and the cyclic imides are examples of these.[7–12] Our research group was the first to demonstrate that the structural analogues of cyclic imides have an antidepressant-like profile of action after acute treatment in the classical model of Porsolt's forced-swimming (behavioural despair) test (FST), an assay generally used for the prediction of antidepressant activity which does not involve pharmacological interaction.[10] According to Porsolt et al. (1977),[22–25] immobility seen in rodents during swimming reflects behavioural despair, as seen in human depression, and it is well known that the antidepressant drugs cause a significant decrease in the immobility time in mice. In this test, it has been shown that the majority of the extracts, compounds or standard drugs studied significantly reduce the duration of the immobility time in comparison to control animals.

To confirm the results obtained in the FST, many researchers have used in their experiments the tail suspension test (TST).[26] The tail suspension test has become one of the most widely used models for assessing antidepressant-like activity in mice. The same way as observed in FST, the TST is based on the fact that animals subjected to the short-term inescapable stress of being suspended by their tail will develop an immobile posture.[26–28]

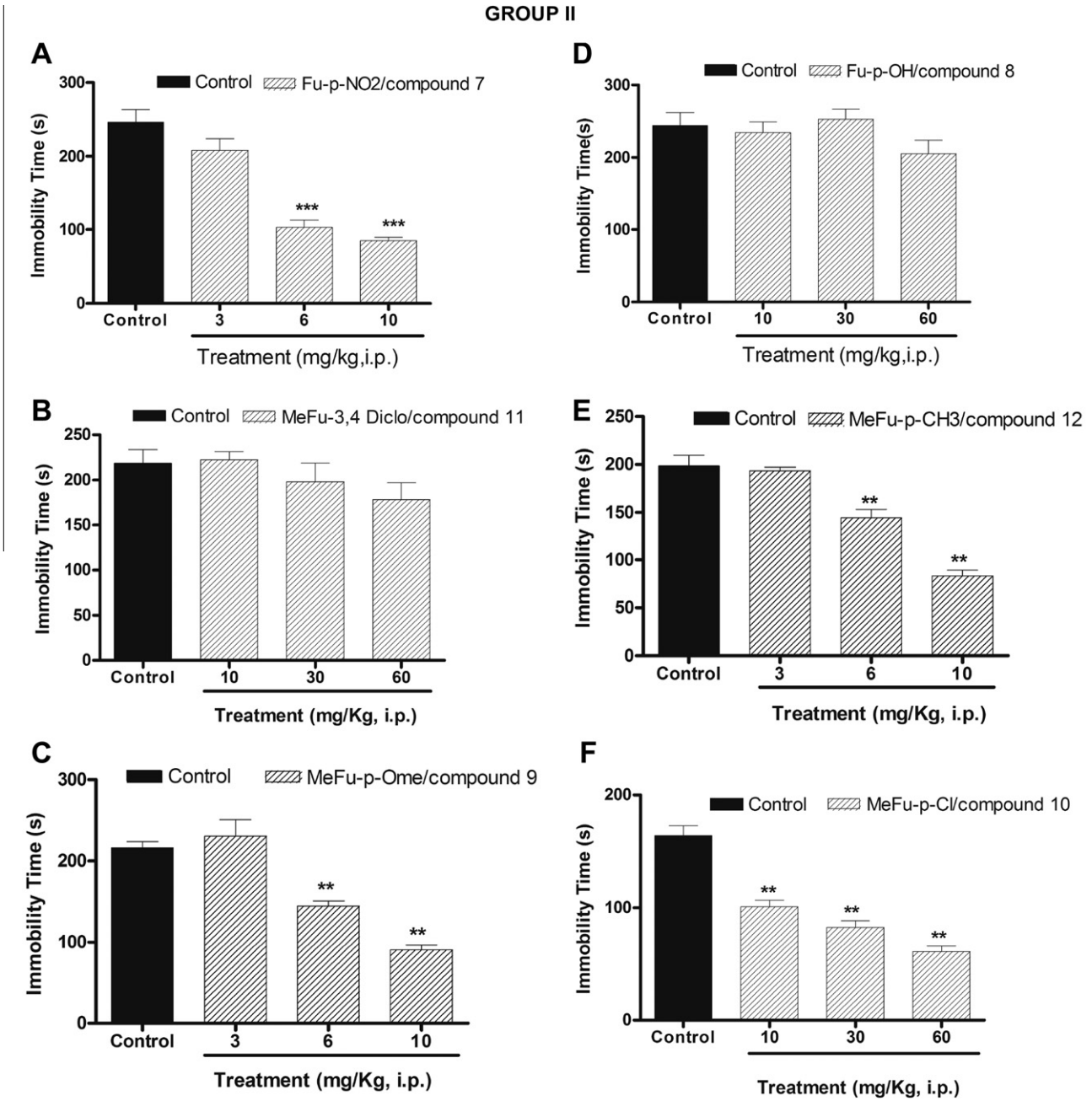


Figure 3. Effect of compounds included in group 2 (3–10 mg/kg or 10–60 mg/kg, ip), with acute administration in mice, on immobility time when evaluated in the forced swimming model. Data are reported as means ± SEM. $N = 8–10$ mice. $^{***}P < 0.001$ or $^{**}P < 0.01$, compared to the control group (ANOVA followed by Dunnett's analysis).

Both tests has been validated as a suitable tool for predicting the antidepressant properties of drugs.[22–27] This inescapable stressful situation can be evaluated by assessing different behavioural strategies.[22–28] The administration of compounds prior to the test acutely reduced the total immobility time in these tests. Several compounds may affect the normal pattern of behaviour during the tests, suggesting antidepressant-like action as observed through the behavioural response to an inescapable source of stress. False-positive results can be obtained with certain drugs, in particular psychomotor stimulants, which decrease immobility time by stimulating locomotor activity.[29] The anti-immobility effect of compounds in study seems not to be associated with any motor effects, since mice treated with these compounds did not exhibit increased of ambulation when tested in an open-field.

According to the results for the FST in mice, all compounds were active, except **8**, **11** and **24**. In addition, the anti-immobility effect of compounds in FST were also observed in TST. The most active compound was the sulphonyl-hydrazone **10**, which showed 72.02% of activity at a concentration of 60 mg/kg. This compound was more active that imipramine (10 mg/kg), as shown in Table 1. However, this effect was only observed with a dose six times higher than the reference drug.

