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Sulphonamide and Sulphonyl-hydrazone Cyclic Imide Derivatives: Antinociceptive Activity, Molecular Modeling and *In Silico* ADMET Screening

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In this paper, we describe the antinociceptive activity, molecular modeling and *in silico* ADMET screening of a series of sulphonyl-hydrazone and sulphonamide imidobenzene derivatives. Among these compounds, the sulphonyl-hydrazones **9** and **11** showed the most potent analgesic activity (ID_{50} = 5.1 and 6.8 μmol/kg, respectively). Interestingly, all derivatives evaluated in this study have a better analgesic profile than the control drugs, acetyl salicylic acid and acetaminophen. Derivative **9** was the most promising compound; with a level of activity that was 24 times higher than the control drugs. Our SAR study showed a relationship among the distribution of the frontier orbital HOMO coefficients, HOMO-LUMO energy gap of these molecules and their reactivity. The best analgesic compounds (including **6**, **9**, **10**, **11** and **12**) fulfilled the Lipinski "rule-of-five", which is theoretically important for good drug absorption and permeation.

Key words: Sulphonylhydrazones, Sulphonamides, Analgesic activity, SAR, ADMET

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INTRODUCTION

Pain is a fundamental event that is normally associated with some kind of health problems, e.g. the manifestation of inflammatory dysfunctions (Lima et al., 2000). However, pain becomes a problem when it occurs often and severely. More than two thirds of patients with advanced cancer will experience pain. Tragically, cancer pain frequently goes untreated, and when it is treated, relief is often inadequate. In fact, more than half of cancer patients suffer unrelieved pain due to inadequate treatment (Plante and VanItallie, 2010; Portenoy, 2011).

The traditional pain treatments (e.g., those based on the use of nonsteroidal anti-inflammatory drugs - NSAIDs, and opioid analgesics) exhibit several side effects. Thus, in the past 20 years, it has increased the interest in the area of the so-called 'adjuvant analgesics' or drugs that have primary indications other than pain, but may be analgesics in selected circumstances (Portenoy, 2000; Mitra and Jones, 2011).

In this context, particularly regarding the therapy of chronically debilitating pain, the search for new analgesic

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agents that are potent, selective and with reduced toxicity is of extreme importance.

The therapeutic potential of cyclic imides has been known for several decades, and they have been used in treating several different pathologies (Hargreaves et al., 1970; Filho et al., 1998; Abdel-Aziz et al., 2011). These organic compounds are described as presenting several pharmacological activities, including antibacterial, antitumor, diuretic and antiviral profiles, similar to sulphonamides and sulphonyl-hydrazones (Lima et al., 1999; Betz et al., 2002; Rollas et al., 2002; Bhattacharya et al., 2004; Sondhi et al., 2006; Hu et al., 2007; Nishimori et al., 2007; Frlan et al., 2008). Moreover, the literature has reported some N-substituted maleimides as inhibiting cyclooxygenase (COX), similar to some NSAIDs, acetyl salicylic acid, indomethacin, and ibuprofen (Kalgutkar et al., 1996).

In a previous publication, we reported the synthesis of imidobenzenesulphonyl compounds (**1** and **2**), which showed promising analgesic profile in the acetic acid-induced mice writhing test (Fig. 1). Acetic acid injected intraperitonially induces the release of several inflammatory mediators, including prostaglandins (Dray, 1995; Filho et al., 1996). Compound **2** was the most effective, being 13 times better than acetyl salicylic acid, possibly due to additional non-covalent interactions with the COX active site (Walter et al., 2004).

In this paper, we described the analgesic potential of sulphonamide and sulphonyl-hydrazones cyclic imide derivatives, using the writhing test in mice and the evaluation of their theoretical, chemical and toxicological properties, by using a molecular modelling approach.

MATERIALS AND METHODS

Chemistry

The sulphonamides and the sulphonyl-hydrazones were synthesized in 3-4 reaction steps. The first step was the Diels-Alder reaction between the *N*-(*p*-chlorosulphonyl)phenylmalemide and two dienes: furan or 2-methylfuran. The reactions of furan and 2-methylfuran were carried out at room temperature in diethyl ether, by stirring for 10 days. The sulphonamides (**3-6**) were obtained by condensation of the Diels-Alder adducts with different amines in methanol, at approximately 0°C. For the synthesis of the sulphonyl-hydrazones (**9-14**), adducts were condensed with hydrazine hydrate, followed by reaction with different benzaldehydes (Fig. 2), as described by our research group (Oliveira and Nunes, 2006). The solvents and reagents were acquired from Sigma-Aldrich and Merck. All the compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, IR, and elemental analysis. 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). ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker AC-200F spectrometer at 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 in parts per million. For the CHN analysis, a CHN elemental analyzer PERKIN ELMER 2400 was used. In the thin layer chromatography, aluminium sheets with silica gel 60 F-254 and 0.2 mm thickness were used.

