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Synthesis and PAMPA Permeability Assay of New Sulfonyl Hydrazone Derivatives

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Abstract

This work describes the synthesis of seven new sulfonyl hydrazones, which were proposed from the general structure of acyl hydrazones and 2,4-dinitrosulfonamides. Sulfonyl hydrazones are a class of compounds known to exhibit a wide range of biological activity. In this sense, the study of the pharmacokinetic properties of the bioactive molecules is of extreme importance; therefore, in this article the permeability of these compounds with *in vitro* PAMPA assay mimetizing the permeability through the gastrointestinal tract as well as lipophilicity through miLogP was investigated. All compounds presented good permeability results; it was possible to make a structure-activity relationship with the obtained results and a comparison between the results.

Keywords

Sulfonyl Hydrazones, PAMPA Permeability, Organic Synthesis, Medicinal Chemistry

1. Introduction

Sulfur is present in many classes of compounds of great interest in medicinal chemistry, for example thiosemicarbazones [1] [2], thioureas [3], thiazolidinones [4], sulfonamides [5] [6], among others. Sulfonamides have been known and studied in the scientific environment for a long time, due to their biological properties, in particular their antibacterial activity [7] [8] [9].

In medicinal chemistry, bioisosterism is used as a strategy to modify structural compounds or subunits of bioactive compounds that present molecular vo-

lumes, forms, electron distributions and similar physicochemical properties resulting in similar biological properties. In applying this principle, it is sought to obtain a congeneric series in order to find more efficient and effective compounds against pharmacodynamic and pharmacokinetic properties [10] [11].

In this sense, in the study of Segretti *et al.*, the proposed scaffold was based on the chemical structure of a sulfonamide and an acyl hydrazone. It should be noted that acyl hydrazone is also a class of compounds well known in the area of medicinal chemistry, since it has many biological activities such as antidiabetics [12], antitumor [13] [14], antileishmania [15], among others. That is, Segretti and collaborators started from two compounds with notorious biological activity to plan another compound of a new class—the sulfonyl hydrazones [16]. The sulfonyl hydrazones have similar chemical and biological properties as sulfonamides [8], and are of therapeutic interest because of their activities such as, antimicrobial [17], anticancer [18], anti-trypanosoma cruzi [19], inhibition of the enzyme acetylcholinesterase [20], among others.

In the light of the above, this study proposes to use non-classical bioisosterism to construct a new congener series of sulfonyl hydrazones, based on the general structure of acylhydrazones and 2,4-dinitrosulfonamide, as can be observed in **Figure 1**.

In recent years the evaluation of pharmacokinetic properties of chemical structures has attracted great attention of several authors in medicinal chemistry [21] [22] [23] [24].

Poor pharmacokinetics properties have been the primary cause of failure in a drug candidate development process [25] [26]. In this sense, several efforts have been made to develop new methods to evaluate the pharmacokinetics properties of bioactive compounds. Pharmacokinetics studies drug candidates in terms of their absorption, distribution, metabolism and excretion (ADME) properties [27].

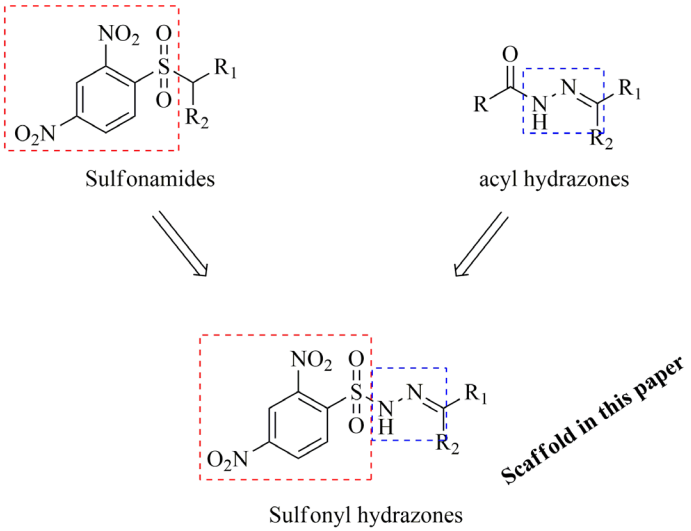


Figure 1. Scaffold in this paper based in the sulfonamide and acyl hydrazones.