On comparing the results, the sulphonamide oxabicyclo **2** was more active than the other Diels–Alder adduct derivatives (group I). The presence of a methyl group in the oxabicyclo in compounds **3** and **4** seems to increase the immobility time in the antidepressant test. In group III, the best result was obtained with the 1,8-benzylnaphthalimide derivatives **21** and **22**. The substitution of

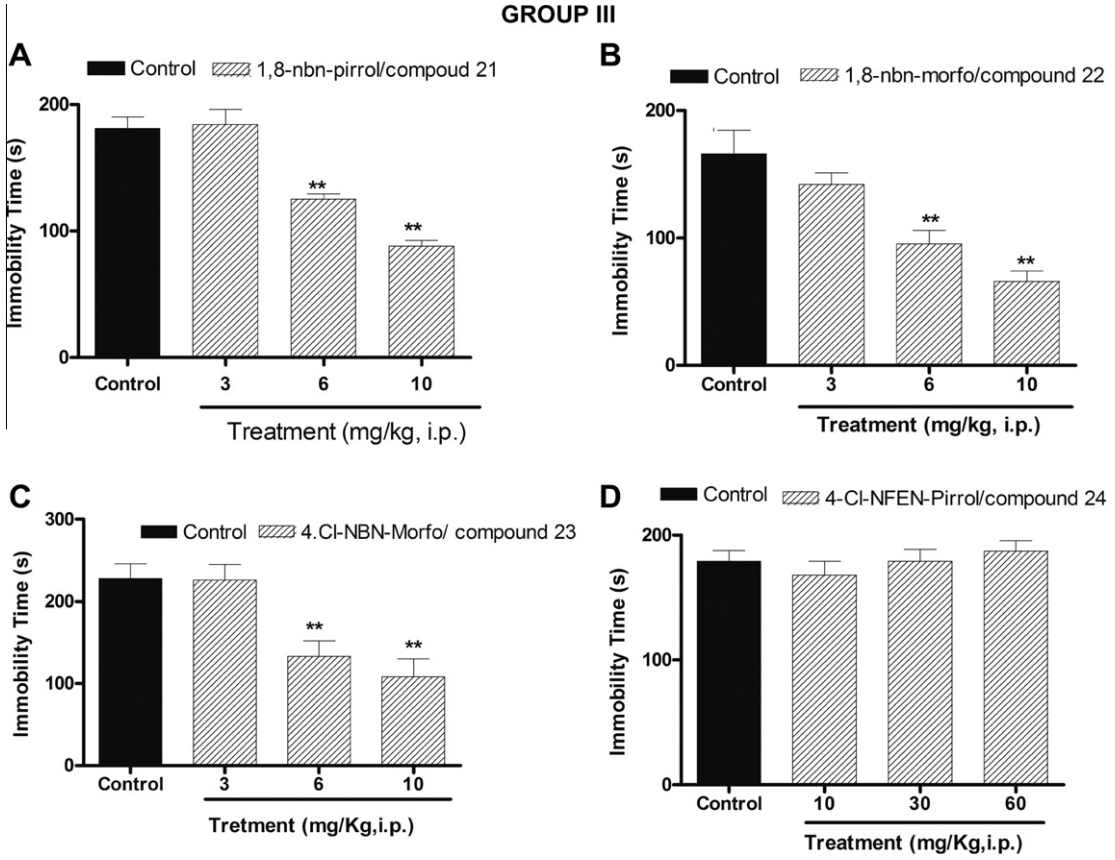


Figure 4. Effect of compounds included in group 3 (3–10 mg/kg or 10–60 mg/kg, ip), with acute administration in mice, on immobility time when evaluated in the forced swimming model. Data are reported as means ± SEM. $N = 8–10$ mice. $^{**}P < 0.01$, compared to the control group (ANOVA followed by Dunnett's analysis).

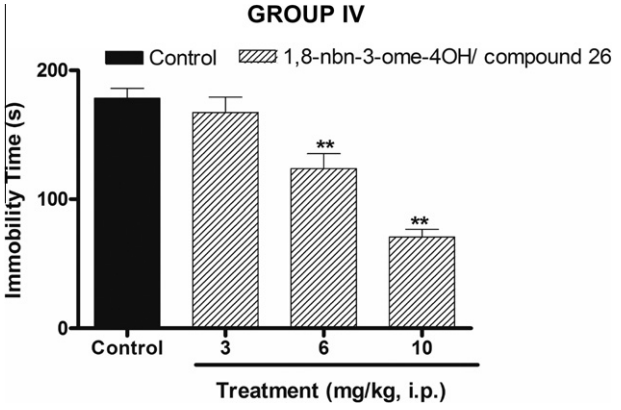


Figure 5. Effect of compounds included in group 4 (3–10 mg/kg, ip), with acute administration in mice, on immobility time when evaluated in the forced swimming model. Data are reported as means ± SEM. $N = 8–10$ mice. $^{**}P < 0.01$, $^{***}P < 0.001$ compared to the control group (ANOVA followed by Dunnett's analysis).

the hydrogen with a chloro group in the fourth position on the naphthalic ring is not so important in terms of the activity. In this case, the sulphonamide **23**, substituted with a chloro atom, was as active as **22** (without the chloro). These compounds showed around 50% of activity at a concentration of 10 mg/kg. According to Table 1, compounds **21** and **22** were more active that imipramine, a commercial drug, at a concentration of 10 mg/kg. However, at a lower concentration (3 mg/kg), **21**, **22** and **23** were not active. Moreover, in this group, the derivative of phenylethylnaphthalimide **24** was totally inactive. The addition of a methyl group between the imide and the benzenesulphonamide, rather than the benzylnaphthalimide, moiety increases the degree of mobility of this molecule and may be responsible for the lack of activity.

In the results obtained for the sulphonyl-hydrazones (groups II, IV and V), compound **10** of group II, with the oxobicyclo derivative linked to a methyl group, was the most active compound. However, in the same group, **7**, with a nitro group as a substituent, was the least active compound, and **8** and **11** were inactive. It can be assumed that the oxabicyclo derivatives (**7** and **8**) were less active than the oxabicyclos linked to a methyl group (**9–12**). However, other oxabicyclo derivatives need to be synthesized in order to confirm this assumption. In groups IV and V, the phthalimide moiety seems to be important for the activity. In the FST, compounds **30** and **31** led to reductions in the immobility time of 66.64% and 68.30%, respectively. The sulphonyl-hydrazone benzylnaphthalimide derivative **26** was less active than the corresponding benzylphthalimide **30**.

It should be noted that the antidepressant-like activity of these compounds detected in the forced swimming test is not due to CNS stimulant properties, since they have no significant effects on the motor activity in comparison to the control group at the doses assayed in this test (Table 2). It is well known that psychostimulants, such as caffeine, also decrease the immobility time in the FST but, in contrast to antidepressants, cause marked motor stimulation, indicating that the effects may be nonspecific.[28–31]

4. Conclusions

As part of our ongoing investigations, seven sulphonamides and nine sulphonyl-hydrazones of cyclic imides including maleimide, benzylnaphthalimide, phenylethylnaphthalimide and benzylphthalimide, were synthesized. In the case of the maleimide

