Design, Synthesis and 3-D Characterization of 1-Benzenesulfonyl-1,2,3,4-Tetrahydroquinolines as Lead Scaffold for Antiparasitic Drug

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Abstract: Ten 1-benzenesulfonyl-1,2,3,4-tetrahydroquinoline (BSTHQ) were synthesized and characterized and their antiprotozoal activities were investigated. This small library was designed by combining two chemical moieties that are known to be biologically active by itself. The BS group seems to be favorable for the antiparasitic activity, since the derivatives presented lower IC_{50} value than the precursor heterocycle. Most compounds were moderately active against *T cruzi*, but **3** showed a promising IC_{50} value (9.76μM) with low cytotoxicity (L6). Also, **3, 6** and **9** showed interesting activity and reasonable selectivity against *P. falciparum*. These derivatives are considered as lead scaffolds and merit further exploration through structure optimization.

Keywords: Antiparasitic, Benzenesulfonyl, Tetrahydroquinolines, Stereoelectronic Properties.

INTRODUCTION

Neglected tropical diseases caused by protozoan parasites like trypanosomiasis, leishmaniasis, and malaria are distributed throughout the world and two million people are estimated to die each year from such diseases. Not only the people from developing countries have principally affected, but also those from the developed ones, due to of migrations and the frequent association of parasitic diseases with immunocompromised patients. According to the last WHO report [1], half of the world's population is at the risk from malaria, being *Plasmodium falciparum* (*P. f.*) and *Plasmodium vivax* (*P.v.*) the most important malaria parasites of humans cases. The WHO hax announced recently, the emergence of parasites resistant to the effective drugs currently in use (artemisinin-based combination therapies), has undermine the global malaria control efforts thus far achieved [1, 2]. Sleeping sickness caused by the parasites *Trypanosoma brucei rhodesiense* (*T. b. r.*) and *Trypanosoma brucei gambiense* (*T.b.g.*), is a fatal diseases that cause about patients 40.000 dying each year in over 25 counties of sub-Saharan Africa [3]. Chagas disease, caused by *Trypanosoma cruzi* (*T. c.*) and found in much of South America, all of Central America and Mexico, is also an important cause of mortality and morbidity in the region [3]. The *Leishmania donovani* (*L. d.*) parasite is broadly distributed in humans and animals, and is mostly found in tropical and subtropical areas [3].

Many of the drugs currently in use for the treatment of parasitic infections have major limitations including significant toxicity, variable efficacy, lack of oral bioavailability, extensive courses of parenteral administration, and problems of cost and supply [4]. Furthermore, there is considerable evidence that their extended use is leading to the development of resistance [2]. The urgent need for the discovery of new safe and effective drugs against these protozoan infections is obvious.

As a part of an ongoing lead discovery project we design and prepared a library of N-benzenesulfonyl derivatives of bioactive heterocyclic compounds. This approach of combining privileged structures to develop new compounds, which may have pharmacological relevance, has shown to be very successful [5]. Our design approach was based on the combination of two groups that are known to be active. Indeed, 1-benzenesulfonyl-1,2,3,4-tetrahydroquinolines, BSTHQs (**1-10**), in which general structure is depicted in Fig. (**1**), combine two moieties with well known biological activity: benzenesulfonyl (BS) and a 1,2,3,4-tetrahydroquinoline heterocycle (THQ). The THQ moiety is present in compounds with diverse characteristics such as antimalarial activity [6], anticancer activity [7], nonsteroidal glucocorticoid receptor ligands [8], agonists of β3 adrenergic receptors [9], histamine H3 receptor antagonists [10], among others. Some derivatives were also found to act as dual PPARα/γ agonists for potential treatment of type-2 diabetes [11]. On the other hand, BS is a substituent frequently present in biologically active molecules [12-14], where the presence of the BS group leads to analogs with similar or better biological activities than their precursors [15].

Some BSTHQ derivatives have been already synthesized, mostly by cyclization reactions to generate the THQ heterocyclics from secondary amines already carrying the BS group [16, 17], All these cyclization methods included various steps and tedious work-up. Another way to prepare the BSTHQ is by reacting THQ or some of its derivatives with sulfonylchlorides in the presence or not of solvent and a base like pyridine [18-20]. From the ten BSTHQ we report here, **5** is a new compound, while the synthesis of the rest has been reported previously. Even though BSTHQs **1-4**, **6-10** have

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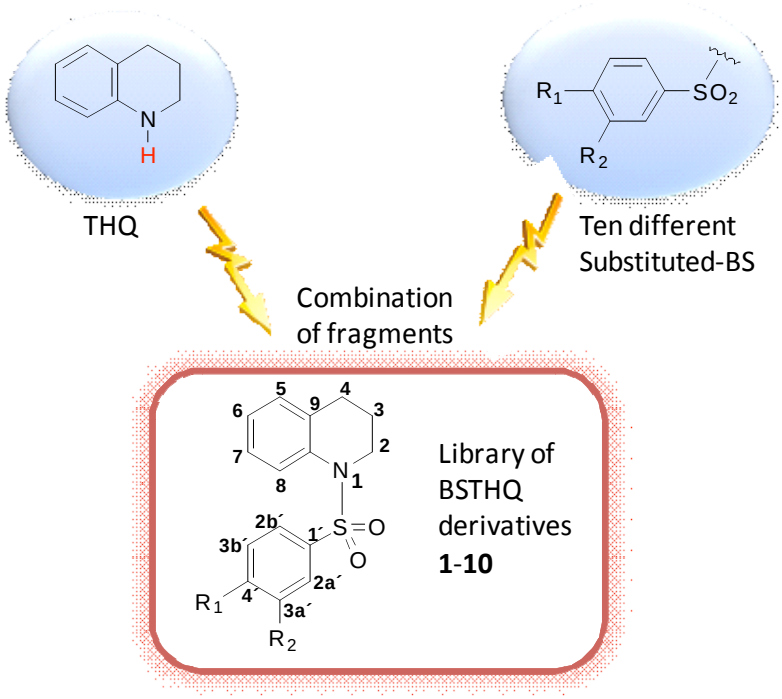


Fig. (1). General structure for the BSTHQ derivatives.

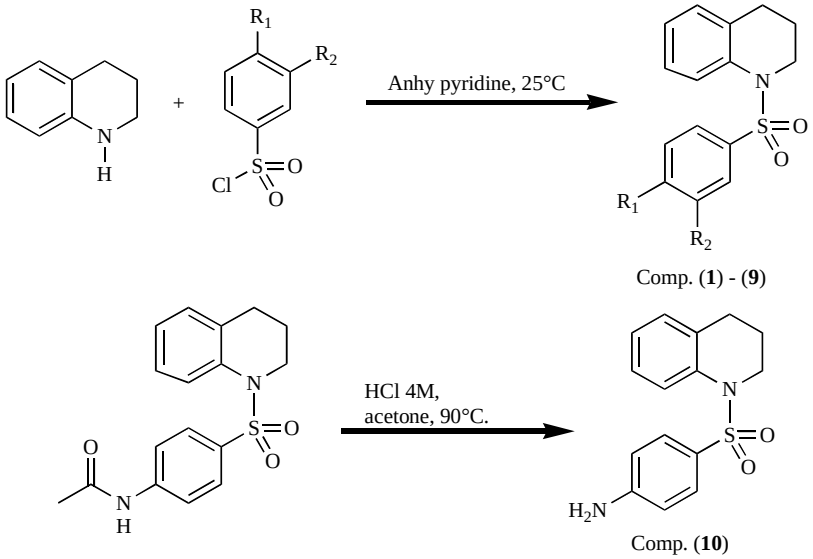
been synthesized before, their pharmacological properties have not been explored in-depth. To the best of our knowledge, only compounds **1**, **6** and **9** have been described with a certain activity as HIV-transcriptase inhibitors [21], low potency calcium channel antagonist [22] and gonadotropin releasing hormone antagonist [23], respectively.