Oral administration is the most common route of drug administration. To produce its pharmacological effect, drugs candidates need to cross one or more biological barriers to be absorbed in systemic circulation and distributed to the target organs [22]. Chemical molecules can encounter several types of biological barriers in living systems such as gastrointestinal (GI) epithelial cells, blood capillary wall, hepatocyte membrane, target cell membrane, blood-brain barrier (BBB) and others [28].

There are also different mechanisms of permeation through biological barriers including passive diffusion (transcellular and paracellular), active uptake and efflux transport [22] [28]. Passive diffusion is an important mechanism to study the permeability of new drugs candidates [28]. PAMPA (Parallel Artificial Membrane Permeability Assay) and Caco-2 cells are the most common methods employed to predict drug absorption potential [29].

PAMPA procedure introduced by Kansy *et al.* [30] is a passive diffusion method that simulates the passage of a drug molecule across the biological barrier and provides their potential of absorption [29] [31]. In the PAMPA, a 96-well coated filter plate *in vitro* system was employed and the permeability of substances from a donor compartment across an artificial lipid membrane to an acceptor compartment is measured [29] [32]. In the original PAMPA system proposed by Kansy *et al.* [31], phosphatidylcholine has been used as lipid to simulate the biological membrane and thereby mimicking gastrointestinal absorption [30].

Thus, the present work presents the synthesis, characterization and PAMPA assay, mimicking the permeability through the gastrointestinal tract barrier, for the different sulfonyl hydrazones.

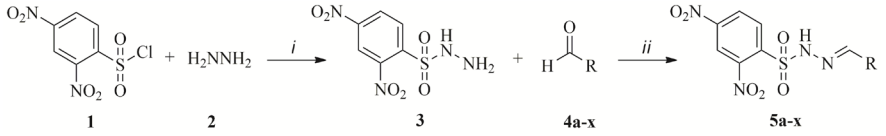
2. Materials and Methods

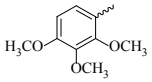
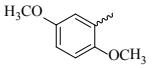
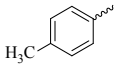
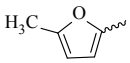
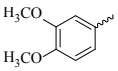
2.1. Synthesis and Characterization of the Compounds

For the synthesis of the sulfonyl hydrazone series derived from 2,4-dinitrobenzene sulfonyl chloride, 2,4-dinitrosulfonylhydrazide was first synthesized according to the scheme shown in **Table 1** in step *i*. First, 10 mmol (1.332 g) of 2,4-dinitrobenzenesulfonyl chloride and 10 mL of acetonitrile were added to a 25 mL flask, which was cooled in an ice bath for 15 minutes under vigorous stirring. Subsequently, 40 mmol of hydrazine was added and the solution was allowed to stir for 8 hours at room temperature. For the synthesis of the sulfonyl hydrazones 1 mmol of 2,4-dinitrobenzenesulfonylhydrazide, 1.5 mmol of different aldehydes, 10 mL of acetonitrile and 0.5 mL of hydrochloric acid 10% were added to a 25 mL flask and the reaction was allowed to proceed for 24 hours, according to scheme shown in **Table 1** in step *ii*.

In order to elucidate the sulfonyl hydrazone structures, these were characterized by nuclear magnetic resonance of hydrogen and carbon (^{1}H and ^{13}C NMR) and mass spectrometry (Atmospheric Pressure Chemical Ionization—APCI).

Table 1. Synthesis of sulfonyl hydrazone **5a-g**.



Compound	R	Compound	R
5a		**5e**	
5b		**5f**	
5c		**5g**	
5d			

(i) solvent acetonitrile, ice bath for 15 minutes and 8 hours at room temperature by stirring. (ii) solvent acetonitrile, 0.5 mL of hydrochloric acid (10%) and 24 hours at room temperature by stirring.

(5a) N'-benzylidene-2,4-dinitrobenzenesulfonohydrazide. Yield 78%, solid, orange color, m.p. 236.5˚C - 236.9˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 9.16 (d, 1H, H3, $J_{H3\text{-}H5}$ = 2.57 Hz); 8.39 (dd, 1H, H5, $J_{H5\text{-}H3}$ = 2.57 Hz, $J_{H5\text{-}H6}$ = 8.92 Hz); 8.36 (d, 1H, H6, $J_{H6\text{-}H5}$ = 8.92 Hz); 11.33 (s, 1H, Hα), 8.15 (s, 1H, H δ), 7.78 (m, 4H, H2', H3', H5' e H6'), 7.48 (m, 1H, H4'); ^{13}C RMN (100 MHz, $CDCl_3$) δ/ppm: 132.8 (C1), 144.5 (C2), 116.5 (C3), 147.5 (C4), 129.7 (C5), 130.7 (C6 e C4'), 123.2 (C1'), 128.7 (C2' e C6'), 127.3 (C3' e C5'); HR-MS (APCI+) *m/z* calculated for $C_{13}H_{10}N_4O_6S$ $[2M + H - SO_2]^+$: 636.5496; found 636,4397.