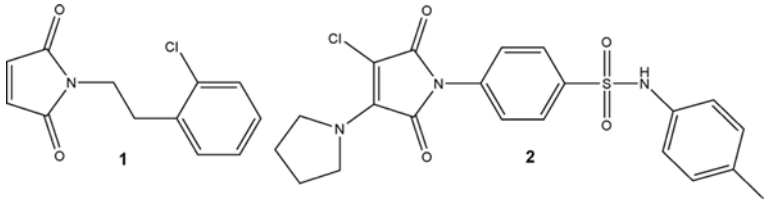

Fig. 1. Maleimide (**1**) and sulphonamide cyclic imide derivative (**2**) with analgesic profile.

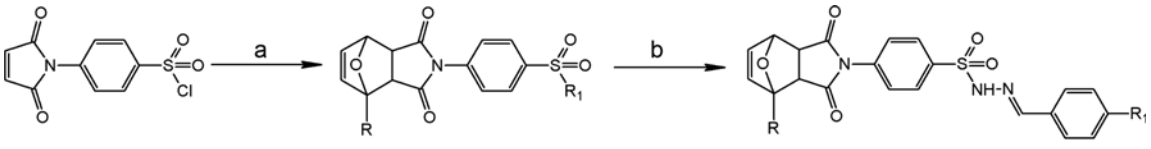

Fig. 2. (**a**) i. furan or 2-methylfuran, Et_2O, r.t; ii. amine or N_2H_4, MeOH, ~ 0°C, (**b**) EtOH, r.t., 1 h, benzaldehydes.

Biological assays

The abdominal constrictions test (writhing tests) was performed, according to the procedures described previously (Collier et al., 1968; Souza et al., 1998; Duarte et al., 2006; Morales et al., 2006). The animals were pretreated by intraperitoneal route with the compound administered in three doses always starting to 10 mg/kg, increasing or decreasing depending on the results obtained, with the initial dose 30 min before the injection with acetic acid (0.6%, 0.45 mL/mouse, respectively. The control animals received a similar volume (10 mL/kg, i.p.) of vehicle (an aqueous solution of DMSO 2%).

After the challenge, pairs of mice were placed in separate boxes and the number of abdominal constrictions was cumulatively counted, over a 20 min period. Antinociceptive activity was expressed as the reduction in the number of constrictions in mice pretreated. The result was compared with the positive control, the standard drugs commercially used (acetyl salicylic acid and acetaminophen). All experiments were carried out at 23 ± 2ºC. Antinociceptive activity was expressed as the number of abdominal contractions between the control animals and mice pre-treated with the studied compound.

Statistical analysis

The results are presented as the mean ± S.E.M., and the statistical significance between the groups was analysed by the means of variance, followed by Dunnett's multiple comparison test. *P* values of less than 0.05 were considered as indicative of significance. The ID_{50} values (concentration of the compound that reduced responses by 50% with respect to control values) were estimated by graphical interpolation from individual experiments. ID_{50}'s are presented as the mean values with 95% confidence interval.

Computational details

To identify stereo-electronic parameters of the sulphonamide and sulphonyl-hydrazone cyclic imide derivatives, which could be correlated with the biological activity, we performed a molecular modeling study, using the Spartan'08 program (Wavefunction Inc). Initially, systematic conformational analyses of the compounds were performed by using increments of 30 to 30 degrees in the flexible bonds, through the Merck Molecular Force Field (MMFF) method. The lower energy conformer of each molecule with largest CPK area was selected for a single point calculation, using the Density Functional Theory method and basis set 6-31-G*. Then we calculated the HOMO and LUMO coefficients and energies of the compounds, electronic density maps and dipole moments. Also, the lipophilicity (cLogP) for each compound was calculated, using the Crippen method available in the Spartan program (Jordão et al., 2011).