Furthermore, compounds **1-10** were qualified as drug candidates for oral bioavailability when the parameters set by Lipinsky´s rule were applied. Based on all these information, the combination of a BS and a biologically active heterocycle THQ appears to be a very promising hypothesis for lead discovery. In the present work, we report the synthesis, and *in vitro* activity against protozoan parasites of ten BSTHQ compounds. Finally, we also present herein a complete NMR spectroscopy and 3D structural characterization, which was carried out to explain some REA and in view of future CADD studies.

RESULTS AND DISCUSSION

Chemistry

In the present investigation, a modification of the one step method proposed by Fisher [20] and Sargent L.J [18] were selected for the preparation of **1-10**. We have used



Scheme 1. Synthesis of BSTHQ.

Table 1. Structure, Yield, Melting Point, and Oral Bioavailability Evaluation Parameters of Synthesized BSTHQ

Compd	R_1[a]	R_2	Yield[b]	m.p.[c] (lit)	%Purity[d]	PM[e]	ClogP[f]	HBA[g]	HBD[h]	TPSA[i]
1	H	H	87	62.5-63.0	97	273.3	3.46	3	0	37.4
2	$NHCOCH_3$	H	67	175.0-175.5	99	330.4	2.94	5	1	66.5
3	NO_2	H	82	112.0-113.0 (116-117)[16]	85	318.3	3.20	6	0	83.2
4	CH_3	H	78	91.0-92.0 (83-85)[16, 28, 29]	97	287.4	3.96	3	0	37.4
5	F	H	82	75.0-76.0	92	291.3	3.60	3	0	37.4
6	Cl	H	80	93.0-93.5 (94-95)[19]	97	307.8	4.17	3	0	37.4
7	Br	H	77	126.5-127.0 (128-129)[16]	97	352.2	4.32	3	0	37.4
8	OCH_3	H	85	80.5-81.0	96	303.4	3.63	4	0	46.6
9	H	NO_2	82	103.5-104.0	96	318.3	3.20	6	0	83.2
10	NH_2	H	68	123.5-124.0 (125-126)[30]	98	288.4	2.73	4	2	63.4

[a]Structures were proved by analytical HRMS and by and ^1H and ^{13}C NMR ($^1H.$,^{13}C, COSY, HSQC, HMBC) spectrometry and FT-IR spectroscopy. [b]Isolated yield. [c]Uncorrected. [b]Measured by HPLC. [e]PM = molecular weight. [f]ClogP = calculated partition coefficient [26]. [g]HBA = hydrogen bond acceptor. [h]HBD = hydrogen bond donor. [i]TPSA = topological polar surface area [27].

similar procedures for the successful synthesis of N-benzenesulfonyl-benzotriazole [24] and 2-methyl-1,2,3,4-tetrahydroquinoline derivatives [25]. Scheme **1** outlines the synthetic strategy. Substituents at the 3- or 4-position of the BS group were carefully selected and account for electronic and/or lipophilic differences within the series. We also attended a simple work-up process to allow us using these conditions in automation systems and parallel synthesis to rapid enlarge the library, and include other nitrogenated-heterocycles or different substitutions and substitution patterns in the benzenesulfonyl ring, during the optimization with detailed SAR studies.

Compounds **1-9** (Table **1**) were prepared by addition of a solution of THQ in anhydrous pyridine to an appropriate and commercially available benzenesulfonyl chloride under nitrogen atmosphere. Compound **10** was obtained *via* hydrolysis of the *N*-acetylsulfonyl-THQ (**2**) with HCl 4M in acetone for 3 h. Crystalline and stable compounds were obtained after their purification as described in experimental section. Table **1** shows the structure of compounds along with their melting point (m.p.), yield and purity (see experimental section for more detailed procedures).

The synthesized compounds can be considered as future drugs, according to Lipinsk´s rule. They show optimum lipophilicity, calculated as CLogP [26] within the range of 2.20-4.32 and their molecular weights are in the acceptable range of 273-352. Compounds **1-10** show a HBA below 10 and HBD below 5, which is also within the limit. The complete topological polar surface area (TPSA) [27] is <140.

The chemical structure of compounds **1-10** was characterized by, HRMS, HPLC/MS, EIMS, IR and ^1H and ^{13}C NMR. The FT-IR displayed characteristic absorptions for sulfonylamide group in the regions 1330-1360 cm^{-1} ($\nu SO_{2\ asim}$) and 1140-1180 cm^{-1} ($\nu SO_{2\ sim}$), as well as other typical signals for the THQ moiety and substituents in the BS. The HRMS or HPLC/MS spectra showed the molecular ion, [M^+] which corresponds to the calculated mass. The ^1H NMR spectra (DMSO-d6) showed signals that were in agreement with the structure of the compounds **1-10**. Signals at δ lower than 5,0ppm accounted for the six aliphatic protons of the THQ ring. The protons of the CH_3 group of **2**, **4** and **8** were also in that region. All the aromatic protons appeared at δ values higher than 7,0ppm. Furthermore, the ^{13}C NMR spectrum of **1-10** showed the aliphatic carbons between 22,0-55,0ppm, and aromatic carbons between 112,0 and 170,0ppm along with C=O signals of **2**. The complete and unambiguous ^1H and ^{13}C NMR assignments were achieved using a combination of COSY, HSQC and HMBC experiments. This extensive NMR analysis was performed for both the structural characterization and future Quantitative Structure Stereoelectronic Relationship studies.

Antiprotozoal Activity

Table **2** reports the activity of compounds **1-10** against *T. b .r.*, *T. c.*, *L. d*, and *P. f.*, as well as their cytotoxicity against L6 (rat skeletal myoblasts) cells. All the activity determinations were carried out at the Screening Center of the Swiss Tropical Institute and the values represent the average of two determinations done in duplicate.

