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Microwave-assisted synthesis of 1,2,3,4-tetrahydroisoquinoline sulfonamide derivatives and their biological evaluation

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Abstract: Herein we report an alternative eco-friendly method for the synthesis of 1,2,3,4-tetrahydroisoquinoline sulfonamide derivatives. All obtained compounds were screened for their *in vitro* inhibition of albumin denaturation, antioxidant, antitryptic and antibacterial activity, and have shown significant results. The lipophilicity was established using both reversed-phase thin layer chromatography and *in silico* calculations.

Keywords: SiO_2/PPA; microwave synthesis; inhibition of albumin denaturation; H_2O_2 scavenging activity; antitryptic activity; antibacterial activity.

INTRODUCTION

Sulfonamide drugs are the first broad-spectrum chemotherapeutic antibacterial agents to be used in practical medicine. Chemically, they are derivatives of 4-amino sulfonic acid amide. Despite the widespread use of antibiotics in medicine, sulfonamides continue to be used in the treatment of various infectious diseases caused by microorganisms sensitive to sulfonamide preparations.[1] Sulfonamides have a variety of biological activities, such as cytotoxic, anticancer, anticonvulsant, antispasmodic, carbonic anhydrase inhibitors, and others.[2]

Isoquinoline skeleton synthesis is a topic that is contained in many works, including monographs,[3,4] chapters in monographs,[5,6] and review reports.[7,8] The interest in this class of heterocyclic compounds is due to the large number of isoquinoline alkaloids contained in many different plants around the world,[3–8] as well as their diverse and significant biological activity of both the alkaloids themselves and their synthetic derivatives.

In the last decade, new techniques and methods have been used for the synthesis of organic compounds, which significantly improve organic synthesis.[9] Nowadays, the microwave-assisted organic synthesis is widely used.[10,11] The

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method is “unconventional”. The advantage of this technology includes reducing the reaction time by improving the yield and purity of the products, which makes it a “green” and environmentally friendly method. A number of authors have reported microwave-assisted preparation of 1,2,3,4-tetrahydroisoquinoline compounds.[12,13]

Herein, alternative synthesis of sulfonamides (amides and cyclic) and their inhibition of albumin denaturation, antitryptic, antibacterial, and H_2O_2 scavenging activity has been reported. Lipophilicity as R_M value as a fundamental property has also been evaluated. A green method for the synthesis of 1,2,3,4-tetrahydroisoquinoline sulfonamide derivatives was applied as an alternative, using microwave irradiation and heterogeneous catalyst PPA/SiO_2. All compounds have been characterized by physical and spectral analysis.

EXPERIMENTAL

General methods

Chromatographic grade methanol analyses was used for HPLC (VWR, Austria). Water for HPLC was prepared with a Millipore purifier (Millipore, USA). Ibuprofen, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, sodium chloride, potassium chloride, hydrogen peroxide, ascorbic acid, trypsin, egg albumin, Tris–HCl buffer, and perchloric acid were purchased from Sigma–Aldrich. Human albumin 20 % – BB, 200 g/l was purchased from BB-NCIPD Ltd., Bulgaria. Chromatographic plates Kieselgel 60 F_{254} were purchased from Merck.

All the reagents and chemicals for the synthesis were purchased from commercial sources (Sigma–Aldrich) and used as received. Melting points were determined on a Boetius hot stage apparatus and are non-corrected. The spectral data were recorded on a Bruker Avance II + 600 spectrometer (BAS-IOCCP-Sofia, Sofia, Bulgaria). The ^{1}H-NMR and ^{13}C--NMR spectra were taken in $CDCl_3$ or DMSO at 600 MHz and 150.9 MHz, respectively. Chemical shifts are given in ppm relative and were referenced to TMS (δ = 0.00 ppm) as an internal standard with the coupling constants indicated in Hz. The NMR spectra were taken at room temperature (ac. 295 K). Mass analyses were carried out on a QExactive quadrupole--orbitrap mass spectrometer (ThermoFisher Scientific). TLC was carried out on precoated 0.2 mm Fluka silica gel 60 plates.