(5b) N-(4-chlorobenzylidene)-2,4-dinitrobenzenesulfonohydrazide. Yield 89%, solid, orange color, m.p. 207.0˚C - 207.5˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 9.17 (d, 1H, H3, $J_{H3\text{-}H5}$ = 2.48 Hz), 8.38 (dd, 1H, H5, $J_{H5\text{-}H3}$ = 2.48 Hz, $J_{H5\text{-}H6}$ = 9.44 Hz); 8.10 (d, 1H, H6, $J_{H6\text{-}H5}$ = 9.44 Hz); 11.42 (s, 1H, Hα); 8.11 (s, 1H, Hδ); 7.35 - 7.50 (m, 4H, H2', H3', H5', H6') ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 131.0 (C1), 138.9 (C2), 177.1 (C3), 144.6 (C4), 127.8 (C5), 130.4 (C6), 132.1 (C1'), 130.5 (C2' e C6'), 123.8 (C3' e C5'), 134.9 (C6'), 144.9 (Cδ). HR-MS (APCI+) *m/z* calculated for $C_{13}H_9ClN_4O_6S$ $[M + H - SO_2]^+$: 321.0391; found 321.0375.

(5c) N-(4-methylbenzylidene)-2,4-dinitrobenzenesulfonohydrazide. Yield 66%, solid, orange color, m.p. 220.4˚C - 221.0˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 9.16 (d, 1H, H3, $J_{H3\text{-}H5}$ = 2.52 Hz), 8.36 (dd, 1H, H5, $J_{H5\text{-}H3}$ = 2.52 Hz, $J_{H5\text{-}H6}$ = 9.32 Hz), 8.10 (d, 1H, H6, $J_{H6\text{-}H5}$ = 9.32 Hz), 11.30 (s, 1H, Hα), 7.67 (d, 2H, H2', H6', $J_{H2'\text{-}H3',\,H6'\text{-}H5'}$ = 8.31 Hz), 7.27 (d, 2H, H3', H5', $J_{H3'\text{-}H5',\,H6'\text{-}H2'}$ = 8.56 Hz), 2.43 (s, 3H, H7') ^{13}C RMN (100 MHz, $CDCl_3$) δ/ppm: 130.4 (C1), 144.8 (C2), 116.7 (C3), 148.1 (C4), 127.6 (C5), 129.8 (C6), 129.9 (C1'), 123.5 (C2', C3', C5', C6'), 141.6 (C4'), 21.6 (C7'); HR-MS (APCI+) *m/z* calculated for $C_{14}H_{12}N_4O_6S$ $[M + H - SO_2]^+$: 301.0937; found 301.1003.

(5d) N-(3,4-dimethoxybenzylidene)-2,4-dinitrobenzenesulfonohydrazide. Yield 87%, solid, copper color, m.p. 266.0˚C - 267.0˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.87 (d, 1H, H3, $J_{H3\text{-}H5}$ = 2.57 Hz); 8.36 (dd, 1H, H5, $J_{H5\text{-}H3}$ = 2.57 Hz, $J_{H5\text{-}H6}$ = 9.66 Hz); 8.10 (d, 1H, H6, $J_{H6\text{-}H5}$ = 9.66 Hz); 11.96 (s, 1H, Hα); 8.61 (s, 1H, Hδ); 7.42 (d, 1H, H2', J = 2.90 Hz); 7.26 (dd, 1H, H6', $J_{H6'\text{-}H5'}$ = 2.90 Hz, $J_{H6'\text{-}H2'}$ = 8.32 Hz); 7.06 (d, 1H, H5', $J_{H5'\text{-}H6'}$ = 8.32 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 136.5 (C1), 149.6 (C2), 116.6 (C3), 159.0 (C4), 122.8 (C5), 129.5 (C6), 126.2 (C1'), 111.4 (C2'), 144.2 (C3'), 148.4 (C4'), 108.4 (C5'), 122.3 (C6'), 55.4 (C7'), 55.3 (C8'); HR-MS (APCI+) *m/z* calculated for $C_{15}H_{14}N_4O_8S$ [M + H – SO_2]$^+$: 347.0992; found 347.1022.