As a general observation, the presence of BS seemed to be favorable for the antiparasitic activity against *T. c.*, *P. f.* and *L. d.* with all derivatives showing a decreased IC_{50} value with respect to the heterocycle precursor, THQ. The exceptions were compounds **3** and **7** against *L. d.* The opposite effect was observed against *T. b. r.*, in which BSTHQ derivatives were less active than THQ, being the only exception as compound **3** (*p*-NO_2). These results were different from the ones previously observed in a series of 2-methyl-1,2,3,4-tetrahydroquinoline, in which the presence of the BS demonstrated to be favorable for *T. b. r.* activity [25]. Moreover, in that series, the *p*-nitro derivative was found to be the only compound with an IC_{50} value larger that its heterocycle precursor. Besides, the presence of different substituents on the BS seemed to have a particular influence depending on the parasite. On the other hand, all compounds exhibited low cellular toxicity (at least more than 1000-fold lower) compared to podophyllotoxin, which was used as a reference.

When antiparasitic potential of all compounds were analyzed by applying the WHO/TDR screening activity criteria

Table 2. Antiparasitic Activity of Compounds 1-10 Expressed as IC_{50} Values (μM)[a]

	T. b. r.	*T. c.*	*L. d.*	*P. f.* K1[b]	Cytotoxicity. L-6	SI *T. c.*[c]	SI *P. f.* [c]
	IC_{50}	IC_{50}	IC_{50}	IC_{50}	IC_{50}		
Melarsoprol	0.008						
Benznidazole		1.54					
Miltefosine			0.25				
Chloroquine				0.25			
Podophyllotoxin					0.01		
THQ	16.63	85.14	130.49	>37.54	396.28	45.3	10.55
1	23.47	36.05	43.47	>18.31	69.72	1.93	3.80
2	172.10	39.38	57.89	>15.15	17.36	0.40	1.14
3	16.10	9.76	163.83	12.83	63.68	6.52	4.96
4	65.10	29.40	56.08	>17.42	10.75	0.36	0.61
5	95.32	47.36	39.30	>17.18	69.52	1.46	4.04
6	62.34	20.24	26.72	12.45	43.39	2.14	3.48
7	58.98	15.70	141.91	11.05	23.77	1.53	2.15
8	67.65	20.93	40.98	>16.48	25.71	1.22	1.56
9	47.58	34.80	28.96	13.77	73.11	2.10	5.31
10	66.91	39.90	81.77	>17.32	62.96	1.57	3.63

[a]Values represent the average of two determination done in duplicate. [b]Resistant to chloroquine and pyrimethamine. [C]Selectivity Index calculated as SI = IC_{50}L6 / IC_{50} parasite.

specified for each parasite [4], some conclusions could be drawn: *i)* For *L. d.* activity, two compounds (**6** and **9**) showed moderate growth inhibition (IC_{50} value 26.72 and 28.96μM, respectively). Even though the potency was low when compared to miltefosine, the addition of the BS substituent strongly increased the potency to about 5-fold with respect to the THQ, for most of the derivatives. *ii)* All compounds were moderately active against *T. c.*; the *para* substitution on the BS resulted in an increase of activity with the only exceptions being **2** and **10,** which had almost the same activity as **1**. The negative impact of the fluoro substituent (**5**) was also found in the previous series of BS derivatives [25]. The nitro derivative (**3**) was the most active analog against *T. c*., with an IC_{50} value of 9.76 μM, which implies only a 6.3-fold reduced potency compared to that of benznidazole as the reference (IC_{50} 1.54 μM). Changing the nitro from *para* (**3**) to *meta* (**9**) reduced the activity three-fold and resulted in one of the least active analogs. It has been described that, at the lead-generation stage in drug discovery, a successful hit would have an IC_{50} value around 10 μM. After lead-compound identification, extensive lead-optimization is typically needed to lower this value to 10 nM. Due to the interesting activity (IC_{50} of 9.76 μM for *T. c.*) and the low cytotoxicity (IC_{50} value of 63.68 μM), compound **3** represents the most interesting molecule with potential as antiprotozoal agent [31]. *iii)* The addition of the BS increased the activity by three-fold at best against *P. f.* Electron-withdrawing substituents were favorable and led to the most potent analogs (**3**, **6**, **7**, and **9**). Compound **7** was the most potent but it also showed high toxicity. The remaining three compounds showed moderate growth inhibition of *P. f.* with IC_{50} values around 10 μM. Moreover, these compounds were reasonably selective for *P. f.* and can be considered a promising scaffold for further structure optimization [31].

Finally, among the newly prepared derivatives, none of them presented significant activity against *T. b. r.* (IC_{50} > 16mM). In fact, the addition of the BS group increased IC_{50} value with respect to the heterocycle precursor, except for compound **3**, which showed almost the same activity as THQ.

Computational Modeling

From results showed in Table **2**, most of them are in agreement with those previously reported for 1-benzenesulfonyl-2-methyl-1,2,3,4-tetahydroquinoline derivatives [25], it was evident that the link of a BS to the heterocycles produced, in general, a positive impact on *in vitro* antiparasitic activity. The type of substitution proposed might influence not only lipophilic characteristics, but also H-bonding capacity (an N-H was changed by an N-BS) and steric and electronic properties as well. In order to investigate the conformational preferences of the BSTHQ derivatives, an exploratory search by using quantum mechanical calculations was carried out.

Conformational studies of **1-10** were performed with the semiempirical (AM1) and DFT (B3LYP/6-31G(d)) methods, as implemented in Gaussian 03 [32]. First of all, THQ was found to present two equal half-chair conformations. The half-boat conformations were not stable, in agreement with the findings of Charifson *et al.* [14] for tetrahydroisoquinolines. For the BSTHQs, a careful systematic scan of relevant

dihydral angles was used to inspect the positioning of sulfonyl (α angle) and phenyl (β angle) substituents (Fig. (**2**)). Full geometry optimization at the B3LYP/6-31G(d) level of theory was later performed for the lowest energy conformations and each minimum was characterized as a stationary point by vibrational frequency calculations. For all the derivatives the number of imaginary frequencies was zero.

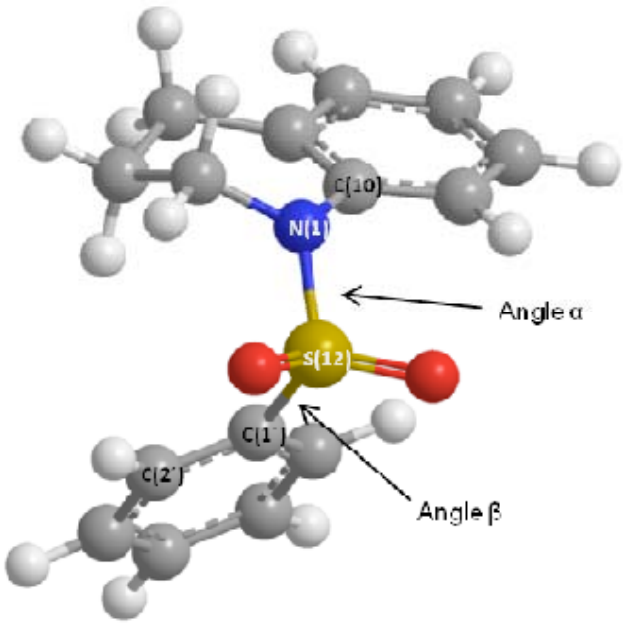


Fig. (2). Minimum structure of **1** obtained by B3LYP/6-31G(d). Angles α and β were scanned in the conformational search of BSTHQs.