*Synthesis of 2-methylsulfonyl-1,2,3,4-tetrahydroisoquinolines (**3**)*

The starting amides **2** (3mmol), paraformaldehyde (5 mmol), and 0.06 g PPA/SiO_2 catalyst were placed in a Teflon microwave vessel and dissolved in toluene (10 ml). The reaction mixture was irradiated in the microwave reactor at 100ºC at a set microwave power of 1200 W. Maximum conversion of the starting amides to 2-methylsulfonyl-1,2,3,4-isoquinoline compounds was achieved after 60 min. After the reaction was finished, the reaction mixture was cooled and filtered to separate the catalyst (PPA/SiO_2). The filtrate was transferred to a round bottom flask and toluene was removed using a rotary evaporator. The residue was washed with H_2O and extracted with dichloromethane (3×20 ml), dried over anhydrous Na_2SO_4 and the solvent was removed by distillation. The obtained compounds were filtered through short column chromatography (silica gel 60, 70–230 mesh, Merck; diethyl ether) and then recrystallized from the same solvent.

Biological experiments

Hydrogen peroxide scavenging activity (HPSA). The ability of sulfonamide derivatives to scavenge hydrogen peroxide was assessed according to the method reported by Ruch[14] with minor modification. The solution of hydrogen peroxide (43 mM) was prepared in potassium phosphate buffer solution (0.2 M, pH 7.4). The sample analysis was performed as follows: in test tubes were mixed 0.6 ml hydrogen peroxide (43 mM), 0.1 ml sample/standard with different concentrations (15–1000 μg/ml), and 2.4 ml potassium phosphate buffer solution. The mixture was stirred and incubated in dark for 10 min at 37 °C. Absorbance was measured at 230 nm with a spectrophotometer (Camspec M508, England) against a blank solution containing phosphate buffer and hydrogen peroxide without the sample. Ascorbic acid was used as standard. Performing the analysis should be considered if the compounds are UV active in this wavelength, as most of the organic compounds have absorbance at 230 nm. In our case, the control sample absorbance in the absence of hydrogen peroxide is measured, i.e. the absorbance of a sample/standard with phosphate buffer for each concentration. The percentage HPSA of the samples was evaluated by comparing with a blank sample and calculated using the following formula:

$$I(\text{HPSA}) = 100\frac{A_{\text{blank}} - (A_{\text{TS}} - A_{\text{CS}})}{A_{\text{blank}}} \quad (1)$$

where A_{blank} is the absorbance of the blank sample (phosphate buffer and hydrogen peroxide), A_{CS} is the absorbance of the control sample (test sample + phosphate buffer) and A_{TS} is the absorbance of the test sample (test sample + phosphate buffer + hydrogen peroxide). The mean IC_{50} value was estimated based on three replicates by means of interpolating the graphical dependence of scavenging hydrogen peroxide on concentration.

Inhibition of albumin denaturation. *In vitro* analysis of anti-inflammatory activity was assessed as the inhibition of albumin denaturation.[15] The analysis was performed according to Sakat method[15] with minor modification. The experiment was performed with egg albumin. The solution of albumin (1 %) was prepared in distilled water (pH 7.4). The tested compounds/standard were dissolved firstly in 1.2 ml DMF and PBS up to 25 ml, so the final concentration of the stock solution is 1000 μg/ml. Then a series of working solutions with different concentrations (20–500 μg/ml) in PBS were prepared. The reaction mixture was containing 2 ml test sample/standard of different concentrations and 1 ml albumin (1 %). The mixture was incubated at 37 °C for 15 min and then heated at 70 °C for 15 min in a water bath. After cooling the turbidity was measured at 660 nm with a spectrophotometer (Camspec M508, England). The experiment was performed three times. Percentage inhibition of albumin denaturation (*IAD*) was calculated against control. The control sample is albumin with the same concentration dissolved in distilled water:

$$IAD = 100\frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \quad (2)$$

Antitryptic activity. This method is known also as an anti-arthritic activity.[16] The analysis was performed according to the method of Oyedapo and Femurewas[16] with minor modification. The reaction mixture was containing 2 ml 0.06 mg/ml trypsin, 1 ml Tris–HCl buffer (20 mM, pH 7.4) and 1 ml test sample/standard (in methanol) of different concentrations (20-500 μg/ml). The mixture was incubated at 37 °C for 5 min. Then 1 ml of human albumin (4 vol. %) was added. The mixture was incubated for an additional 20 min. To the mixture, 2 ml of 70 % perchloric acid was added for termination of the reaction. The cloudy suspension was

cooled and centrifuged at 5000 rpm for 20 min. The absorbance of the supernatant was measured at 280 nm with a spectrophotometer (Camspec M508, England) against the control solution. The UV activity of the test compounds should be considered. The control solution was a test sample/standard in methanol with different concentrations. Ibuprofen was used as standard. The analysis was performed three times. The percentage of the antitryptic activity (*ATA*) of the samples was evaluated by comparing it to a blank sample. The blank sample is prepared as the test sample but with a small exception – perchloric acid is added before albumin:

$$ATA = 100\frac{A_{\text{blank}} - (A_{\text{TS}} - A_{\text{CS}})}{A_{\text{blank}}} \quad (3)$$

where A_{blank} is the absorbance of the blank sample, A_{CS} is the absorbance of the control solution (test sample in different concentrations) and A_{TS} is the absorbance of the test samples. The mean IC_{50} values were estimated by means of interpolating the graphical dependence of *ATA* on concentration.

Antibacterial activity. The synthesized sulfonamides were screened for antibacterial activity against Gram-positive strains (*Bacillus licheniformis* ATCC 14580) and Gram-negative strain (*Escherichia coli* ATCC 8739), using the hole plate method in Mueller–Hinton agar with 100 μL loading of 1 mg/mL solutions in DMSO–water (1:1 volume ratio).[17]

Physicochemical characterisation

Determination of lipophilicity as R_M *values*. Determination of lipophilicity of sulfonamides was estimated according to the method reported by Pontiki and Hadjipavlou-Litina.[18]

Prediction of anti-inflammatory and anti-arthritic activity. A computerized prediction of biological activity (anti-inflammatory and anti-arthritic) for the obtained compounds was performed using the PASS Online program.[19,20]

Statistical analysis

All the analyses were made in triplicates. Data were expressed as mean±*SD*. The level of significance was set at $p < 0.05$.

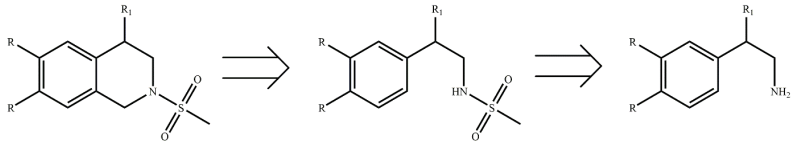
RESULTS AND DISCUSSION

Chemistry

In our previous experiments, we have reported the synthesis of 1,2,3,4-tetrahydroisoquinolines, including sulfonamide derivatives, using a conventional intramolecular *α*-amidoalkylation reaction.[21] Herein we aimed to use microwave irradiation as an environmentally friendly method for the synthesis of *N*-methylsulfonyl-1,2,3,4-tetrahydroisoquinoline compounds using SiO_2/PPA as a heterogeneous catalyst.