In this work, we used the Osiris program (http://www.organic-chemistry.org/prog/peo/) to determine the compound drug-likeness, which was partially based on the topological descriptors, fingerprints of molecular drug likeness structure keys or other properties as clogP and molecular weights (Ghose et al., 1999). In this program the occurrence frequency of each fragment is determined within the collection of the traded drugs, and within the supposedly non-drug-like collection of Fluka compounds. We also submitted the most active compounds to an *in silico* ADMET screening, using the OSIRIS program to analyze their overall drugscore and toxicity risks (mutagenic, irritant, tumorigenic, and reproductive effects), compared to the available drugs used for chemotherapy.

RESULTS

Abdominal constrictions test

All compounds were evaluated in acetic acid-induced abdominal constrictions (writhing) tests, using mice as described in the literature (Souza et al., 1998; Duarte et al., 2006). This initial screening assay (10 mL/kg, i.p.) revealed that all compounds were more active than acetyl salicylic acid and acetaminophen, the standard drugs, at this concentration (Fig. 3). In fact all compounds are more potent than these standard drugs, when comparing the ID_{50} (e.g. compound **9** was about 24 times more potent than acetyl salicylic acid and acetaminophen) I (Table I).

Then, an overall analysis of these results revealed the following order of potency: **9 > 6 > 10 > 12 > 13 > 5 > 14 > 4 > 3 >** acetyl salicylic acid > acetaminophen. The ID_{50} of compound **11** was not possible to be determined, since the pain inhibition was over 50% with the lowest dose (3 mg/kg) used in pharmacological

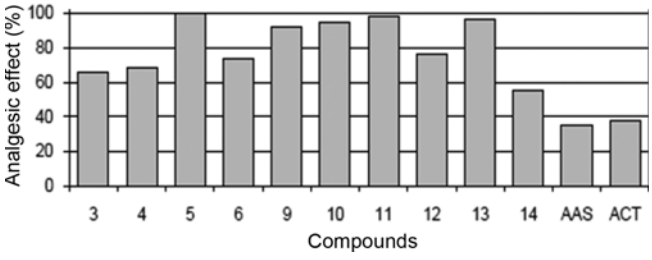

Fig. 3. Comparison of the analgesic effect (%) of sulphonamides and sulphonyl-hydrazone cyclic imide derivatives with acetyl salicylic acid (AAS) and acetaminophen (ACT) at screening concentration (10 mg/kg) in acetic acid-induced writhing in mice.

Table I. Comparison of the analgesic effect (ID_{50} in mg/kg and mmol/kg) of sulphonamides and sulphonyl-hydrazone cyclic imide derivatives and the standard drugs (acetyl salicylic acid - AAS and acetaminophen - ACT) in acetic acid-induced writhing in mice

Compound	ID_{50} (mg/kg)	ID_{50} (μmol/kg)	Energy (eV)			Dipole (debye)	Lipinski Rule of 5			
			HOMO	LUMO	ΔE		cLogP	HBA	HBD	Molecular weight
3	32.01	85.49	-6.72	-1.48	5.24	9.21	0.04	8.00	0.00	374.41
4	26.61	68.16	-6.31	-1.66	4.65	7.84	-0.68	9.00	0.00	390.41
5	15.91	40.95	-6.57	-1.54	5.03	7.47	0.25	8.00	0.00	388.44
6	4.32	10.68	-6.31	-1.65	4.66	7.66	-0.46	9.00	0.00	404.44
9	2.40	5.12	-6.75	-3.33	3.42	8.42	1.71	12.00	1.00	468.44
10	5.62	12.39	-6.17	-1.61	4.56	6.95	1.55	10.00	1.00	453.47
11	< 3	6.83	-6.41	-1.81	4.60	5.18	1.28	10.00	2.00	439.44
12	8.40	18.01	-5.30	-1.36	3.94	6.03	1.95	10.00	1.00	466.51
13	15.44	32.00	-6.70	-2.78	3.92	11.24	1.92	12.00	1.00	482.47
14	28.95	63.84	-5.94	-1.45	4.49	4.97	1.50	10.00	2.00	453.47
AAS	24	133.0	-	-		4.67	1.17	2.00	1.00	180.15
ACT	18.8	125.0	-	-		2.68	0.55	3.00	2.00	151.16

The stereoelectronic properties of these derivatives have also been shown, including HOMO and LUMO energies (eV), energy gap (ΔE), Dipole moment (debye) and calculated Lipinski parameters of lipophilicity (cLogP), volume (Å^3), area (Å^2), molecular weight, number of hydrogen bond acceptor (HBA) and donor (HBD).