(5e) N-(3,4,5-trimethoxybenzylidene)-2,4-dinitrobenzenesulfonohydrazide. Yield 90%, solid, orange color, m.p. 188.9˚C - 189.1˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.98 (d, 1H, H3, $J_{H3\text{-}H5}$ = 2.69 Hz); 8.38 (dd, 1H, H5, $J_{H5\text{-}H3}$ = 2.69 Hz, $J_{H5\text{-}H6}$ = 8.30 Hz); 8.18 (d, 1H, H6, $J_{H6\text{-}H5}$ = 8.30 Hz); 11.54 (s, 1H, Hα); 7.79 (d, 1H, H6', $J_{H6'\text{-}H5'}$ = 8.80 Hz); 6.93 (d, 1H, H5', $J_{H5'\text{-}H6'}$ = 8.92 Hz); 3.93 (s, 6H, H7', H9'); 3.85 (s, 3H, H8'); ^{13}C NMR (400 MHz, Acetone-*d6*) δ/ppm: 129.9 (C1), 142.9 (C2), 117.4 (C3), 145.6 (C4), 121.9 (C5), 123.6 (C6), 157.0 (Cδ), 117.4 (C1'), 138.1 (C2'), 130.2 (C3'), 154.2 (C4'), 109.1 (C5'), 120.9 (C6'), 56.3 (C7'), 60.7 (C8'), 62.0 (C9'); HR-MS (APCI+) *m/z* calculated for $C_{16}H_{16}N_4O_9S$ [M + H – SO_2]$^+$: 377.1097; found 377.1144.

(5f) N-(2,5-dimethoxybenzylidene)-2,4-dinitrobenzenesulfonohydrazide. Yield 93%, solid, orange color, m.p. 197.6˚C - 199.0˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 9.12 (d, 1H, H3, $J_{H3\text{-}H5}$ = 2.32 Hz), 8.33 (d, 1H, H5, $J_{H5\text{-}H3}$ = 2.32 Hz, $J_{H5\text{-}H6}$ = 9.42 Hz), 8.05 (d, 1H, H6, $J_{H6\text{-}H5}$ = 9.42 Hz), 11.32 (s, 1H, Hα), 8.50 (s, 1H, Hδ), 6.88 (d, 1H, H3', $J_{H3'\text{-}H4'}$ = 9.05 Hz), 7.00 (d, 1H, H4', $J_{H4'\text{-}H3'}$ = 9.05 Hz, $J_{H4'\text{-}H6'}$ = 2.94 Hz), 7.50 (d, 1H, H6', $J_{H6'\text{-}H4'}$ = 2.94 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 129.9 (C1), 144.0 (C2), 116.7 (C3), 144.8 (C4), 122.1 (C6), 163.5 (Cδ), 118.4 (C1'), 153.0 (C2' e C5'), 110.6 (C3'), 113.4 (C4'), 55.9 (C7'), 56.2 (C8'); HR-MS (APCI+) *m/z* calculated for $C_{15}H_{14}N_4O_8S$ [M + H – SO_2]$^+$: 347.0992; found 347.1017.

(5g)N-((5-methylfuran-2-yl)methylene)-2,4-dinitrobenzenesulfonohydrazide. Yield 72%, solid, orange color, m.p. 213.3˚C - 214.0˚C, ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.90 (d, 1H, H3, $J_{H3\text{-}H5}$ = 2.20 Hz); 8.42 (d, 1H, H5, $J_{H5\text{-}H6}$ = 9.48 Hz, $J_{H5\text{-}H3}$ = 2.20 Hz); 8.04 (d, 1H, H6, $J_{H6\text{-}H5}$ = 9.39 Hz); 12.86 (s, 1H, Hα); 7.62 (s, 1H, Hδ); 7.08 (d, 1H, H2'); 6.48 (d, 1H, H3') 2.55 (s, 3H, H5') ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 131.0 (C1), 146.7 (C2), 118.2 (C3), 156.8 (C4 or C1'), 129.8 (C5), 123.5 (C6), 145.3 (Cδ), 116.3 (C2'), 108.7 (C3'), 13.9 (C5'); HR-MS (APCI+) *m/z* calculated for $C_{12}H_{10}N_4O_7S$ [M + H – SO_2]$^+$: 290.0651; found 290.0835.