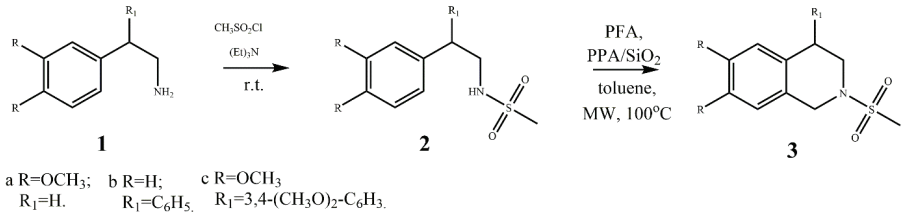
The main tasks are summarized in the given retrosynthesis Scheme 1: preparation of starting amines, transforming the amines to sulfonamides, and cyclisation of the obtained amides to 1,2,3,4-tetrahydroisoquinolines.

The starting amines **1a** and **b** are commercially available. For the obtaining of amine **1c**, a procedure[21] developed in the Department of Organic Chemistry, University of Plovdiv, was applied.



Scheme 1. Retrosynthesis scheme of 1,2,3,4-tetrahydroisoquinoline sulfonamides.

The next step, according to the retrosynthesis scheme above, is the obtaining of amides **2a**–**c** (Scheme 2). For this purpose, the Schotten–Baumann method was used.[22,23]



Scheme 2. Synthesis of sulfonamides (**2**) and 1,2,3,4-tetrahydroisoquinolines (**3**).

The possibility of applying PPA/SiO_2 as a heterogeneous acid catalyst in the intramolecular *α*-amidoalkylation reaction was studied. For this purpose, the conventional heating was replaced by the microwave radiation. The PPA/SiO_2 system was used for the cyclization step. The reaction is carried out in a Milestone Ethos One microwave reactor, which allows the control of the time, the temperature of the samples, and the power used.

A significant advantage of the use of the heterogeneous catalyst (PPA/SiO_2) in the intramolecular *α*-amidoalkylation reaction for the synthesis of *N*-sulfonyl--1,2,3,4-tetrahydroisoquinolines is the simplified procedure for the isolation of the final product. After completion of the reaction, the reaction mixture was cooled, the catalyst was removed by simple filtration, and the solvent was distilled off on a rotary evaporator. The resulting 1,2,3,4-tetrahydroisoquinolines (**3**) (Scheme 2) were filtered through short column chromatography (silica gel 60, 70–230 mesh, Merck; diethyl ether) and then recrystallized from the same solvent.

After using the PPA/SiO_2 system during the reaction, it is regenerated and prepared for its next participation. For this purpose, it is transferred to a 50 ml round-bottomed flask and dried under vacuum at 100 °C for 2 h. The solvent is distilled and there are practically no waste products. The applied method for the synthesis of *N*-sulfonyl-1,2,3,4-tetrahydroisoquinolines offers a convenient, fast, economical, and environmentally friendly synthesis.

Comparing the yields of compounds (**3**) obtained by the proposed microwave-assisted intramolecular *α*-amidoalkylation reaction with the yields of the same compounds obtained by conventional heating in a mixture of acetic:triflu-

oroacetic acid = 4:1 (volume ratio) or in a polyphosphoric acid/silica gel system (20 wt. % SiO_2),[21] we found that the yields of compounds **3b** and **c** were higher and the reaction time shorter when the microwave radiation is used instead of conventional heating in acetic:trifluoroacetic acid in a ratio of 4:1 (volume ratio) at the same temperature (100 °C, Table I). It was also found that, when compared to conventional heating and the use of the heterogeneous PPA/SiO_2 catalyst, the yields of the microwave-assisted intramolecular *α*-amidoalkylation reaction were comparable for the same reaction time.