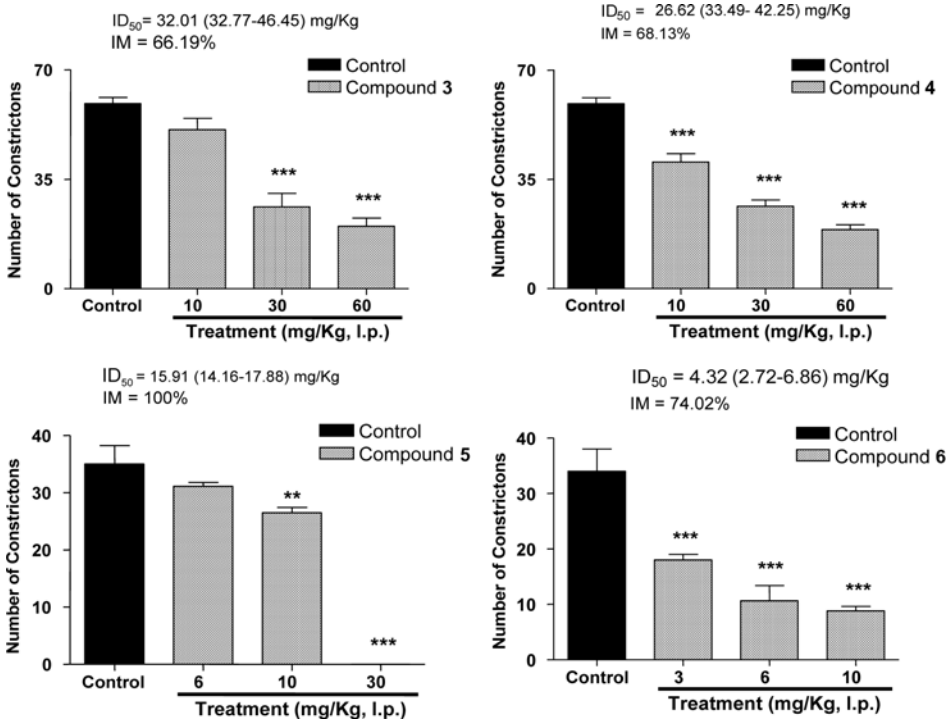

Fig. 4. Effect of Suphonamides (Compounds **3**-**6**) administered intraperitoneally against acetic acid-induced writhing response in mice. Each column represents the mean of six to eight mice and the error bar indicates the S.E.M. Control values C indicate the mice injected with vehicle and the asterisks denote the significance levels when compared with control groups (one-way ANOVA followed by Newman- Keuls test): $^{**}p < 0.01$, $^{***}p < 0.001$. IM = maximum inhibition.

assays. In this case, it is assumed that the ID_{50} is less than 3.0 mg/kg or 6.83 mmol/kg.

The results obtained with the synthesized sulphonamides when evaluated in the acetic acid induced model showed that compounds **3** and **4** exhibited the same pharmacological profile with IMs calculated of 66.19% and 66.13%, respectively (Fig. 4). Compound **6** showed an antinociceptive effect in a dose-dependent manner with calculated IM 74.02%. However, compound **5** was the most effective by inhibiting 100% of the painful

process with a dose of 30 mg/kg.

The results on the effects of mice treatment with sulphonyl-hydrazones (Fig. 5) showed that compounds **9**, **10** and **11** reduced the number of writhing induced by acetic acid in a dose-dependent mode (IMs calculated of 92.02%, 94.50% and 97.71% respectively). Particularly, we observe a rather pronounced analgesic effect of compound **11** with the lowest dose used in the pharmacological experiments. This compound reduced the analgesia induced by acetic acid in more than 50%. The compounds **12** and **13** reduced pain response of animals in 76.20 and 95.83%, respectively, when compared with their respective controls groups, while the compound **14** was the least effective of the tested derivative group.

Molecular modeling studies

In the series of sulphonamides, derivative **6** with the morpholine group linked to the sulphonamide group, and the methyl group linked to oxabicyclo was the most active compound. Importantly, the morpholine, without the methyl group, decreased the activity to around one sixth of the value (Table I). The overall replacement of morpholine with a pyrrolidine group, with or without a methyl group, decreased the activity of the compound; probably due to weaker van der Waals interactions between the derivatives and the receptor (Table I).