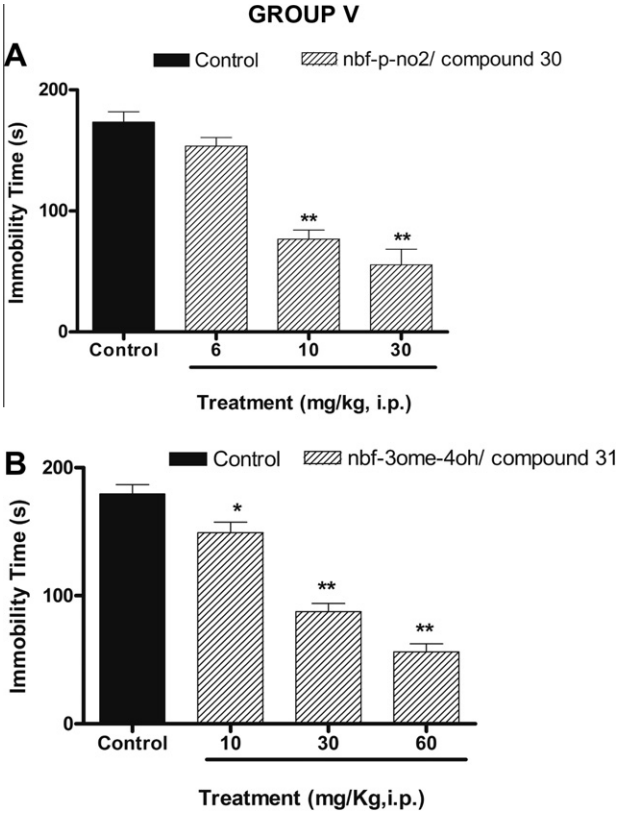


Figure 6. Effect of compounds included in group 5 (6–30 mg/kg or 10–60 mg/kg, ip), with acute administration in mice, on immobility time when evaluated in the forced swimming model. Data are reported as means ± SEM. $N = 8–10$ mice. $^{*}P < 0.05$, $^{**}P < 0.001$, $^{***}P < 0.001$ compared to the control group (ANOVA followed by Dunnett's analysis).

derivatives, the intermediates (sulphonyl chlorides) were submitted to a Diels–Alder reaction with two different dienes, 2-methylfuran and furan. These compounds were evaluated as antidepressant-like agents. This behaviour was observed using the FST and TST in mice. Almost all compounds exhibited an antidepressant-like effect. The sulphonyl-hydrazone (**10**) was the most active in the antidepressant test (FST) at a concentration of 60 mg/kg. Another important result was obtained with the sulphonamides (**21**) and (**22**). They were more active than imipramine, used at a concentration 10 mg/kg. However, none of the compounds tested had superior efficacy compared to fluoxetine. Moreover, analysis of the structure–activity relationship suggested that benzylnaphthalimide is an important group for the observed activity, being better than the phthalimide derivatives.

The exact underlying molecular mechanism of action is presently under investigation. According to current literature, the antidepressant effects of sulphonyl-hydrazone not yet been investigated. However, antidepressant effects of sulfonamides are well known. *N*-[3,5-Dichloro-2-(methoxy)phenyl]-4-(methoxy)-3-(1-piperazinyl)benzenesulfonamide (SB-399885) a 5-HT_6 receptor antagonist exibe effect antidepressant like in FST test[32] and, LY392098 a member of a novel class of biarylpropylsulfonamides potentiates AMPA receptor-mediated responses in FST and TST tests.[33]

The findings reported 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 improved therapeutic approaches. However, further studies are needed to evaluate the antidepressant-like effect these compounds with chronic treatment, as well as assess the toxicity of these.

5. Materials and methods

5.1. Drugs and solvents

The drugs and solvents used were: imipramine chlorhydrate and fluoxetine purchased from Sigma–Aldrich Chemical Company (St. Louis, USA) and the compounds synthesized. Due to the hydrophobic nature of these synthetic compounds, they were solubilised in corn oil, while imipramine and fluoxetine were dissolved in saline solution (NaCl 0.9%) only. The volume administered to each animal was 0.10 mL/10 g body weight.

5.2. Synthesis and features of compounds

All solvents and reagents were purchased from Merck and Sigma–Aldrich. All the compounds were characterised by ^{1}H NMR, ^{13}C NMR, IR, and microanalysis. The purity of these compounds was determined by TLC using several solvent systems of different polarity. Infrared spectra were determined with a Perkin Elmer 16PC spectrophotometer (Perkin Elmer, Wellesley, MA, USA). ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AC-200F spectrometer (Rheinstetten, Germany) (400 MHz and 100 MHz, respectively). $CDCl_3$ and DMSO were used as solvents with tetramethylsilane (TMS) as the internal standard; chemical shifts (δ) were determined in parts per million. For the CHN analysis, a Perkin Elmer 2400 CHN elemental analyser (Boston, MA, USA) was used. In the thin layer chromatography, aluminium sheets with Silica Gel 60 F-254 and 0.2 mm thickness were employed.

The synthesis of compounds **2–12** is described in the literature.[34] The synthesis and the physico-chemical data of the compounds **21–24, 26, 30** and **31** are described below, along with the data for the precursors (**15–20**, **25**, **27–29**). The compounds **21–23**, as well as, their precursors (**15**, **16**, **18** and **19**) were recently published by our research group.[36]

5.2.1. 2-Benzyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (15)[35]

The 1,8-naphthalic anhydride (3.00 g, 15.00 mmol) was added in a solution of benzylamine (1.65 mL, 15.00 mmol) in ethanol. The mixture was refluxed for refluxed for 6 h. The crystal was formed on cooling of the solution. The solid was filtered through a Büchner funnel and washed twice with 20 mL of cold ethanol. Yield: 91%. Mp: 197.9–198.6 °C (Lit 192 °C.[36] ^{1}H NMR ($CDCl_3$) δ 5.37 (s, 2H, CH_2), 7.22–7.26 (t, 1H, ArH), 7.20–7.33 (t, 2H, ArH), 7.56–7.58 (dd, 2H, ArH, $J = 7.03$ Hz), 7.65–7.68 (t, 2H, ArH), 8.08–8.10 (dd, 2H, ArH, $J = 8.01$ Hz), 8.52–8.54 (dd, 2H, ArH, $J = 7.03$ Hz). ^{13}C NMR ($CDCl_3$) δ 43.49 (CH_2); 122.46, 126.83, 127.47, 127.98, 128.40, 129.03, 131.28, 131.42, 133.93, 137.29 (C Ar); 164.10 (C=O).