TABLE I. Comparison of yields (%) of compounds (**3**)

Compound	Reaction conditions		
	t = 100 °C, τ = 1 h (MW, PPA/SiO_2)	Room temperature, τ = 8 h (AcOH:TFA = 4:1 volume ratio)	Reflux, τ = 1 h (PPA/SiO_2)
3a	81	–	–
3b	93	80	91
3c	95	87	97

The yields of the final *N*-sulfonyl-1,2,3,4-tetrahydroisoquinoline compounds were prepared at a ratio of 3 mmol of the starting amides to 0.06 g of PPA/SiO_2 catalyst. The obtained compounds are characterized by their melting points, ^{1}H- and ^{13}C-NMR, IR and HRMS spectra.

Biological evaluation

All synthesized sulfonamides were tested for their *in vitro* inhibition of albumin denaturation (*IAD*), antioxidant and antitryptic activity (*ATA*). The obtained *in vitro* results were compared to the predicted *in silico* ones. The results are presented in Table II.

H_2O_2 scavenging activity

It has been demonstrated that free radicals play an important role in the pathogenesis of specific diseases and aging.[24,25] The obtained synthesized sulfonamides were screened *in vitro* scavenging activity using hydrogen peroxide. The antioxidant activity values of the synthesized sulfonamides vary from 1659.86 to 3160.97 μM. Hydrogen peroxide is an oxidant and is formed continuously in living tissues as a result of a number of metabolic processes. The scavenging of hydrogen peroxide is a very important step that prevents the reaction between iron ions and H_2O_2, which generate extremely reactive oxygen species – $^{\bullet}$OH radicals. Compared to ascorbic acid (497.37 μM), the obtained sulfonamides demonstrated lower *in vitro* antioxidant activity. Compound **3c** (1659.86 μM) demonstrate higher antioxidant activity, when compared to the ibuprofen and the rest of the synthesized sulfonamides (Table II, Fig. 1).

TABLE II. *In vitro* and *in silico* biological activity results. Hydrogen peroxide scavenging activity (*HPSA*), inhibition of albumin denaturation (*IAD*), and antitryptic activity (*ATA*) were expressed as IC_{50}. Ascorbic acid (AA) and ibuprofen (Ibu) were used as standards. R_M is a non-dimensional quantity because it is a function of R_f and is determined by thin-layer chromatography. cAnti-I and cAnti-A are expressed as Pa (probability "to be active") estimates the chance that the studied compound is belonging to the sub-class of active compounds (resembles the structures of molecules, which are the most typical in a sub-set of "actives" in PASS training set). The value of the most active compound is 1; Ibu – Ibuprofen; R_M – lipophilicity; cAnti-I – calculated anti-inflammatory activity; cAnti-A – calculated anti-arthritic activity

Compd.	IC_{50}±*SD* / μM			R_M±*SD*	*Pa*	
	HPSA	*IAD*	*ATA*		cAnti-I	cAnti-A
AA	497.37±42.47	–	–	–	–	–
Ibu	1854.78±60.11	336.13±27.10	1259.49±44.31	0.99±0.032	0.903	0.573
2a	2659.52±90.50	2993.77±223.39	143.26±10.14	0.96±0.028	0.341	0.472
2b	2720.93±31.92	1679.44±63.27	506.85±40.82	1.22±0.031	0.270	0.249
2c	1902.01±62.72	840.39±4.63	98.44±9.18	1.16±0.025	0.270	0.298
3a	3160.97±47.97	1424.30±142.75	260.64±14.63	1.11±0.033	0.330	0.598
3b	2753.76±111.57	747.21±24.52	628.17±51.57	0.97±0.025	0.376[a]	0.665
3c	1659.86±25.71	108.45±1.52	75.91±7.14	0.99±0.028	0.306[a]	0.612

[a]Inflammatory Bowel disease treatment – inflammatory bowel disease (IBD) is a term for two conditions (Crohn's disease and ulcerative colitis) that are characterized by the chronic inflammation of the gastrointestinal (GI) tract. Prolonged inflammation results in damage to the GI tract. Biological therapy for inflammatory bowel disease, especially the TNF inhibitors, are used in people with more severe or resistant Crohn's disease and sometimes in ulcerative colitis. The treatment is usually started by administering drugs with high anti-inflammatory effects. The Pass program, which is also available online, was used to determine the predicted anti-inflammatory values of our synthesized compounds. For the determination of the anti-inflammatory activity in the PASS database on the basis of which the theoretical calculations are made, there are data on molecules that affect the treatment of inflammatory processes in the intestine