The BS group was shown to be pseudo-axial in energy-minimized conformations. Moreover, the presence of BS moiety bound to the THQ do not affect the steric properties of the heterocycle, thus the minimum conformation of THQ and the heterocycle in any BSTHQ were perfectly superimposed. We found two minimum-energy conformations for each BSTHQ derivative. Angles and energy for these conformations are informed in Table **3**. The values found for the relevant angles were independent of the substituent in BS moiety, which means that no 3D structure characteristic could be the reason for differences in activity displayed by derivatives. Besides, no linear correlation could be found between the activity and any single variable such as electronic, lipophilic or steric parameters (data not shown). Therefore, a combination of the electronic distribution on the phenyl group, the size of the substituent and the lipophilicity of the compounds could explain the differences on the antiparasitic activity.

In an analogy with our previously report on 1-BS-2-methyl-1,2,3,4-tetrahydroquinolines [25]. the presence of a hydrogen bond interaction between H8 and one of the oxygen of SO_2 was evident for BSTHQs. This dipolar interaction was supported by computational and NMR data. In experimental NMR, H8 of derivatives appeared at 1.2ppm average downfield, with respect to the same proton of unsubstituted THQ (δ 7.6 → δ 6.4). The same behavior was found when NMR spectra were calculated by using a B3LYP/6-31G(d) level of theory. The unexpected unshielding (Δδ of 1.0-1.2ppm) of protons that make part of a C-H----O hydrogen bonds has been studied by Shanchez-Viesca *et al.* in different compounds [33]. Further confirmation was achieved by analysis of the parameters reported by Desiraju *et al*. [34] and Taylor *et al*. [35] from crystallographic data. When weak H-bonds like C-H---O occurred, distances H----O and angle C-H---O are in the range of 2.0-3.0Å and 90°-130°, respectively. For **1-10**, the calculated minimum-energy geometry showed distances of 2.28-2.29Å for H----O and angles C-H---O of 115°-116°, thus supporting the possibility of an intramolecular H-bond between C8-H----O.

EXPERIMENTAL

General Considerations

All the benzenesulfonyl chlorides were purchase from Sigma-Aldrich. The pyridine used for the synthesis was dried and stored over pellets of NaOH. Reaction progress

Table 3. Minimum-Energy Conformations Data for Each BSTHQ Derivative

Compd	R1	R2	Absolute minimum			Local minimum			ΔE[c]
			Angle α	Angle β	Total Energy[b]	Angle α	Angle β	Total Energy[b]	(Eabs – Eloc)
1	H	H	296.1	80.4	-742942.41	74.2	100.6	-742942.04	0.36
2	$NHCOCH_3$	H	296.8	79.8	-873470.38	72.4	100.2	-873470.37	1.01
3	NO_2	H	296.2	79.9	-871266.56	73.4	100.2	-871265.62	0.94
4	CH_3	H	295.7	80.5	-767615.27	74.0	99.7	-767614.29	0.97
5	F	H	296.2	80.1	-805211.97	72.9	99.7	-805211.02	0.95
6	Cl	H	296.0	79.7	-1031342.25	73.2	99.8	-1031341.29	0.95
7	Br	H	295.8	79.6	-2356332.96	73.3	99.8	-2356331.99	0.97
8	OCH_3	H	295.3	79.3	-814807.40	72.9	98.6	-814806.47	0.92
9	H	NO_2	296.7	81.6	-871266.53	72.3	97.7	-871265.62	0.91
10	NH_2	H	296.3	81.2	-777679.03	74.0	99.9	-777678.10	0.94

[a]Values are given for the 2S enantiomer.
[b]Zero Point Corrected Energies (kcal/mol) for global minima.
[c]Energy difference (kcal/mol) between the conformers with the 2-CH3 group in axial/equatorial position.

was monitored by TLC (silica gel 60 F_{254}, Merck) visualizing with UV light. The silica gel used in the purification of the products was Merck grade 60, 230-400 mesh, 60Å. All others reagents and solvents used were purchased from Anhedra.

Melting points (m.p.) were determined using an OptiMelt (Standard Research Systems) apparatus, by microcapillary methods and are uncorrected. Infrared spectra were recorded on a Varian FTS800 FT-IR Scimitar Series and samples were determined in KBr disk (1%). Vibration bands are denoted with a sub-indices sim = symmetrical and as = asymmetrical. NMR experiments were performed on a Bruker advance II 400MHz, ultra shield TM spectrometer at 400.16(^{1}H) and 100.62(^{13}C), which has an inverse multinuclear detection sonda, digital resolution and a variable temperature unit. Chemical shift values are reported in ppm (δ) and were taken with DMSO-d_6 as a solvent (referred to residual DMSO al 2.5 ppm for ^{1}H and 39.5 ppm for ^{13}C). Coupling constants (J) are in Hz (refer to Table **1** for atom numbering). The multiplicities of the signals are described using the following abbreviations s = singlet, d = doublet, t = triplet, q = quartet, quintet = quint, m = multiplet.

High resolution mass spectroscopy experiments were taken in a Micromass Q-TOF micro Hybrid Quadrupole/Orthogonal High Resolution Time of Flight MS with Micromass capillary HPLC (Waters Corporation). HPLC/MS spectra were recorded on a Shimadzu LC20AT equipped with a SPD M20A diode array detector, a SIL-20A autosampler and a LCMS 2010 mass detector. The column used for the LC/MS analysis was a Water XBridge column (RP18, 3.5µ, 4.6 x 50mm) and it was eluted at 1 mL/min with a gradient of methanol in water. The gradient was run as follows: t = 0 min, 10% MeOH; t= 10 min, 90% MeOH; t = 12 min, 100% MeOH; t = 14 min, 100% MeOH. A wavelength of 220 nm was selected for purity assessment.

Experimental Procedure, Spectral Data for Compounds 1-10

General Procedures for the Synthesis

Compounds **1-9** were synthesized by adding 4.00 mmoles of an appropriate substituted benzenesulfonyl chloride to a solution of THQ (3.00 mmoles, 0.40g, 0.37 mL) in 1.5 mL of anhydrous pyridine at room temperature. The reaction mixture was vigorously stirred at 60-80° until no more starting materials could be detected by TLC (hexane: acetone 7:3). This mixture was then cooled at -5°C and chilled water was added to precipitate the product. The solid was filtered off, washed exhaustively with HCl 0.01M and water, and dried over $CaCl_2$ and anhydrous $MgSO_4$. Colored solids were obtained at yields of 85-90%.

Compound **10** was synthesized by hydrolysis of compound **2**: 3mmols of **2** were dissolved in 18mL of acetone, heated at 40°C and 10mL HCl 4M was added dropwise. After that, the reaction mixture was heated at 60-70° and stirred until no more starting material could be detected by TLC (hexane: acetone 5:5). The mixture was cooled and a solution of Na_2CO_3 was added to pH 9. The acetone was evaporated in vacuum and the solid filtered off, before being washed with water and dried over $CaCl_2$ and anhydrous $MgSO_4$. A white solid was obtained with a yield of 92%.