5.2.2. 2-Benzyl-6-chloro-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (16)[35]

The 4-chloro-1,8-naphthalic anhydride (3.00 g, 12.8 mmol) was added in a solution of benzylamine (2.81 mL, 25.7 mmol) in ethanol. The reaction was carried out as described for the compound (**15**). Yield: 85%. Mp: 176.0–176.2 °C (Lit. 168.5–170.5 °C).[37] IR (KBr): 1689 and 1656 [ν N(C=O)$_2$)], 1340 (ν C–N), 741 (ν Ar.) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.40 (s, 2H, CH_2), 7.04–7.06 (d, 2H, ArH, $J = 8.20$ Hz), 7.14–7.16 (d, 2H, ArH, $J = 8.20$ Hz), 7.39–7.41 (d, 1H, ArH, $J = 7.42$ Hz), 7.43 (t, 1H, ArH), 7.81–7.83 (d, 1H, ArH, $J = 7.42$ Hz), 8.40–8.38 (d, 1H, ArH, $J = 7.80$ Hz), 9.43–9.41 (d, 1H, ArH, $J = 7.42$ Hz). ^{13}C NMR ($CDCl_3$) δ 43.60 (CH_2); 121.41, 122.90, 127.29, 127.56, 127.76, 128.44, 128.91, 129.00, 129.13, 130.61, 131.22, 132.12, 137.01, 139.05 (C Ar); 163.37 (C=O), 163.62

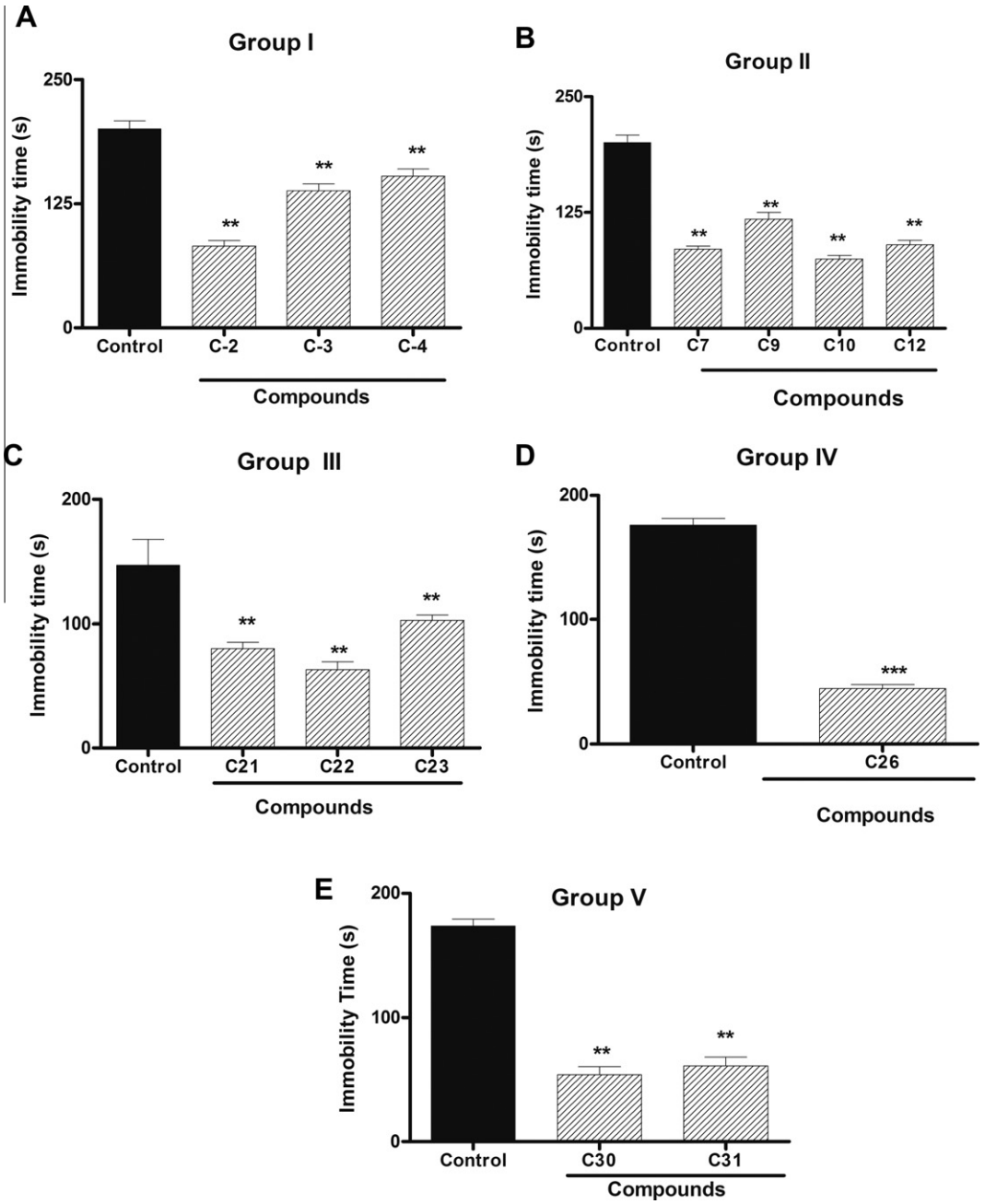


Figure 7. Effect of compounds included all groups (A-group I, B-group II, C-group III, D-group IV and E-group V) with acute administration in mice, on immobility time when evaluated in the TST. Data are reported as means ± SEM. $N = 8–10$ mice. $^{**}P < 0.001$, $^{***}P < 0.001$ compared to the control group (ANOVA followed by Dunnett's analysis).

(C═O). Anal. Calcd for $C_{19}H_{12}ClNO_2$: C, 70.92; H, 3.76; N, 4.35. Found: C, 70.51; H, 3.74; N, 4.37.

5.2.3. 4-Chloro-1,8-*N*-phenylethylnaphthalimide (17)[35]

The 4-chloro-1,8-naphthalic anhydride 3.00 g (12.8 mmol) was added in a solution of phenylethylamine (3.25 mL, 25.7 mmol) in ethanol. The reaction was carried out as described for the compound (**15**). Yield: 87%. Mp: 126.7–128.3 °C. IR (KBr): 1702 and 1656 [ν N(C═O)$_2$)], 1346 (ν C–N), 738 (ν Ar.). (Compound cited by Mederski[38] ^{1}H NMR ($CDCl_3$) δ 2.99–3.03 (t, 2H, CH_2), 4.34–4.38 (t, 2H, CH_2), 7.20–7.24 (t, 1H, ArH), 7.28–7.32 (t, 2H, ArH), 7.35–7.36 (d, 2H, ArH, $J = 7.02$ Hz), 7.73–7.75 (d, 1H, ArH, $J = 7.81$ Hz), 7.76–7.80 (t, 1H, ArH), 8.40–8.42 (d, 1H, ArH, $J = 7.81$ Hz), 8.48–8.50 (d, 1H, ArH, $J = 8.40$ Hz), 8.57–8.59 (d, 1H, ArH, $J = 8.01$ Hz).^{13}C NMR ($CDCl_3$) δ 34.19 (NCH_2CH_2); 41.86 (NCH_2CH_2); 121.37, 122.85, 126.46, 127.27, 127.74, 128.48, 128.82, 128.95, 129.10, 130.48, 130.96, 131.86, 138.59, 138.93 (C Ar), 163.13 (C═O), 163.40 (C═O).