The sulphonyl-hydrazones (**9**-**14**) differ in terms of the substituent linked to the aromatic ring next to the sulphonyl-hydrazone moiety, and the methyl group linked to the oxabicyclo system. Compound **9** with the nitro group at the *para*-position of the aromatic ring showed the best activity. However, there is no signifi-

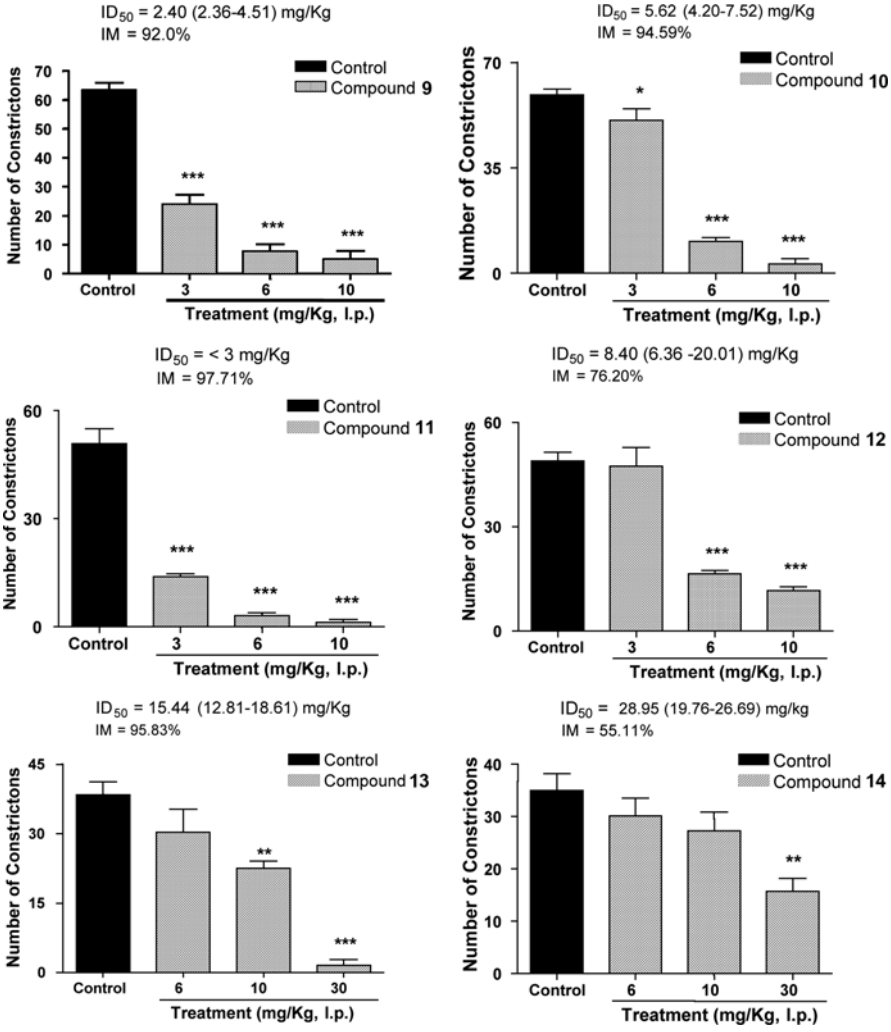

Fig. 5. Effect of Sulphonyl-hydrazones (Compounds **9**-**14**) administered intraperitoneally against acetic acid-induced writhing response in mice. Each column represents the mean of six to eight mice and the error bar indicates the S.E.M. The control values C indicate the mice injected with vehicle and the asterisks denote the significance levels when compared with the control groups (one-way ANOVA followed by Newman- Keuls test): $^{**}p < 0.01$, $^{***}p < 0.001$. IM = maximum inhibition.

cant difference in the distribution of the HOMO and LUMO coefficients or the electrostatic potential in these derivatives (Fig. 6). Interestingly, the lowest energy gap ($\Delta E_{HOMO\text{-}LUMO}$) of these derivatives were obtained for the most active derivative (**9**), and highest for the least active derivative (**14**), indicating that the differences in the reactivity of these molecules may affect their biological activity (Table I).