General Procedure for Purification of the Derivatives

The products isolated as described previously were then purified as follows: A) All the compounds were obtained in a colored solid from the reaction mixture. To eliminate the colored impurities, the compounds were dissolved in a mixture of hexane: acetone 7:3 and filtered through a mixture of silica gel 60 and active carbon. The solvent was evaporated in a vacuum and was dried over $CaCl_2$ for 24 h. A light yellow solid resulted with a yield of 92-98%. B) Some derivatives seemed to decompose in silica gel. These were washed with cold ethanol (-5°C) to eliminate the colored impurities. The yields were 77-80% of a pink solid. C) All compounds were finally recrystallized from ethanol or methanol to give 80-85% of the products as white or yellow crystals.

Purity of Compounds 1-10

All compounds were tested for purity by High Performance liquid Chromatography (HPLC). The system consist of an Agilent 1000 series solvent delivery system coupled with an automated injector system and a UV-Visible detector. The column used was a Water RP-C18 (50 x 3 mm) with particles of 3 microns which was maintained at room temperature. A flow rate of 1.0mL/min with methanol-water mixtures was used as mobile phase. Detection was made at 254mn and the injection volume was 20µL. The inspection of the chromatograms showed a purity of more than 96% for all the compounds (see Table **1**), measured as the percentage of area under the sample peak. The solvent peak (methanol) was observed at 0.578.

The melting point ranges were also measured as a criteria of purity, and are reported with the spectral data in the following section.

Specific Procedures and Spectral Data for Compounds 1-10

1-(benzenesulfonyl)-1,2,3,4-tetrahydroquinoline (1). (R_1 = H; R_2 = H)

Purification by procedures A and C (ethanol). Colorless crystals (2.61 mmol, 87%), m.p. 62.5-63.0°C (from ethanol). Purity 97% (methanol 60%). IR (υ_{max}/cm^{-1}): 2927, 2850 (CH_3), 1344 ($SO_{2\ as}$), 1162 ($SO_{2\ sim}$). ^{1}H NMR : 7.7 (tt, 1H, 7.2 and 1.2Hz, H4'); 7.6 (d, 1H, 8.0Hz, H8); 7.6 (dd, 2H, 8.0 and 1.6Hz, H2'); 7.5 (td, 2H, 8.0 and 1.2Hz, H3'); 7.2 (ddd, 1H, 8.8, 6.0 and 2.8Hz, H7); 7.0-7.1 (m, 2H, H6 and H5); 3.8 (t, 2H, 6.0Hz, H2); 2.4 (t, 2H, 6.6Hz, H4); 1.6 (quint, 2H, 6.6Hz, H3). ^{13}C NMR (assigned using HSQC): 139.4 (Cq-1'); 136.7 (Cq-10); 133.8 (Cq-4'); 131.05 (Cq-9); 129.9 (CH-3'); 129.8 (CH-5); 127.2 (CH-2'); 126.7 (CH-7); 125.3 (CH-6); 124.3 (CH-8); 46.7 (CH-2); 26.4 (CH_2-4); 21.9 (CH_2-3). COSY: $^3J_{vec}$: H2 – H3; H3 – H4. $^3J_{ortho}$: H6 –H7; H5 –H6; H7 –H8; H2' – H3'; H3' – H4'. $^4J_{meta}$: H5 – H7; H6 – H8; H2' – H4'. HMBC (f_1 = 400.16Hz, f_2 =100.62Hz) (C→H): C4→H5, H3; C3→H2, H4; C2→H4, H3; C6→H8; C7→H5; C8→H6; C5→H7, H4; C9→H8, H6, H4, H3; C10→H7, H5, H2, H4; C1'→H3'; C2'→H4', H3';

C3'→H2'; C4'→H2'.HRMS calcd mass for $C_{15}H_{15}NO_2SNa$: 296.072; found: 287.073.

1-(4-acetamide-benzenesulfonyl)-1,2,3,4-tetrahydroquinoline (2). (R_1 = NHCOCH$_3$; R_2 = H)

Purification by procedures A and C (ethanol). Colorless crystals (2.01 mmol, 67%), m.p. 175.0-175.5°C (from ethanol). Purity 99% (methanol 55%). IR (υ_{max}/cm^{-1}): 3345 (NH), 2932, 2858 (CH_3), 1702 (CO amide), 1327 ($SO_{2\ as}$), 1308 (CN amide), 1150 ($SO_{2\ sim}$). ^{1}H NMR : 10.3 (s, 1H, H5'); 7.7 (d, 2H, 8.8Hz, H3'); 7.6 (d, 1H, 8.0Hz, H8); 7.5 (d, 2H, 8.8Hz, H2'); 7.2 (ddd, 1H, 8.8, 5.2 and 3.6Hz, H7); 7.0-7.1 (m, 2H, H6 and H5); 3.7 (t, 2H, 5.8Hz, H2); 2.4 (t, 2H, 6.6Hz, H4); 2.0 (s, 3H, H7'); 1.6 (quint, 2H, 6.2Hz, H3). ^{13}C NMR assigned using HSQC): 169.6 (C6'=O); 143.9 (Cq-4'); 136.9 (Cq-10); 131.0 (Cq-9); 132.9 (Cq-1'); 129.7 (CH-5); 128.8 (CH-2'); 126.6 (CH-7); 125.1 (CH-6); 124.2 (CH-8); 119.0 (CH-3'); 46.6 (CH-2); 26.4 (CH_2-4); 24.6 (CH_3-7'); 21.5 (CH_2-3). COSY: $^3J_{vec}$: H2 – H3; H3 – H4. $^3J_{ortho}$: H6 – H7; H5 –H6; H7 –H8; H2' – H3'. $^4J_{meta}$: H5 – H7; H6 – H8. HMBC (f_1= 400.16Hz, f_2=100.62Hz) (C→H): C4→H5, H3; C3→H2. H4; C2→H4, H3; C6→H8; C7→H5; C8→H6; C5→H7, H4; C4'→H2'; C9→H8, H6, H4, H3; C10→H7, H5, H2, H4; C1'→H3', H2'; C2'→H3'; C3'→H5', H2'; C4'→H2', H3', H5'; C6'→H5', H7'; C7'→H5'. HRMS calcd mass for $C_{17}H_{19}N_2O_3S$: 331.094; found: 331.092.