5.2.4. 4-[(1,3-Dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)methyl]benzenesulphonyl chloride (18)[35]

The cyclic imide (**15**) (2.00 g, 7.00 mmol) was slowly added in chlorosulphonic acid cold (2.76 mL, 42.0 mmol). After addiction, the mixture was stirred at 50 °C for around 10 min, until the evolution of HCl ceased. The reaction mixture was poured onto ice and extracted with chloroform. The organic phase was separated and dried with anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure. Yield: 93%. Mp; 113.1–115.5 °C. IR (KBr) 1699 and 1655 [ν N(C═O)$_2$)], 1337 and 1172 (ν –SO_2), 1235 (ν –CN), 776 (ν Ar.). ^{1}H NMR ($CDCl_3$) δ 5.24 (s, 2H, CH_2), 7.30–7.32 (d, 2H, ArH, $J = 8.01$ Hz), 7.51–7.54 (d, 2H, ArH, $J = 8.20$ Hz), 7.85–7.80 (t, 2H, ArH), 8.48–8.46 (d, 2H, ArH, $J = 8.01$ Hz), 8.51–8.49 (d, 2H,

Table 1
Effect of compounds imipramine (10 mg/kg, ip) and fluoxetine administered intraperitonealy in mice on immobility time when evaluated in the forced swimming model

Treatment	Dose (mg/kg)	Molecular weight (g/mol)	Dose (μmol/kg)	Immobility time mean ± SEM (S)	Reduction of immobility time (%)
Group I					
Vehicle	—			205.66 ± 12.42	0
Compound **2**	60	374.41	160	92.95 ± 6.70***	54.80
Compound **3**	10	388.44	26	133.00 ± 8.75**	33.33
Compound **4**	10	404.44	25	131.00 ± 7.33**	36.30
Imipramine	10	280.41	36	87.80 ± 4.72***	57.30
Fluoxetine	20	309.33	66	54.26 ± 4.72***	73.61
Group II					
Vehicle				218.54 ± 8.11	0
Compound **7**	10	468.44	21	178.37 ± 18.72*	18.38
Compound **9**	10	467.49	21	90.37 ± 6.50***	58.64
Compound **10**	60	471.91	127	61.00 ± 4.80***	72.02
Compound **12**	10	451.49	22	83.00 ± 6.26***	62.02
Imipramine	10	280.41	36	75.44 ± 8.25***	65.48
Fluoxetine	20	309.33	66	35.16 ± 8.25***	83.91
Group III					
Vehicle				188.50 ± 7.18	0
Compound **21**	10	420.48	24	67.37 ± 6.14***	64.25
Compound **22**	10	436.48	23	66.00 ± 8.3***	64.89
Compound **24**	10	468.95	21	82.00 ± 7.9***	56.49
Imipramine	10	280.41	36	68.45 ± 8.7***	63.59
Fluoxetine	20	309.33	66	44.65 ± 6.14***	76.31
Group IV					
Vehicle				178.25 ± 7.23	0
Compound **26**	10	515.54	19	70.75 ± 6.15***	60.30
Imipramine	10	280.41	36	64.17 ± 6.13***	63.86
Fluoxetine	20	309.33	66	37.89 ± 7.9***	78.71
Group V					
Vehicle				166 ± 12.23	0
Compound **30**	30	465.78	64	55.37 ± 3.78***	66.64
Compound **31**	60	464.65	129	52.25 ± 6.32***	68.52
Imipramine	10	280.41	36	49.85 ± 7.9***	69.96
Fluoxetine	20	309.33	66	33.18 ± 3.94***	80.01

*P <0.05, **P <0.01 and ***P <0.001 as compared with vehicle. All comparations were made by ANOVA followed by Dunnett's test.

Table 2
Effect of compounds administered intraperitonealy in mice evaluated in open field test

Treatment	Dose (mg/kg)	Number of rearing mean ± SEM (s)	Number of crossing mean ± SEM
Vehicle	—	39.45 ± 6.21	96.63 ± 5.32
Compound **2**	60	42.95 ± 4.70	86.74 ± 6.12
Compound **3**	10	33.00 ± 8.15	96.00 ± 7.32
Compound **4**	10	38.00 ± 7.13	101.12 ± 4.56
Compound **7**	10	38.37 ± 8.22	98.14 ± 8.22
Compound **9**	10	40.37 ± 6.40	92.54 ± 7.35
Compound **10**	60	41.00 ± 4.60	98.45 ± 9.15
Compound **12**	10	43.00 ± 5.27	92.74 ± 8.35
Compound **21**	10	37.45 ± 4.46	108.45 ± 9.35
Compound **22**	10	36.67 ± 7.3	98.85 ± 3.85
Compound **24**	10	42.00 ± 9.11	86.74 ± 8.22
Compound **26**	10	40.75 ± 3.15	96.10 ± 4.38
Compound **30**	30	45.37 ± 6.78	106.45 ± 6.35
Compound **31**	60	42.65 ± 6.72	92.54 ± 17.05

ArH, J = 8.01 Hz). ^{13}C NMR ($CDCl_3$) δ 43.51 (CH_2); 109.99, 122.60, 126.27, 127.53, 127.97, 131.71, 132.03, 135.27, 138.44 (C Ar); 164.18 (C═O).

5.2.5. 4-[(6-Chloro-1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)methyl]benzenesulphonyl chloride (19)[35]

The cyclic imide (**16**) 2.0 g (6.21 mmol) was slowly added in chlorosulphonic acid cold 2.55 mL (37.3 mmol). The reaction was carried out as described for the compound (**18**). Yield: 67%. Mp: 136.0–138.2 °C. IR (KBr) 1702 and 1659 [ν N(C═O)$_2$)], 1343 and 1173 (ν –SO_2), 1233 (ν C–N), 780 (ν Ar.) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 5.16 (s, 2H, CH_2), 7.32–7.34 (d, 2H, ArH, J = 8.20 Hz), 7.57–7.55 (d, 2H, ArH, J = 8.20 Hz), 7.77–7.81 (m, 2H, ArH), 8.20–8.22 (d, 1H, ArH, J = 7.81 Hz), 8.34–8.32 (d, 1H, ArH, J = 7.42 Hz), 8.37–8.39 (d, 1H, ArH, J = 7.42 Hz). ^{13}C NMR (DMSO-d_6) δ 43.47 (CH_2); 121.58, 122.87, 126.26, 127.86, 128.21, 128.83, 129.09, 130.72, 131.63, 132.35, 137.44, 138.30, 138.43, 147.14 (C Ar); 163.22 (C═O), 163.51 (C═O).

5.2.6. 4-Chloro-1,8-*N*-(p-chlorosulfonyl)phenethylnaphthalimida (20)

The cyclic imide (**17**) 3.0 g (8.93 mmol) was slowly added in chlorosulphonic acid cold 3.57 mL (53.60 mmol). The reaction was carried out as described for the compound (**18**). Yield: 92%. Mp: 200.2–200.9 °C. IR (KBr): 1702 and 1662 [ν N(C═O)$_2$)], 1345 and 1171 (ν –SO_2), 1229 (ν C–N), 780 (ν Ar.). ^{1}H NMR (DMSO-d_6) δ 2.86–2.90 (t, 2H, CH_2), 4.11–4.15 (t, 2H, CH_2), 7.22–7.24 (d, 2H, ArH, J = 8.00 Hz), 7.54–7.56 (d, 2H, ArH, J = 8.00 Hz), 7.84–7.86 (d, 1H, ArH, J = 7.80 Hz), 8.21–8.23 (d, 1H, ArH, J = 7.80 Hz), 8.36–8.40 (m, 3H, ArH). ^{13}C NMR (DMSO-d_6) δ 33.79 (CH_2), 41.68 (CH_2), 109.99, 121.69, 122.99, 126.46, 128.25, 128.74, 128.85, 129.13, 130.60, 131.41, 132.13, 138.13, 140.09, 146.43, 163.02 (C═O), 163.30 (C═O).