2.2. Parallel Artificial Membrane Permeability Assay—PAMPA

The PAMPA assay was performed according to the methodology described by Venzke *et al.* [23]. In the model mimicking intestinal permeability (PAMPA

GIT) the lipid used was 1% phosphatidylcholine (m/v) in dodecane. The % MR parameter is evaluated in the PAMPA assay by the retained concentration of the compound on the phosphatidylcholine membrane. The donor solutions of compounds **5a-g** were prepared by diluting the DMSO stock solutions (1000 ppm) in 1:1 ratio (v/v) in phosphate buffered saline and stirring overnight. Also, 150 μL of the donor solutions were added to the filter plate wells, and 300 μL of the acceptor solutions (50% DMSO in phosphate buffer) were added to the receiver plate wells. The filter plate was coupled to the receiver plate and incubated during five hours at room temperature. The experiments were performed in quadruplicate.

3. Results and Discussion

As a single sulfonyl chloride is used for the synthesis of the whole series, the spectra showed characteristic signals consistent with the hydrogens of this ring. The signals in the region between 7.80 and 9.00 ppm refer to the hydrogens located between or adjacent to the nitro groups (NO_2). These electron withdrawing groups provide a disbanding of the hydrogens, resulting in larger chemical shifts. In the spectra, there is a singlet in the region between 11.00 and 12.00 ppm attributed to a nitrogen-bound hydrogen. It is bound to the sulfoxide group, a strongly electron withdrawing group, thus, changing the NH signal to higher displacement values, as can be observed. Another indicative that confirms the formation of the sulfonyl hidrazones is the presence of a singlet, referring to the metilenic hydrogen, at 8.00 and 9.00 ppm. In addition to the characteristic signals mentioned, the values of the integrals for each hydrogen, the signals of the carbons and the data of the mass spectrometry corroborate the described structures. The loss of SO_2 via elimination-rearrangement is trivial in sulfonyl hydrazones and leads to the generation of $[M + H - SO_2]^+$ [33].

Analyzing the values in Table 2, it can be verified that the presence of the electron withdrawing group in the aromatic ring (compound **5b**) decreases the permeability, on the other hand, the presence of electron-donor groups, such as methyl and methoxy, in general, tends to increase permeability. It is worth noting that compound **5d** presented the lowest permeability of the series, even with the presence of electron donor groups, avoiding the general tendency observed, this probably occurred by the position in which the two large groups are found.

Compound **5f** presented the best permeability result of the series, even containing the two bulky groups which are present in compound **5d**, but the difference is the position of the methoxy group on the aromatic ring, since in the sulfonyl hydrazone **5f** one of the groups is in the position 2 of the aromatic ring, which favors intermolecular interactions with *NH*, this is in some way improving the permeability of the compound. This same characteristic can be observed for **5e**, corroborating with this justification. For the latter, the small decrease in permeability is probably due to the number of bulky groups in the structure. Therefore, it can be affirmed that the effect caused by position 2 of the methoxy group exceeds the effect of bulky groups.

Table 2. Apparent permeability, membrane retention and miLogP of compounds **5a-g**.

Compound	P_{app}[a] (cm·s^{-1})	%MR[b]	miLogP[c]
5a	2.92×10^{-6}	52.88	2.29
5b	3.94×10^{-6}	37.81	2.96
5c	1.75×10^{-5}	35.2	2.45
5d	6.59×10^{-6}	15.67	3.45
5e	1.78×10^{-5}	14.45	1.92
5f	1.32×10^{-5}	13.98	1.93
5g	2.51×10^{-5}	11.26	1.92

(a) Apparent permeability. (b) Membrane retention. (c) Calculated by molinspiration.

4. Conclusion

Sulfonyl hydrazones have a wide range of biological applications, being a class of compounds of great interest in the field of medicinal chemistry. Therefore, we evaluated 7 unpublished sulfonyl hydrazones as to their pharmacokinetic properties, as these properties are essential for the development of drug prototypes; the results obtained were motivating for the continuity of new trials. Regarding the lipophilicity, the compounds with the best permeabilities (**5c**, **5e**, **5f** and **5g**) have log P between the range considered ideal to have a balance between solubility and permeability ($0 < \log P < 3$) corroborates in part with the permeation observed in the PAMPA TGI assay. In addition, the compounds **5e**, **5f** and **5g** showed low retention of membrane, with MR = 14.45%, 13.98% and 11.26% respectively, results that are also important in the research and development of new drugs.

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Supplementary Material

Supplementary data associated with this article can be found in the online.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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