1-(4-nitro-benzenesulfonyl)-1,2,3,4-tetrahydroquinoline (3). (R_1 = NO$_2$; R_2 = H)

Purification by procedures A and C (ethanol). Yellow crystals (2.46 mmol, 82%), m.p. 112.0-113.0°C (from ethanol). Purity 85% (methanol 60%). IR (υ_{max}/cm^{-1}): 2970, 2932 (CH_3), 1523 ($NO_{2\ as}$), 1345 ($SO_{2\ as}$), 1305 ($NO_{2\ sim}$), 1163 ($SO_{2\ sim}$). ^{1}H NMR : 8.3 (d, 2H, 8.8Hz, H3'); 7.9 (d, 2H, 8.8Hz, H2'); 7.6 (d, 1H, 8.0Hz, H8); 7.2 (td, 1H, 8.4 and 2.0Hz, H7); 7.1-7.2 (m, 2H, H6 and H5); 3.8 (t, 2H, 6.0Hz, H2); 2.4 (t, 2H, 6.6Hz, H4); 1.6 (quint, 2H, 6.3Hz, H3). ^{13}C NMR (assigned using HSQC): 150.5 (Cq-4'); 144.6 (Cq-1'); 136.1 (Cq-10); 131.3 (Cq-9); 130.0 (CH-5); 128.8 (CH-2'); 126.9 (CH-7); 125.8 (CH-6); 125.3 (CH-3'); 124.3 (CH-8); 47.0 (CH-2); 26.3 (CH_2-4); 21.7 (CH_2-3). COSY: $^3J_{vec}$: H2 – H3; H3 – H4; $^3J_{ortho}$: H6 –H7; H5 –H6; H7 –H8; H2' – H3'. $^4J_{meta}$: H5 – H7; H6 – H8. HMBC (f_1= 400.16Hz, f_2=100.62Hz) (C→H): C4→H5, H3; C3→H2, H4; C2→H4, H3; C6→H8; C7→H5; C8→H6; C5→H7, H4; C9→H8, H6, H4, H3; C10→H7, H5, H2, H4; C1'→H3', H2'; C2'→H3'; C3'→H2'; C4'→H2'. HRMS calcd mass for $C_{15}H_{14}N_2O_4SNa$: 341.057; found: 341.058.

1-(4-methyl-benzenesulfonyl)-1,2,3,4-tetrahydroquinoline (4). (R_1 = CH$_3$; R_2 = H)

Purification by procedures A and C (methanol). Colorless crystals (2.34 mmol, 78%), m.p. 91-92°C (from methanol). Purity 97% (methanol 60%). IR (υ_{max}/cm^{-1}): 2949, 2858 (CH_3), 1336 ($SO_{2\ as}$), 1152 ($SO_{2\ sim}$). ^{1}H NMR (DMSO-d6, 400.16Hz): 7.6 (d, 1H, 8.4Hz, H8); 7.4 (d, 2H, 8.0Hz, H2'); 7.3 (d, 2H, 8.0Hz, H3'); 7.2 (m, 1H, 8.8 and 3.6Hz, H7); 7.1-7.2 (m, 2H, H6 and H5); 3.7 (t, 2H, 6.0Hz, H2); 2.4 (t, 2H, 6.6Hz, H4); 2.3 (s, 3H, H5'); 1.6 (quint, 2H, 6.3Hz, H3). ^{13}C NMR (assigned using HSQC): 144.2 (Cq-4'); 136.8 (Cq-10); 136.6 (Cq-1'); 130.9 (Cq-9); 130.3 (CH-3'); 129.8 (CH-5); 127.2 (CH-2'); 126.7 (CH-7); 125.2 (CH-6); 124.1 (CH-8); 46.6 (CH-2); 26.5 (CH_2-4); 21.5 (CH_2-3); 21.4 (CH_3-5'). COSY: $^3J_{vec}$: H2 – H3; H3 – H4. $^3J_{ortho}$: H6 –H7; H5 –H6; H7 –H8; H2' – H3'. $^4J_{meta}$: H5 – H7; H6 – H8. HMBC (f_1= 400.16Hz, f_2=100.62Hz) (C→H): C4→H5, H3; C3→H2, H4; C2→H4, H3; C6→H8, H7; C7→H5; C8→H6, H7; C5→H7, H4; C9→H8, H6, H4, H3; C10→H7, H5, H2, H4; C1'→H3'; C2'→H3'; C3'→H2', H5'; C4'→H2'; C5'→H3'. HRMS calcd mass for $C_{16}H_{17}NO_2SNa$: 310.088; found: 310.089.

1-(4-fluoro-benzenesulfonyl)-1,2,3,4-tetrahydroquinoline (5). (R_1 = F; R_2 = H)

Purification by procedures B and C (ethanol). Colorless crystals (2.46 mmol, 82%). m.p. 75.0-76.0°C (from ethanol). Purity: 92% (methanol 60%). IR (υ_{max}/cm^{-1}, KBr): 2973, 2858 (CH_3), 1346 ($SO_{2\ as}$), 1172 ($SO_{2\ sim}$); 1008 (CF). ^{1}H NMR : 7.6 (d, 1H, 8.0Hz, H8); 7.6 (ddd, 2H, 8.8 and 2.3Hz, JHF$_{(meta)}$ =5.2Hz, H2'); 7.4 (td, 2H, 8.8 and 2.5Hz, JHF$_{(ortho)}$=8.8Hz, H3'); 7.2 (ddd, 1H, 8.8, 6.0 and 3.2Hz, H7); 7.1-7.2 (m, 2H, H6 and H5); 3.7 (t, 2H, 6.0Hz, H2); 2.4 (t, 2H, H4); 1.6 (quint, 2H, 6.4Hz, H3). ^{13}C NMR (assigned using HSQC): 165.0 (d, 1JHF = 251.0Hz, Cq-4'); 135.8 (d, ^4JCF = 3.0Hz, Cq-1'); 136.5 (Cq-10); 131.1 (Cq-9); 130.3 (d, ^2JCF = 10.0Hz, CH-2'); 129.8 (CH-5); 126.7 (CH-7); 125.5 (CH-6); 124.3 (CH-8); 117.1 (d, ^3JCF = 23.0Hz, CH-3'); 46.7 (CH-2); 21.5 (CH_2-3); 26.3 (CH_2-4). COSY: $^3J_{vec}$: H2 – H3; H3 – H4; $^3J_{ortho}$: H6 – H7; H5 – H6; H7 – H8; H2' – H3'. $^4J_{meta}$: H5 – H7; H6 – H8. HMBC (f_1= 400.16Hz, f_2=100.62Hz) (C→H): C4→H5, H3; C3→H2, H4; C2→H4, H3; C6→H8, H7; C7→H5; C8→H6; H7 C5→H7, H4; C9→H8, H6, H4, H3; C10→H7, H5, H2, H4; C1'→H3', F; C2'→H3', F; C3'→H2', F; C4'→H2', H3', F. HPLC/MS(EI) m/z: 293 [M+H$^+$], 314 [M+Na].