5.2.7. 2-[4-(Pyrrolidin-1-ylsulphonyl)benzyl]-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (21)[35]

In a solution of the sulphonyl chloride (**18**) (400 mg, 1.03 mmol) in 30 mL of methanol were slowly added 2 equiv of pyrrolidine (170 μL, 2.07 mmol) at approximately 0 °C. After addiction, the mixture was stirred for 30 min at room temperature 0 °C. The product was filtered and washed twice with 20 mL of cold methanol. The product was recrystallized in chloroform. Yield: 61%. Mp

207.2–207.8 °C. IR (KBr): 1702 and 1658 [ν –N(C=O)$_2$)], 1331 and 1161 (ν –SO$_2$–), 770 (ν arom.) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.54–1.62 (m, 4H, –(CH$_2$)$_2$–), 3.06–3.10 (t, 4H, –CH$_2$–N–CH$_2$–), 5.32 (s, 2H, –CH$_2$–), 7.57–7.59 (d, 2H, ArH, J = 8.20 Hz), 7.71–7.73 (d, 2H, ArH, J = 8.20 Hz), 7.84–7.88 (t, 2H, ArH), 8.45–8.46 (d, 2H, ArH, J = 7.22 Hz), 8.48–8.50 (d, 2H, ArH., J = 7.22 Hz). ^{13}C NMR (DMSO-d_6) δ 25.33 (–CH$_2$–CH$_2$–CH$_2$–CH$_2$–), 43.40 (CH$_2$–N-ArH), 48.41 (CH$_2$–N–CH$_2$–); 122.55, 127.99, 128.20, 128.82, 131.76, 132.03, 132.83, 135.37, 135.61, 143.17 (C Ar.); 164.23 (C=O). Anal. Calcd for $C_{23}H_{20}N_2O_4S$: C, 65.70; H, 4.79; N, 6.66; S, 7.63. Found: C, 65.44; H, 4.56; N, 6.63; S, 7.40.

5.2.8. 2-[4-(Morpholin-1-ylsulphonyl)benzyl]-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (22)[35]

In a solution of the sulphonyl chloride (**18**) (400 mg, 1.03 mmol) in 30 mL of methanol were slowly added 2 equiv of morpholine (180 μL, 2.07 mmol) at approximately 0 °C. The reaction was carried out as described for the compound (**21**). Yield: 62%. Mp: 221.7–223.3 °C. IR (KBr) 1703 and 1660 [ν N(C=O)$_2$)], 1336 and 1163 (ν –SO$_2$–), 1227 and 1104 (ν –COC–) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 2.79–2.82 (t, 4H, –CH$_2$–N–CH$_2$–), 3.57–3.59 (t, 2H, –CH$_2$–O–CH$_2$–), 5.54 (s, 2H, –CH$_2$–), 7.61–7.63 (d, 2H, ArH., J = 8.20 Hz), 7.65–7.67 (d, 2H, ArH., J = 8.20 Hz), 7.86–7.90 (t, 2H, ArH), 8.47–8.49 (d, 2H, ArH., J = 8.20 Hz), 8.50–8.52 (d, 2H, ArH., J = 7.22 Hz). ^{13}C NMR (DMSO-d_6) δ 43.72 (CH$_2$–N-ArH), 46.58 (CH$_2$–N–CH$_2$–), 66.75 (CH$_2$–O–CH$_2$–); 123.05, 127.76, 128.77, 130.44, 132.39, 135.10, 143.39 (C Ar.); 164.89 (C=O). Anal. Calcd for $C_{23}H_{20}N_2O_5S$: C, 63.29; H, 4.62; N, 6.42; S, 7.35. Found: C, 63.04; H, 4.68; N, 6.29; S, 7.37.

5.2.9. 2-[4-(Morpholin-1-ylsulphonyl)benzyl]-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (23)[35]

In a solution of the sulphonyl chloride (**19**) (400 mg, 0.95 mmol) in 30 mL of methanol were slowly added 2 equiv of morpholine (165 μL, 1.90 mmol) at approximately 0 °C. The reaction was carried out as described for the compound (**21**). Yield: 74%. Mp: 171.1–172.7 °C. IR (KBr) 1701 and 1663 [ν –N(C=O)$_2$)], 1341 and 1168 (ν –SO$_2$–), 1227 and 1105 (ν-COC–) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 2.81–2.78 (t, 4H –CH$_2$–N–CH$_2$–), 3.58–3.55 (t, 4H, –CH$_2$–O–CH$_2$), 5.30 (s, 2H, –CH$_2$–), 7.32–7.30 (d, 2H, ArH, J = 8.00 Hz), 7.54–7.52 (d, 2H, ArH, J = 8.00 Hz), 7.94–7.92 (m, 2H, ArH.), 8.85–8.33 (d, 1H, ArH, J = 7.81 Hz), 8.51–8.48 (m, 2H, ArH.). ^{13}C NMR (DMSO-d_6) δ 43.57 (CH$_2$–N-ArH), 46.50 (CH$_2$–N–CH$_2$–), 65.91 (CH$_2$–O–CH$_2$–); 121.88, 123.18, 126.25, 127.65, 128.36, 128.54, 129.07, 129.12, 130.93, 131.78, 132.51, 133.79, 138.44, 143.47 (C Ar.); 163.48 (C=O), 163.76 (C=O). Anal. Calcd for $C_{23}H_{19}ClN_2O_5S$: C, 58.66; H, 4.07; N, 5.95; S, 6.81. Found: C, 58.45; H, 4.05; N, 5.94; S, 7.03.

5.2.10. 6-Chloro-2-[4-(pyrrolidin-1-ylsulphonyl)phenethyl]-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (24)

In a solution of the sulphonyl chloride (**20**) (400 mg, 0.95 mmol) in 30 mL of methanol were slowly added 2 equiv of pyrrolidine (167 μL, 1.90 mmol) at approximately 0 °C. The reaction was carried out as described for the compound (**21**). Yield: 77%. Mp: 245.2–248.7 °C. IR (KBr): 1700 and 1662 [ν N(C=O)$_2$)], 1343 and 1158 (ν SO$_2$), 780 (ν Ar.). ^{1}H NMR (CDCl$_3$) δ: 1.94 (t, 4H, –CH$_2$–CH$_2$–), 3.19 (m, 6H, –CH$_2$–N–CH$_2$– and –CH$_2$-Ph), 4.42 (t, 2H, –CH$_2$–N–C=O), 7.51–7.28 (d, 2H, ArH., J = 8.5 Hz), 7.89–7.74 (m, 4H, ArH.), 8.64–8.44 (m, 3H, ArH.). ^{13}C NMR (CDCl$_3$) δ: 25.44 (N–CH$_2$–*C*H$_2$–*C*H$_2$–), 34.23 (*C*H$_2$-Ar), 41.41 (O=C–N–*C*H$_2$), 48.16 (CH$_2$–N–CH$_2$); 121.49, 123.01, 128.01, 129.85, 131.15, 131.45, 131.91, 131.95, 132.34, 135.17, 139.60, 144.02 (C Ar); 163.53 (C=O), 163.79 (C=O). Anal. Calcd for $C_{24}H_{21}ClN_2O_4S$: C, 61.47; H, 4.51; N, 5.97; S, 6.84. Found: C, 61.27; H, 4.34; N, 5.98; S, 6.83.