The addition of a methyl group to the oxabicyclo ring in the structure of the compounds led to a decrease in the activity of compounds **13** and **14**. The superposition of derivatives **6**, **9**, **10**, **11** and **12** (most active of this series) showed a specific conformation, apparently being related to the highest activities (not shown). In fact, compounds with conformations similar to derivative **9** showed better activity (Fig. 6).

The electrostatic potential map of the series revealed two conserved regions in all derivatives related to the presence of the oxygen atoms from the pyrrolidinodione and sulphonyl groups. These conserved regions may be related to the biological activity observed for the whole series. The oxabicyclo derivatives (**9**-**14**) showed an increase in the electron density of the hydrazone system in the central portion of the molecule, which apparently reduces the biological activity (Fig. 6).

In silico ADMET evaluation and comparison with current drugs

In the *in silico* evaluation, the analysis of different descriptors of all compounds (calculated octanol/water partition coefficient, molecular weight, molecular volume, and number of hydrogen bond donor and acceptor groups) revealed that they are sufficiently hydrophobic to penetrate the biological membranes, as determined by the Lipinski "rule-of-five" (cLogP < 5, MW > 500, HBD < 5 and HBA < 10) (Lipinski et al., 2001). Therefore, our results suggest a good theoretical oral bioavailability for most of the series (Table I).

Currently, there are many approaches available to assess the drug-likeness and drug-score of a compound, some based on topological descriptors (Tetko, 2005). In the Osiris program (http://www.organic-chemistry.org/prog/peo/) the occurrence frequency of each fragment is determined within the collection of marketed drugs, and within the supposedly non-drug-like collection of Fluka compounds. In this study, we submitted the most potent compounds (**6**, **9**, **10**, **11** and **12**) to *in silico* ADMET screening, using the Osiris program, to analyze their overall drug-score and drug-likeness potential and toxicity risks (irritant, tumorigenic, and reproductive effects) (Fig. 7). In addition, we compared them to acetyl salicylic acid and acetaminophen, drugs that are currently used for analgesic treatment.

Interestingly, the drug-likeness values for most of the compounds were better than those for acetyl salicylic acid and acetaminophen (not shown). The only exception was **9** with the nitro group, which is described in the literature as a group with mutagenic and cytotoxic profiles in other drugs, such as antiparasitic drugs (Collier et al., 1968; Tocher, 1997; Buschini et al., 2007). Nevertheless, the overall potential of **9**, represented by the drug-score value, was found to be similar to salicylic acid and acetaminophen (Fig. 7). This theoretical feature highlights this derivative as a potential analgesic prototype option for further evaluation and modification for the improvement, as this research proceeds. The other active compounds showed higher values than

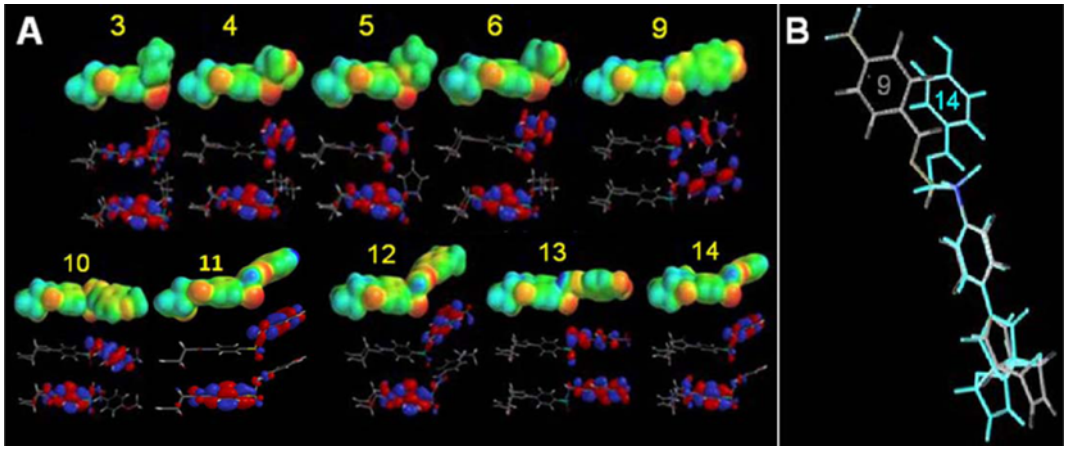

Fig. 6. Comparison of electronic parameters, including molecular electrostatic potential map (up), HOMO (medium) and LUMO (down) orbital coefficients distribution of sulphonamides and sulphonyl-hydrazones (**A**) and Structural alignment of most active (**9**) and the less active (**14**) derivatives (**B**). Molecular electrostatic potential in a 0.002 eV/au^3 surface and energy range varying from -165.0 kJ/mol (deepest red) to 210.0 kJ/mol (deepest blue).