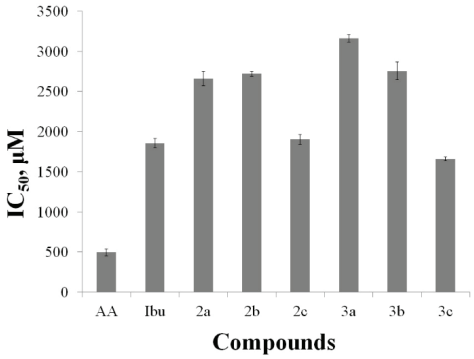


Fig. 1. HPSA of sulfonamides. Ascorbic acid (AA) used as standard. The results of antioxidant activity were expressed as IC_{50}.

Although hydrogen peroxide is not very reactive, it can cause cytotoxicity by generating hydroxyl radicals in the cell.[26] Hydroxy radicals are the most reactive and are thought to be responsible for some tissue damage caused by inflammation. In living organisms, the superoxide anion radical ($O_2^{-\bullet}$) and H_2O_2 are transformed into $^{\bullet}OH$ and $^{\bullet}O_2$, which are responsible for cell damage. The inf-

lammatory process causes the generation of a superoxide anionic radical at the inflammation site and this is associated with the formation of other oxidizing species such as $^{\bullet}OH$. Scavengers of hydroxyl radicals can increase the synthesis of prostaglandins.[18] Therefore, the removal of H_2O_2 is very important in the prevention of the generation of $^{\bullet}OH$.

Inhibition of albumin denaturation

Inflammation is the response of living tissues to injury. It involves a complex array of enzyme activation, mediator release, fluid extravasation, cell migration, tissue breakdown, and repair.[27] The denaturation of proteins is a well-documented cause of inflammation in rheumatoid arthritis. Several anti-inflammatory drugs have shown a dose-dependent ability to inhibit thermally-induced protein denaturation.[28] The obtained sulfonamides were screened for the inhibition of albumin denaturation. This method provides the extent information on to which albumin is protected from denaturation when heated. For this purpose, we have used egg albumin. The percentages of inhibition of synthesized sulfonamides are presented in Fig. 2. The results of the study are presented as IC_{50}. As ibuprofen has proven properties, we have decided to use it as a benchmark to compare the activities of newly synthesized sulfonamides. The IC_{50} values of ibuprofen, estimated as *IAD* is 336.13 μM (Table II, Fig. 2). All the obtained results show the IC_{50} values of sulfonamides are in the range from 108.45 to 2993.73 μM (Table II, Fig. 2). Comparing the compounds to the standard, compound **3c** exhibited the highest degree of albumin protection and compound **2a** is the least active.

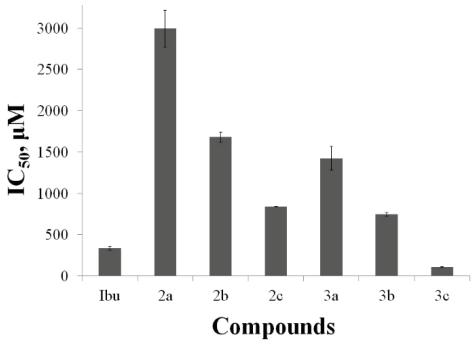


Fig. 2. The inhibition of albumin denaturation activity of synthesized sulfonamides. Ibuprofen is used as standard. The results were expressed as IC_{50}.