1-(4-chloro-benzenesulfonyl)-1,2,3,4-tetrahydroquinoline (6). (R_1 = Cl; R_2 = H)

Purification by procedures B and C (ethanol). Colorless crystals (2.40 mmol, 80%), m.p. 93.0-93.5°C (from ethanol). Purity 97% (methanol 60%). IR (υ_{max}/cm^{-1}): 2965, 2860 (CH_3), 1343 ($SO_{2\ asim}$), 1164 ($SO_{2\ sim}$); 767 (CCl). ^{1}H NMR : 7.63 (dd, 2H, 8.8 and 2.4Hz, H2'); 7.6 (d, 1H, 8.0Hz, H8); 7.6 (dd, 2H, 8.8 and 2.8Hz, H3'); 7.2 (ddd, 1H, 8.8, 5.6 and 3.6Hz, H7); 7.2-7.2 (m, 2H, H6 and H5); 3.8 (t, 2H, 6.0Hz, H2); 2.4 (t, 2H, 6.6Hz, H4); 1.6 (quint, 2H, 6.2Hz, H3). ^{13}C NMR (assigned using HSQC): 138.7 (Cq-1'); 138.3 (Cq-4'); 136.5 (Cq-10); 131.2 (Cq-9); 130.0 (CH-2'); 129.1 (CH-3'); 129.9 (CH-5); 126.8 (CH-7); 125.5 (CH-6); 124.2 (CH-8); 46.8 (CH-2); 26.3 (CH_2-4); 21.6 (CH_2-3). COSY: $^3J_{vec}$: H2 – H3; H3 – H4. $^3J_{ortho}$: H6 – H7; H5 – H6; H7 – H8; H2' – H3'. $^4J_{meta}$: H5 – H7; H6 – H8. HMBC (f_1= 400.16Hz, f_2=100.62Hz) (C→H): C4→H5, H3; C3→H2, H4; C2→H4, H3; C6→H8, H7; C7→H5; C8→H6; H7 C5→H7, H4; C9→H8, H6, H4, H3; C10→H7, H5, H2, H4; C1'→H3'; C2'→H3'; C3'→H2'; C4'→H2', H3'. HPLC/MS(EI) m/z: 208 [M+H$^+$], 330 [M+Na].

1-(4-bromo-benzenesulfonyl)-1,2,3,4-tetrahydroquinoline (7). (R_1 = Br; R_2 = H)

Purification by procedures B and C (ethanol). Colorless crystals (2.31 mmol, 77%), m.p. 126.5-127.0°C (from ethanol). Purity 98% (methanol 60%). IR (υ_{max}/cm^{-1}): 2973, 2916 (CH_3), 1342 ($SO_{2\ as}$), 1165 ($SO_{2\ sim}$); 768 (CBr). ^{1}H NMR :

7.8 (dd, 2H, 8.8 and 2.2Hz, H3'); 7.6 (d, 1H, 8.4Hz, H8); 7.5 (dd, 2H, 8.4 and 2.2Hz, H2'); 7.2 (ddd, 1H, 8.8, 6.5 and 3.6Hz, H7); 7.1-7.2 (m, 2H, H6 and H5); 3.8 (t, 2H, 5.8Hz, H2); 2.4 (t, 2H, 6.8Hz, H4); 1.6 (quint, 2H, 6.3Hz, H3). ^{13}C NMR assigned using HSQC): 138.6 (Cq-1'); 136.4 (Cq-10); 131.2 (Cq-9); 133.0 (CH-3'); 129.2 (CH-2'); 129.9 (CH-5); 127.7 (Cq-4'); 126.8 (CH-7); 125.5 (CH-6); 124.2 (CH-8); 46.7 (CH-2); 26.4 (CH_2-4); 21.6 (CH_2-3). COSY: $^3J_{vec}$: H2 – H3; H3 – H4. $^3J_{ortho}$: H6 – H7; H5 – H6; H7 – H8; H2' – H3'. $^4J_{meta}$: H5 – H7; H6 – H8. HMBC (f_1= 400.16Hz, f_2=100.62Hz) (C→H): C4→H5, H3; C3→H2, H4; C2→H4, H3; C6→H8, H7; C7→H5; C8→H6; H7 C5→H7, H4; C9→H8, H6, H4, H3; C10→H7, H5, H2, H4; C1'→H3'; C2'→ H3'; C3'→H2'; C4'→H2', H3'. HPLC/MS(EI) m/z: 352-354 [M+H$^+$], 374-376 [M+Na].

1-(4-methoxy-benzenesulfonyl)-1,2,3,4-tetrahydroquinoline (8). (R_1 = OCH_3; R_2 = H)

Purification by procedures A and C (ethanol). Colorless crystals (2.55 mmol, 85%). m.p. 80.5-81.0°C (from ethanol). Purity 96% (methanol 60%). IR (υ_{max}/cm^{-1}): 2970, 2932 (CH_3), 2844 ($OCH_{3\ as}$), 1336 ($SO_{2\ as}$), 1151 ($SO_{2\ sim}$). ^{1}H NMR : 7.6 (d, 1H, 8.4Hz, H8); 7.5 (dd, 2H, 8.8 and 2.6Hz, H2'); 7.2 (ddd, 1H, 8.8, 5.2 and 4.0Hz, H7); 7.0-7.1 (m, 2H, H6 and H5); 7.0 (dd, 2H, 8.8 and 2.6Hz, H3'); 3.8 (s, 3H, H6'); 3.7 (t, 2H, 6.0Hz, H2); 2.4 (t, 2H, 6.6Hz, H4); 1.6 (quint, 2H, 6.3Hz, H3). ^{13}C NMR (assigned using HSQC): 163.2 (Cq-4'); 136.9 (Cq-10); 131.0 (Cq-1'); 130.9 (Cq-9); 129.4 (CH-2'); 129.8 (CH-5); 126.6 (CH-7); 125.1 (CH-6); 124.3 (CH-8); 114.9 (CH-3'); 56.1 (CH_3-5'); 46.6 (CH-2); 26.5 (CH_2-4); 21.4 (CH_2-3). COSY: $^3J_{vec}$: H2 – H3; H3 – H4. $^3J_{ortho}$: H6 – H7; H5 – H6; H7 – H8; H2' – H3'. $^4J_{meta}$: H5 – H7; H6 – H8. HMBC (f_1= 400.16Hz, f_2=100.62Hz) (C→H): C4→H5, H3; C3→H2, H4; C2→H4, H3; C6→H8, H7; C7→H5; C8→H6; H7 C5→H7, H4; C9→H8, H6, H4, H3; C10→H7, H5, H2, H4; C1'→H3'; C2'→H3'; C3'→H2'; C4'→H2', H3'. HPLC/MS(EI) m/z: 304 [M+H$^+$], 326 [M+Na].

1-(3-nitro-benzenesulfonyl)-1,2,3,4-tetrahydroquinoline (9). (R_1 = H; R_2 = NO_2)