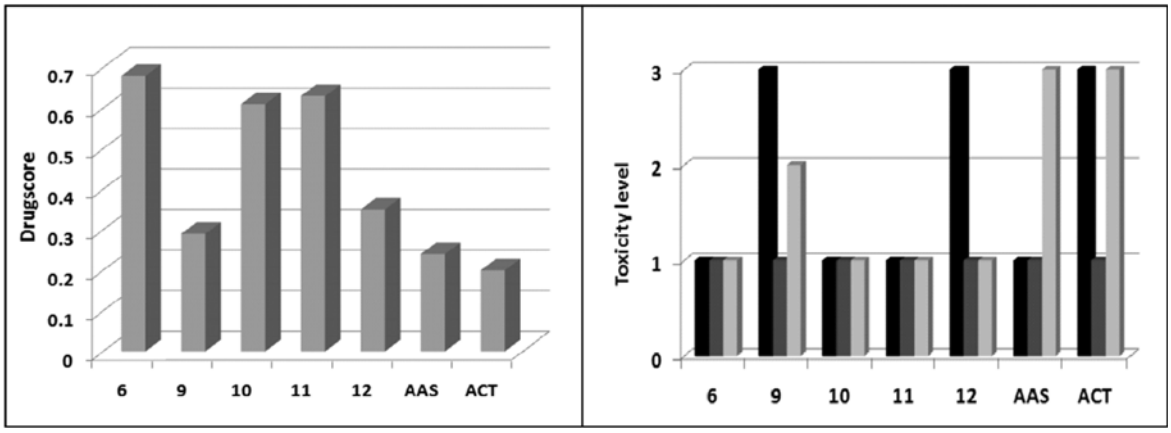

Fig. 7. Comparison of the *in silico* ADMET screening including the overall drugscore and toxicity risks (tumorigenic - black, irritant - gray, and reproductive effects - light gray) of the most active compounds and the available drugs used on chemotherapy - acetyl salicylic acid (AAS) and acetominophen (ACT). The scale of toxicity risk ranges from low (0-1), medium (1-2) and high (2-3) calculated by using Osiris program (http://www.organic-chemistry.org/prog/peo).

the control drugs, also being worthy of further investigation.

The lower or similar theoretical tumorigenic, irritant, and reproductive effects of these more potent derivatives compared to the control drugs suggest a low risk drug-like profile for these compounds (Fig. 7). This reinforces their promising profile for testing in a further study. It is important to note that the toxicity predicted herein is not fully reliable, nor does it guarantee that these compounds are completely free of any toxic effect, but rather should be used as a base to guide the selection of compounds for future *in vitro* and *in vivo* assays.

DISCUSSION

Our group has been working with the synthesis of sulphonamides and sulphonyl-hydrazones of cyclic imides derivatives (Walter et al., 2004; Oliveira and Nunes, 2006; Silva et al., 2006). These compounds have a potential biological action due to the presence of these two important groups in the same structure. The cyclic imide has been long studied because of its pharmacological effect. The sulphonyl moiety has also therapeutic activity, as described previously. These two groups in the same structure allowed the development of interesting molecules with important biological activities, such as, analgesic (Lima et al., 2000; Walter et al., 2004) and antidepressant effects (Duarte et al., 2006). In this context, four sulphonamides (**3**-**6**) and six sulphonyl-hydrazones (**9**-**14**) were synthesized from *N*-(*p*-chlorosulphonyl)phenylmalemide, to evaluate the feasibility of this analgesic profile. In this paper the pharmacological model used was the *in vivo* model of acetic acid induced pain.

Past studies have postulated that acetic acid acts indirectly by inducing the release of endogenous mediators, stimulating the nociceptive neurons, which are sensitive to nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids (Collier et al., 1968; Mogil, 2009). Acetic acid induces pain by enhancing PGE_2 and $PGF_{2\alpha}$ levels (Souza et al., 1998) at the receptors of peritoneal cavity (Bentley et al., 1983; Ramadan, 1997). Therefore, this infers that any active compound acts indirectly by increasing the release of endogenous mediators and stimulating the nociceptive neurons.