5.2.11. 4-[(1,3-Dioxo-1*H*-benzo[*de*]isoquinoline-2(3*H*)-yl)methyl]benzenesulphonyl hydrazide (25)

The hydrazine hydrate (252 μg, 5.2 mmol) was slowly added in a mixture of sulphonyl chloride (**20**) (1.00 g, 2.59 mmol) in ethanol. The reaction was stirred and the temperature was kept at approximately 0 °C during the addiction of the hydrazine. The product was filtered and washed twice with 20 mL of cold methanol. Yield: 90%. Mp: 163.5–163.9 °C. ^{1}H NMR (DMSO-d_6) δ: 3.38 (s_{broad}, 3H, NH–NH$_2$), 5.21 (s, 2H, CH$_2$), 7.30–7.32 (d, 2H, ArH, J = 8.06 Hz), 7.54–7.56 (d, 2H, ArH, J = 8.06 Hz), 7.78–7.82 (t, 2H, ArH, J = 7.33), 8.37–8.39 (d, 2H, ArH, J = 8.06 Hz), 8.41–8.43 (d, 2H, ArH, J = 7.33 Hz). ^{13}C NMR (DMSO-d_6) δ: 43.39 (CH$_2$); 122.45, 126.29, 127.60, 127.90, 128.00, 131.62, 131.93, 135.20, 135.25, 138.42 (C Ar), 164.08 (C=O).

5.2.12. 4-[2-(1,3-Dioxo-1*H*-benzo[*de*]isoquinoline-2(3*H*)-yl)methyl]-*N*′-[(1*E*)-(3-methoxy-4-hydroxyphenyl)methylene]benzenesulphonyl hydrazone (26)

The sulphonyl hydrazide (**25**) (400 mg, 1.21 mmol) was added in a solution of vanillin (184 mg, 1.21 mmol) in ethanol and two drops of hydrochloric acid as catalyst. The mixture was stirred at room temperature for 1 h. The reaction was checked by t.l.c. (ethyl acetate/hexane 1:1). The mixture was poured out in water/ice. The product was filtered and washed with cold water. Yield: 68%. Mp: 235.4–236.2 °C. 3484 (ν OH), 3230 (ν NH), 1696 and 1652 [ν N(C=O)$_2$)], 1326 and 1198 (ν SO$_2$), 1486 (ν C–N). ^{1}H NMR (DMSO-d_6) δ: 3.83 (s, 3H, OCH$_3$), 5.26 (s, 2H, CH$_2$), 6.89–6.91 (d, 1H, ArH, J = 8.20 Hz), 6.89–6.91 (d, 1H, ArH, J = 8.20 Hz), 7.27–7.29 (d, 1H, ArH, J = 8.20 Hz), 7.33–7.35 (d, 2H, ArH, J = 8.20 Hz), 7.48 (s, 1H, ArH), 7.55–7.57 (d, 2H, ArH, J = 8.00 Hz), 7.85–7.89 (t, 2H, ArH), 8.45–8.47 (d, 2H, ArH, J = 7.50 Hz), 8.50–8.52 (d, 2H, ArH, J = 8.20 Hz), 8.62 (s, 1H, N=CH), 11.23 (s, 1H, NH). ^{13}C NMR (CDCl$_3$) δ: 56.23 (CH$_2$), 109.99, 116.20, 122.56, 124.65, 125.69, 126.28, 127.55, 127.93, 128.11, 131.68, 132.00, 135.21, 138.38, 148.68, 150.94, 161.40, 164.13 (C=O). Anal. Calcd for $C_{27}H_{21}N_3O_6S$: C, 62.90; H, 4.11; N, 8.15; S, 6.22. Found: C, 62.65, H, 4.45, N, 8.35, S, 6.09.

5.2.13. 2-Benzyl-1*H*-isoindol-1,3(2*H*)-dione (27)

The phthalic anhydride (5.0 g, 34.0 mmol) and benzylamine (4.0 mL, 34.0 mmol) were refluxed in acetic acid for 3 h. The reaction was checked by t.l.c. (ethyl acetate/hexane 1:1). The product was precipitate in cold water and filtered in Büchner funnel. The product was recrystalized in ethanol. Yield: 96%. Mp: 116.1–117.1 °C (Lit. 118 °C[39]) ^{1}H NMR (CDCl$_3$) δ: 4.84 (s,2H, CH$_2$), 7.27–7.33 (m, 3H, ArH), 7.43–7.44 (d, 2H, ArH, J = 7.03 Hz), 7.67–7.69 (m, 2H, ArH), 7.82–7.84 (m, 2H, ArH). ^{13}C NMR (CDCl$_3$) δ: 41.60 (CH$_2$); 123.30, 127.79, 128.57, 128.63, 132.07, 133.94, 136.33 (C Ar); 167.99 (C=O).

5.2.14. 4-[(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]benzenesulphonyl chloride (28)

The phthalimide (2.00 g, 8.43 mmol) was added in 6 equiv of cold chlorosulphonic acid (3.90 mL, 59.0 mmol), followed by heating at around 60 °C until the evolution of HCl ceased. The mixture was poured in a mixture of water and ice. The product was filtered and washed with cold water. Yield: 84%. Mp: 120.3–123.6 °C. (Lit.[40] 124–125 °C). ^{1}H NMR (DMSO-d_6) δ: 4.75 (s, 2H, CH$_2$), 7.25–7.27 (d, 2H, ArH, J = 8.39 Hz), 7.55–7.57 (d, 2H, ArH, J = 8.21 Hz), 7.81–7.88 (m, 4H, ArH). ^{13}C NMR (CDCl$_3$) δ: 41.27 (CH$_2$), 123.92, 126.47, 127.50, 135.27, 137.85, 147.58 C Ar, 168.68 (C=O).

5.2.15. 4-[(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]benzenesulphonyl hydrazide (29)

The hydrazine hydrate (103 mL, 3.0 mmol) was added in a solution of sulphonyl chloride (**28**) (550 mg, 1.60 mmol) in methanol at

around 0 °C. The reaction was checked by t.l.c. (ethyl acetate/hexane 1:1). The product was filtered and washed with cold methanol. Yield: 85%. Mp: 160.2–161.4 °C. ^{1}H NMR (DMSO-d_6) δ: 3.38 (s_{largo}, 2H, NH_2), 4.87 (s, 2H, CH_2), 7.53–7.55 (d, 2H, ArH, J = 8.20 Hz), 7.76–7.78 (d, 2H, ArH, J = 8.20 Hz), 7.86–7.93 (m, 4H, ArH), 8.40 (s, 1H, NH), ^{13}C NMR (DMSO-d_6) δ: 41.17 (CH_2); 124.01, 128.45, 128.66, 132.27, 135.33, 138.01, 142.04 (C Ar); 168.39 (C=O).