Purification by procedures A and C (ethanol). Yellow crystals (2.46 mmol, 82%). m.p. 103.5-104.0°C (from ethanol). Purity 96% (methanol 60%). IR (υ_{max}/cm^{-1}): 2970, 2932 (CH_3), 1531 ($NO_{2\ as}$), 1350 ($SO_{2\ as}$ and $NO_{2\ sim}$), 1170 ($SO_{2\ sim}$). ^{1}H NMR : 8.5 (ddd, 1H, 8.0, 2.8 and 0.9Hz, H4'); 8.2 (t, 1H, 1.8Hz, H2'a); 7.9 (ddd, 1H, 7.8, 1.6 and 1.3Hz, H2'b); 7.8 (t, 1H, 8.0Hz, H3'b); 7.6 (d, 1H, 8.0 H8); 7.2 (td, 1H, 7.7 and 1.7Hz, H7); 7.1 (td, 1H, 7.3 and 1.0Hz, H6); 7.1 (dd, 1H, 7.6 and 1.2Hz, H5); 3.8 (t, 2H, 6.0Hz, H2); 2.4 (t, 2H, 6.4Hz, H4); 1.6 (quint, 2H, 6.4Hz, H3). ^{13}C NMR (assigned using HSQC): 148.3 (Cq-3'a); 140.7 (Cq-1'); 136.1 (Cq-10); 131.6 (Cq-9) 133.0 (C2'b); 132.0 (C3'b); 129.9 (CH-5); 128.4 (C4'); 126.9 (CH-7); 125.9 (CH-6); 124.4 (CH-8); 121.8 (CH-2'a); 46.9 (CH-2); 26.2 (CH_2-4); 21.7 (CH_2-3). COSY: $^3J_{vec}$: H2 – H3; H3 – H4. $^3J_{ortho}$: H6 – H7; H5 – H6; H7 – H8; H3'b – H2'b; H3'b – H4'. $^4J_{meta}$: H5 – H7; H6 – H8; H2'b – H2a; H2'b – H4'; H2'a – H4'. HMBC (f_1= 400.16Hz, f_2=100.62Hz) (C→H): C4→H5, H3; C3→H2, H4; C2→H4, H3; C6→H8, H7; C7→H5; C8→H6; H7 C5→H7, H4; C9→H8, H6, H4, H3; C10→H7, H5, H2, H4; C2'a→H4', H2'b; C4'→H2'a, H2'b, H3'b; C3'b→H4'; C2'b→H4', H2'a, H3'b; C1'→H2'a, H3'b; C3'a→H2'a, H3'b. HPLC/MS(EI) m/z: 319 [M+H$^+$], 341 [M+Na].

1-(4-amine-benzenosulfonyl)-1,2,3,4-tetrahydroquinoline (10). (R_1 = NH_2; R_2 = H)

Purification by procedure C (methanol). Beige crystals (2.04 mmol, 68%). m.p. 123.5-124.0 °C (from ethanol). Purity 98% (methanol 55%). IR (υ_{max}/cm^{-1}): 3462, 3366 (NH), 2933, 2858 (CH_3), 1595 (NH), 1319 ($SO_{2\ as}$), 1148 ($SO_{2\ sim}$). ^{1}H NMR: 7.6 (d, 1H, 8.0Hz, H8); 7.2 (d, 2H, 8.8Hz, H2'); 7.1 (ddd, 1H, 9.2, 5.6 and 3.6Hz, H7); 7.0-7.1 (m, 2H, H6 and H5); 6.5 (d, 2H, 8.4Hz, H3'); 6.0 (s, 1H, H5'); 3.7 (t, 2H, 5.8Hz, H2); 2.4 (t, 2H, 6.6Hz, H4); 1.6 (quint, 2H, 6.2Hz, H3). ^{13}C NMR (assigned using HSQC): 153.6 (Cq-4'); 137.4 (Cq-10); 130.7 (Cq-9); 129.6 (CH-5); 129.2 (CH-2'); 126.4 (CH-7); 124.7 (CH-6); 124.2 (CH-8); 124.2 (Cq-1'); 113.2 (CH-3'); 46.4 (CH-2); 26.0 (CH_2-4); 21.3 (CH_2-3). COSY: $^3J_{vec}$: H2 – H3; H3 – H4. $^4J_{meta}$: H5 – H7; H6 – H8. *J* con NH_2: H3' – H5'; H2' – H5'. HMBC (f_1= 400.16Hz, f_2=100.62Hz) (C→H): C4→H5, H3; C3→H2, H4; C2→H4, H3; C6→H8, H7; C7→H5; C8→H6; H7 C5→H7, H4; C9→H8, H6, H4, H3; C10→H7, H5, H2, H4; C1'→H3'; C2'→H3', H5'; C3'→H2', H5'; C4'→H2'. HRMS calcd mass for $C_{15}H_{16}N_2O_2S$: 311.083; found: 311.084.

Computational Data of Compounds 1-10

All the BSTHQ derivatives were first minimized with the semiempirical AM1 method. The conformational search was carried out through a systematic scan of the relevant dihedral angles (α and β angles) using the "Opt = modredundant" keyword in Gaussian 03 [32] with 36 steps of 10° degrees size. The potential energy surface was explored to find the global minima by scanning the C10-N1-S12-C1′ torsion angle (α angle). Then, for each minimum thus found the N1-S12-C1′-C2′ torsion angle (β angle) was scanned at fixed α. A full geometry optimization at the B3LYP/6-31G(d)[1] level of theory was later performed for the lowest energy conformations found. Finally, each minimum was characterized as a stationary point by vibrational frequency calculations ("freq = noraman"). For all the derivatives the number of imaginary frequencies was zero. Molecular orbital's, Mülliken charges, and the charges fitting to the electrostatic potential were calculated with B3LYP/6-31G(d) level of theory.. The NMR spectra were also calculated using a B3LYP/6-31G(d) level of theory as well as HF/6-31G(d). In both cases the "nmr = giao" method was used for the NMR calculation with no specification of the symmetry ("nosym").

Antiprotozoal Activity

The *in vitro* activities against the protozoan parasites *T.b.r.*, *T. c.*, *L. d.* and *P. f.* as well as cytotoxicity were determined as described earlier [36]. Compounds were measured in duplicate in the range of 0.2-300μM. The following substances were used as reference drugs: melarsoprol (*T.b. r.*), benznidazole (*T. c.*), miltefosine (*L. d.*), chloroquine (*P. f.*) and podophyllotoxin (cytotoxicity assay using L-6 cells).

[1]Command line for gaussian03: B3LYP/6-31G* opt(loose)nosym scf(maxcycles=500) pop=full iop(6/7=3) pop=mk gfprint

CONCLUSIONS

Ten BSTHQ derivatives were synthesized and structurally characterized. Antiparasitic activity was evaluated as well as cytotoxicity on rat skeletal myoblast (L-6) cells.

The derivatives 1-10 have demonstrated to be more active against the parasites *T. c.* and *P. f.* Even though the library presented in this report is small, some interesting inhibitors against *T. c.* and *P. f.* were discovered. Compound 3 was identified as the most interesting molecule for *T. c.* with a promising IC_{50} value of 9.76μM and low cytotoxicity. On the other hand, compounds 3, 6 and 9 presented interesting activity against *P. f.* with IC_{50} values around 10μM.

Also, a complete characterization and theoretical conformational analysis were carried out. From spectra and molecular modeling data we were able to demonstrate that the presence of the BS moiety bound to the THQ did not affect the steric properties of the heterocycle. Thus, the minimum conformation of the THQ and the heterocycle in any BSTHQ were perfectly superimposed. Moreover, the minimum-energy conformations were independent of the *para* or *meta* substituents of the BS.

Finally, the fact that hits were identified from a small library of ten compounds demonstrated the quality of the criteria used in the fragment-based drug design approach. Further investigations into these BSTHQ structures will be focused on enlarging the present library using parallel synthesis to include not only other nitrogenated-heterocycles, but also different substitution patterns in the BS. This will allow us to perform QSAR studies using multiparametric regression analysis and the application of CADD to identify the target proteins and the mode of action.

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