Analyzing the results, it can be seen that cyclic sulfonamides (**3a**–**c**) are characterized by higher albumin protection compared to non-cyclic ones (**2a**–**c**) (Fig. 2). In addition, it has been observed that the activity of sulfonamides depends on the methoxy group number. As the number of methoxy groups in the structure of sulfonamides increases, so does the stabilization of the albumin molecule. Furthermore, IAD analysis reveals that lipophilicity is a major phys-

icochemical parameter. The studied synthetic sulfonamides show average lipophilicity (R_M) around 1.11 for the non-cyclic sulfonamides and 1.02 for the cyclic sulfonamides, which to some extent affects the albumin protection. Despite their slight difference in R_M values, the cyclic sulfonamides show a greater effect on the stabilization of the albumin molecule. (Table II).

Compound **2c** of the non-cyclic sulfonamides is the most active, while of the cyclic sulfonamides it is **3c**. Although the R_M values of ibuprofen and **3c** did not differ statistically, compound **3c** showed the highest activity (Table II, Fig. 2).

In vitro analysis of sulfonamides by *IAD* is essential for the study of new potential anti-inflammatory agents.

Antitryptic activity

Proteinases have been implicated in arthritic reactions. Neutrophils are known to be a rich source of proteinase which carries many serine proteinases in their lysosomal granules. It was previously reported that leukocyte proteinase plays an important role in the development of tissue damage during inflammatory reactions and that a significant level of protection was provided by proteinase inhibitors.[16,28] *In vitro* anti-arthritic activity was assessed as antitryptic activity.[16] The results present that the sulfonamides show better antitryptic activity compared to ibuprofen (Table II, Fig. 3).

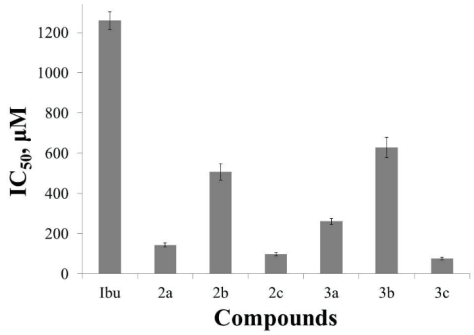


Fig. 3. The antitryptic activity of synthesized sulfonamides. Ibuprofen is used as standard. The results are expressed as IC_{50}.

The IC_{50} results for the *ATA* range from 75.91 to 628.17 μM. The highest activity was demonstrated by compounds **3c** (75.91 μM), **2c** (98.44 μM), **2a** (143.26 μM) and **3a** (260.64 μM). Hence these compounds were shown to be the most promising.

The data from the analysis show that the activity of the sulfonamides depends on the methoxy groups presence. The presence of methoxy groups in the structures of the sulfonamides leads to an increase in their activity. The low activity of **2b** (506.85 μM) and **3b** (628.17 μM) is due to a lack of methoxy groups in their structures. The decreasing order of their antitryptic activity is as follows: **3c** > **2c** > **2a** > **3a** > **2b** > **3b** (Table II, Fig. 3).

Antibacterial activity

The method Mueller–Hinton[17] is intended for testing the sensitivity of fast-growing aerobic bacteria and for demanding microorganisms for which standards have been introduced. For more accurate determination of sensitivity, a method for the determination of the minimum inhibitory concentrations (MIC) of antimicrobial agents by methods with serial dilutions of the preparation in agar is also used. The results show that compound **3c** exhibits antibacterial activity against gram-positive bacteria *Bacillus licheniformis* and gram-negative *Escherichia coli*. The data from the conducted studies are presented in Table III.

TABLE III. Antibacterial activity of the obtained sulfonamides

Compound	*Escherichia coli* ATCC 8739		*B. licheniformis* ATCC 14580	
	Inhibition zone, mm[a]	*MIC*, mg/mL[b]	Inhibition zone, mm[a]	*MIC*, mg/mL[b]
2a–**3b**	–	–	–	–
3c	23	0.06	15	0.06

[a]Assessed by the hole-plate method with 100 μL loading of 1 mg/mL solutions in 1:1 DMSO–water; [b]ampicillin was used as a positive control with *MIC* = 0.0004 mg/mL against both strains

Biological activity is an important factor for any new drug. There is a clear correlation between the *in vitro* tests performed and the antibacterial activity, which showed that compound **3c** is the most active.