5.2.16. 4-[(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-*N*'-[(1*E*)-(3-methoxy-4-hydroxyphenyl)methylene]benzenesulphonyl hydrazone (30)

The sulphonyl hydrazide (**29**) (400 mg, 0.8 mmol) was added in a solution of vanillin (131 mg, 0.8 mmol) in ethanol. The reaction was carried out as described for the compound (**26**). Yield: 74%. Mp: 187.0–189.2 °C. IR (KBr): 3393 (ν NH), 1765 and 1701 [ν N(C=O)$_2$)], 1600 (ν Ph-OH), 1334 and 1168 (ν SO_2), 1278 and 1039 (ν Ar-O–CH_3), 701 (ν ArH) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.61 (s, 1H, OH); 3.93 (s, 3H, OCH_3); 4.85 (s, 2H, CH_2), 7.63–7.27 (m, 6H, ArH and –N=CH–), 8.97–8.79 (m, 5H, ArH), 8.19 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 41.18 (CH_2); 56.37 (OCH_3); 114.50, 123.80, 127.53, 128.42, 128.61, 129.41, 129.64, 132.11, 134.51 (Ar C); 141.16 (Ar C–SO_2 and C=N); 142.01 (Ar *C*–OCH_3); 161.21 (Ar C–OH); 167.24 (C=O). Anal. Calcd for $C_{23}H_{19}N_3O_6S$: C, 59.35; H, 4.11; N, 9.03; S, 6.89. Found: C, 59.68; H, 3.93; N, 9.00; S, 6.57.

5.2.17. 4-[(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-*N*'-[(1*E*)-(4-nitrophenyl)methylene]benzenesulphonyl hydrazone (31)

The sulphonyl hydrazide (**29**) (400 mg, 0.8 mmol) was added in a solution of *p*-nitrobenzaldehyde (121 mg, 0.8 mmol) in ethanol. The reaction was carried out as described for the compound (**26**). Yield: 70%. Mp: 221.7–223.6 °C. IR (KBr): 3148 (ν NH), 1768 and 1700 [ν N(C=O)$_2$)], 1394 and 1116 (ν SO_2), 1594 (ν C–N). ^{1}H NMR (DMSO-d_6) δ: 4.85 (s, 2H, ArH), 7.54–7.57 (d, 2H, ArH, J = 8.40 Hz), 7.90–7.81 (m, 8H, ArH), 8.02 (s, 1H, N=CH), 8.21–8.23 (d, 2H, ArH, J = 8.40 Hz), 12.01 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 40.79 (CH_2); 123.97, 124.69, 128.42, 132.23, 135.28, 140.40, 142.79 (C Ar); 168.36 (C=O). Anal. Calcd for $C_{22}H_{16}N_4O_6S$: C, 56.89; H, 3.47; N, 12.06; S, 6.90. Found: C, 56.68, H, 3.69, N, 11.84, S, 6.87.

5.3. Animals

Male adult Swiss mice (25–35 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 behavioural 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 Behaviour (Act 1992) and approved by the local Committee for Animal Care in Research 311/2008/CEP UNIVALI. The minimum number of animals and duration of observation required to obtain consistent data were employed.

5.4. Behavioural evaluation

5.4.1. Experimental design

The compounds were grouped according to the principal functional group (sulphonamide or sulphonyl-hydrazone), to the origin of the imides and, in the case of the maleimide derivatives, to the dienes that were used in the synthesis, as follows: group 1—sulphonamides, derived from maleimides, using 2-methylfuran and furan as dienes; group 2—sulphonyl-hydrazones derived from maleimides, using 2-methylfuran and furan as dienes; group 3—sulphonamides, derived from naphthalimides; group 4—sulphonyl-hydrazone, derived from naphthalene; and group 5—sulphonyl-hydrazone, derived from phthalimide. For each compound experiments were performed with 3 doses, always starting with 10 mg/kg. The activity of each compound was compared with that of drugs such as fluoxetine (20 mg/kg) and imipramine (10 mg/kg). The doses used for the compounds were based on previous tests with the same in models of antinociception (unpublished data). The doses of fluoxetine and imipramine were used based on literature.[41,42]

5.4.2. Forced-swimming test (FST)

The FST is the most widely used pharmacological model for assessing antidepressant activity.[22–25] This method is based on the observation of animals exposed to a situation of forced swimming, in which they become passive and immobile after a period of vigorous activity (struggling), producing only the movements required to keep their heads above the water. The FST was carried out on mice according to the method of Porsolt et al. (1977).[22] Swimming sessions were conducted by placing the animals in individual Plexiglass cylinders (46 cm high × 20 cm diameter) containing 20 cm of water at 24 ± 1 °C. All animals were forced to swim for 6 min, and the time spent in immobility during the last 4 min of a 6 min observation period was recorded manually by competent observers. The animals were treated with the compounds (3, 10 and 30 mg/kg or 10, 30 and 60 mg/kg, ip), imipramine (10 mg/kg, ip), Fluoxetine (20 mg/kg) or vehicle, 30 min before the test.

5.4.3. Tail suspension test (FST)

The total duration of immobility induced by tail suspension was measured according to the method described by Steru et al. (1985).[26] Briefly, mice both acoustically and visually isolated were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was manually recorded during a 6 min period.[27] Mice were considered immobile only when they hung passively or stay completely motionless. Conventional antidepressants decrease the immobility time in this test.[26]

Percentage decrease in immobility duration (%IM) for test and standard drugs was calculated using following formula:

$$\% \text{ IM} = [(\text{A\_B})/\text{A}] * 100$$

where A is the duration of immobility (s) in control group and B is the duration of immobility (s) in test group.

5.4.4. Evaluation of the spontaneous motor effect in the open-field test

The open-field test was used to evaluate the exploratory activity of the animals, as described in the literature.[43] The open-field arena was made of acrylic (transparent walls and black floor). The arena measured 30 × 30 × 15 cm and was divided into nine squares of equal area. The animals were placed individually in the centre of the arena and allowed to explore freely. The observed parameters were: ambulation or crossing (the number of squares crossed with all four paws) and number of rearings behaviour (exploratory behavior in which the animal rises to support the body in the forelegs), both indicators being recorded for the last 5 min of the 6 min testing period. The compound or vehicle was administered 30 min before the open-field test and evaluated for 6 min. Control animals received vehicle (NaCl 0.9%) in the same proportion and at a constant volume by the same route, under a similar schedule of administration.

5.5. 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 when appropriate, using the software GraphPad Prism version 4.0, with $P < 0.05$ being considered statistically significant.

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