Acetic acid induces mice writhing movements - stretching of hind limbs and bending of trunk, which is a model of visceral pain by causing irritation to peritoneum (Collier et al., 1968; Vasudevan et al., 2007; Fernández-Dueñas et al., 2011). This animal pain model has long been used as a screening tool for the assessment of analgesic or anti-inflammatory properties of new agents (Syková and Vyklický, 1978; Souza et al., 1998). Regardless of the painful stimuli, the mechanism process generally involves sensitization of the nociceptors, transmission of impulses to the spinal cord and to the pain center in the thalamus, followed by integration of the sensation in the sensory cortex as pain (Colleoni and Sacerdote, 2010).

Based on the acetic acid assays features used to evaluate our compounds, the significant inhibitory effects, observed for these new compounds, may have involved peripheral and/or cerebral mechanisms. Thus, the antinociceptive action of our derivatives may be through either peripherally at the site of nociceptors or centrally in the spinal cord or the brain. This can only be pinpointed by investigating the influence of the compounds on the main sensitizers of the peripheral nociceptors, mainly prostaglandins (Rainsford, 2007).

By comparing the results in μmol/kg, apparently the

methyl group linked to the oxobicyclic ring was important for the activity in the sulphonamides. Both compounds **5** and **6** were more active than the correspondents **3** and **4**, without the methyl group, in contrast to sulphonyl-hydrazones. Based on this experimental result, the van der Waals force between the methyl group and the receptor is more important in sulphonamides than in sulphonyl-hydrazones. The sulphonyl-hydrazones have the possibility for more hydrogen bonds with the receptor, in their structure. For this reason, they probably have a different interaction with the receptor. Then, in this case, the presence of this methyl group could avoid the formation of the hydrogen bonds between the hydrazone moiety and the receptor that seems to be important for the bioactivity. Compounds **13** and **14** with the methyl group have a reducing biological effect compared to compounds **9**-**12** (Fig. 4B).

The HOMO-LUMO energy gap ($\Delta E_{HOMO\text{-}LUMO}$), which is related to the reactivity in chemical reactions, is an important feature concerning the ability of a molecule to react, and constitutes an important stability index (Burdett and Coddens, 1988; Faust, 1989; Pearson, 1989; Tuppurainen et al., 1991). In fact, a large $\Delta E_{HOMO\text{-}LUMO}$ implies high stability and low reactivity in chemical reactions, the contrary occurs when the $\Delta E_{HOMO\text{-}LUMO}$ is small (Galeazzi et al., 2003). In our modeling studies, compound **9** with the lowest energy gap was the most active, whereas the less active was compound **3** with the highest energy gap. This suggested that the higher reactivity of the compound **9** allowed for more interactions between this compound and the receptor. However, this relationship is not exactly in accordance for all compounds, indicating that the energy gap is not the only important factor for this activity.

In the *in silico* evaluation, a good theoretical oral bioavailability was obtained by the Lipinski "rule-of-five" for most of the series. This suggested that they are sufficiently hydrophobic to penetrate the biological membranes. These values were better than those observed for acetyl salicylic acid and acetaminophen. Moreover, these compounds showed lower or similar theoretical tumorigenic, irritant, and reproductive effects, compared to that of the control drugs. The most active compound (**9**) showed a drug-score value similar to that of salicylic acid and acetaminophen, in despite of its drug-likeness values that were worst than the control drugs.

In conclusion, in this study, we described the synthesis and antinociceptive activity of a new series of cyclic imide derivatives. In addition, in an attempt to develop a SAR to aid the rationalization of new analgesic drugs, we explored the analgesic profile and several chemical properties of this series of sulphonamide derivatives. Apparently, the sulphonyl-hydrazone moiety and the nature of the substituents introduced into the R2-Ph ring appear to be important in determining the biological activity profile. Our SAR study also showed a relationship between the frontier orbital HOMO coefficient distribution of some of these molecules and their reactivity. Despite their chemical structural differences, the best analgesic compounds fulfilled the Lipinski "rule-of-five," which, theoretically, is important for good drug absorption and permeation. Although the Osiris risk alerts do not provide a fully reliable toxicity prediction, the theoretically obtained low-toxicity profile of this series reinforces their potential as lead molecules for further synthetic and biological exploration, for the development of new drugs in analgesic treatment. The significant activity and theoretical profile of the sulphonyl-hydrazones **9** and **11** were highlighted in this study as the potential molecules for further investigation.

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