Lipophilicity

Lipophilicity is the most regularly applied parameter used in structure activity relationship (SAR) drug discovery studies. It can be experimentally determined or calculated. Lipophilicity has been correlated to permeability, solubility and it increases in target potency and toxicity. We determined the lipophilicity by the reverse phase thin layer chromategraphy (RPTLC) method as R_M values. This is considered to be a reliable, fast, and convenient method for expressing lipophilicity.[29] Aside from the essential role of lipophilicity for the kinetics of biologically active compounds, the antioxidants of hydrophilic or lipophilic character are both needed to act as radical scavengers in the aqueous phase or as chain-breaking antioxidants in biological membranes.[18]

In the present work, we have investigated the antioxidant and *in vitro* biological activity of the newly synthesized sulfonamides. Lipophilicity proved to be an important factor in their activity. The results have shown that sulfonamides are lipophilic compounds with low antioxidant activity. However, it should not be taken as a criterion for whether the compounds will exhibit biological activity. However, the use of lipophilic antioxidants is necessary to neutralize harmful radicals in cell membranes.[18]

In general, the *in vitro* studies results show that the sulfonamides exhibit *IAD* and *ATA*. From both experiments, we have derived the important information

about the properties of potential new drugs, and both experiments are related to preserving the integrity of the albumin molecule. Human serum albumin (HSA) is known to have two major binding sites for drugs: Sudlow sites I and II. Sudlow site I, which is found in subdomain IIA of HSA, binds to bulky heterocyclic compounds such as coumarins, sulfonamides and salicylates. Sudlow site II, found in subdomain IIIA, binds to aromatic carboxylic acids and profens.[30] In addition, it is known that sulfonamides bind to Sudlow site I by stabilizing the structure of the albumin molecule and increasing the anti-oxidant properties of albumin.[31] From the experiment it was found out that the newly synthesized sulfonamides show better expressed ATA activity.

In addition, this result is confirmed by the experimentally performed antibacterial activity, which shows that compound **3c** is the most active. It has high antibacterial, *IAD* and *ATA*, which makes it a reliable and effective drug.

CONCLUSION

To conclude, a microwave-assisted intramolecular α-amidoalkylation reaction as an environmentally friendly method for the synthesis of 1,2,3,4-tetrahydroisoquinoline sulfonamides has been successfully applied. The use of the PPA/SiO_2 system in this reaction proceeds faster with higher yields of the target compounds compared with conventional heating in a CH_3COOH:CF_3COOH = 4:1 milieu. The compounds were biologically evaluated *in vitro* and *in silico* for their antioxidant, *ATA*, *IAD* and antibacterial activities. Lipophilicity as R_M values as a fundamental property has also been evaluated. Compound **3c** shows significant high results for all activities.

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ИЗВОД

МИКРОТАЛАСНА СИНТЕЗА ДЕРИВАТА 1,2,3,4-ТЕТРАХИДРОИЗОХИНОЛИН--СУЛФОНАМИДА И ИСПИТИВАЊЕ ЊИХОВЕ БИОЛОШКЕ АКТИВНОСТИ

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У раду је описан алтернативни, еколошки прихватљив, метод за синтезу деривата 1,2,3,4-тетрахидроизохинолин-сулфонамида. Испитана је способност ових једињења да у *in vitro* условима инхибирају денатурацију албумина, као и антиоксидативна, антитрипсинска и антибактеријска активност, које су биле значајне. Липофилност је утврђена користећи методе реверзно-фазне танкослојне хроматографије и *in silico* израчунавања.

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