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Original scientific paper

Synthesis of sulfonamides bearing 1,3,5-triarylpyrazoline and 4-thiazolidinone moieties as novel antimicrobial agents

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Abstract: Two series of sulfonamides were synthesized from 4-hydrazinylbenzenesulfonamide as the key starting material. 1,3,5-Triarylpyrazoline sulfonamides (**2a**–**i**) were obtained by cyclocondensation of various chalcones in 53––64 % yields, while 4-thiazolidinone derivatives (**4a**–**e**) were synthesized by cyclocondensation between mercaptoacetic acid and different phenylhydrazones in 43–62 % yields. The synthesized compounds were characterized based on FTIR, ^{1}H-NMR, ^{13}C-NMR and HRMS data. The sulfonamides were evaluated for their *in vitro* antimicrobial activities against four bacterial strains (*E. coli*, *P. aeruginosa*, *B. subtillis* and *S aureus*), two filamentous fungal strains (*A. niger* and *F. oxysporum*) and two yeast strains (*C. albicans* and *S. cerevisiae*). Seven pyrazolines, **2a**–**c** and **2e**–**h**, exhibited significant inhibition of different microbial strains. Among them, compound **2b** displayed good antifungal activity against *A. niger* (*MIC* value at 12.5 μg mL^{-1}) over the reference drug.

Keywords: synthesis; sulfonamide; pyrazoline; thiazolidinone; antimicrobial agents.

INTRODUCTION

Sulfonamides have been particularly considered as essential scaffolds for developing new medicines. The sulfonamides possess a wide range of biological activities such as anti-inflammatory,[1] antidepressant,[2] antimicrobial[3,4] and anticancer.[5] In bacterial cells, antibacterial sulfonamides act as competitive inhibitors of the enzyme, dihydropteroate synthase that is involved in folate synthesis.[6]

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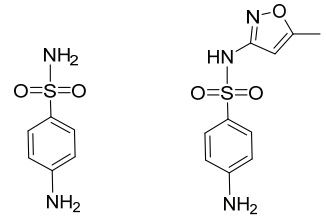
Several sulfonamide drugs developed from aromatic compounds have been used in antimicrobial therapeutic applications. For instance, sulfanilamide and sulfamethoxazole (Fig. 1) are the simplest antimicrobial therapy drugs which were commonly used in treatments against Gram-positive and Gram-negative bacteria, as well as in the treatments of fungi and protozoa infections. These sulfonamides are selectively toxic to bacteria *via* blocking of the synthesis of folic acid.[7,8] However, resistance to these sulfonamides has increased during past years because the susceptible pathogens might develop an ability to take up folic acid from their environment.[9]



Sulfanilamide Sulfamethoxazole Fig. 1. Structures of antimicrobial therapy sulfa drugs.

Pyrazolines are one of the important heterocycles containing two nitrogen atoms in the five-membered ring. These derivatives have been found to possess a broad spectrum of pharmacological actions, such as antimicrobial,[10,11] anticonvulsant,[12] anti-inflammatory[13] and antiviral.[14] Numerous studies have shown that pyrazoline derivatives possess interesting antimicrobial activity against many fungal and bacterial strains. For example, Zampieri *et al.*[15] reported synthesized pyrazoline derivatives bearing imidazole moieties with high activity against two strains, *Candida albicans* and *Mycobacterium tuberculosis* H37Rv. In particular, 1,3,5-substituted pyrazolines were documented as potential antibacterial agents.[16–18] Additionally, 4-thiazolidinones, derivatives of thiazolidine with a carbonyl group at the 4-position, are an important scaffold known to be associated with many biological applications including anticancer, antimicrobial, antiviral and anti-inflammatory.[19–22] In connection with our ongoing research program involving the synthesis and biological evaluation on heterocycles,[23–25] the biological importance of sulfonamides prompted us to synthesize derivatives bearing pyrazoline and 4-thiazolidinone moieties, as well as to evaluate their antimicrobial activity.

EXPERIMENTAL

Chemistry

All the materials were purchased from Acros (Belgium) or Aldrich. The solvents were purchased from Fluka and used without further purification. Melting points were measured with an Electrothermal Model 9200 (UK). The IR spectra were recorded on a Bruker Equinox 55 IR spectrophotometer. The ESI-MS were taken on an Aligent 1100 LC-MSD instrument

with an MS detector (mass range 100–2000 *m*/*z*, energy 3.5 kV, dried gas 8.0 L min^{-1}). ^{1}H-(500 MHz) and ^{13}C-NMR (125 MHz) spectra were recorded on a Bruker Avance 500 NMR spectrometer using acetone-d_6, $CDCl_3$ and DMSO-d_6 as solvents and tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in δ relative to TMS.

Analytical and spectral data are given in Supplementary material to this paper.

*General procedure for the synthesis of dihydro-1*H*-pyrazol-1-ylbenzenesulfonamides (**2**)*

A stirred solution of chalcones **1** (3 mmol) and 4-hydrazinylbenzenesulfonamide (699 mg; 3 mmol) in anhydrous methanol (30 mL) was refluxed for 12 h, monitoring by TLC. After completion of the reaction, the mixture was cooled overnight at 0 °C. The separated solid was filtered and washed with hexane (30 mL). The residue was purified by recrystallization from ethanol and dried under the vacuum to afford the pure compounds **2**.

*General procedure for the synthesis of 4-thiazolidinone sulfonamides (**4**)*

A stirred mixture of phenylhydrazones (1 mmol) and mercaptoacetic acid (1 mL) were refluxed for 2 h. After completion of the reaction, monitored by TLC, ethyl acetate (10 mL) was added into the mixture. The organic residue was washed with $NaHCO_3$ solution (3×20 mL), water and dried by anhydrous Na_2SO_4. Then the solvent was evaporated and the crude product purified by column chromatography on silica gel 60 (230–400 mesh, E Merck, Darmstadt, Germany) with *n*-hexane/ethyl acetate (30:70 volume ratio) as the eluent.

Antimicrobial assay

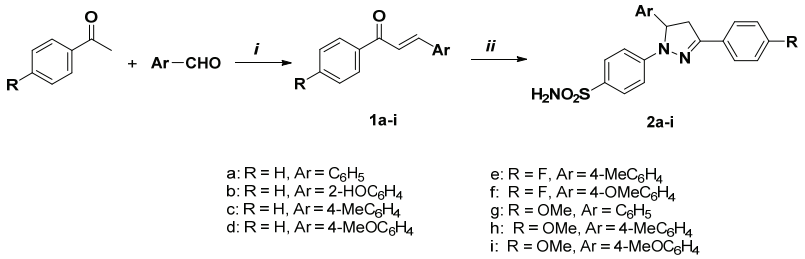
The antimicrobial activity and the minimal inhibitory concentration (*MIC*) of the synthesized compounds were determined by the broth dilution method in 96-well microtiter microplates, as reported previously.[28] Briefly, stock solutions of the synthesized compounds at concentration of 2 mg mL^{-1} were prepared by dissolving 2 mg of the test compound in 1 mL dimethyl sulfoxide (DMSO). The stock solutions were serially diluted in 1 mL of corresponding sterile media (Eugon Broth (Difco, USA) for bacteria and mycophil (Difco, USA) for yeast). to obtain concentrations of 12.5–50 μg mL^{-1} and inoculated with a suspension (100 μL) of the respective microorganism. Four bacterial strains including two Gram negative bacteria (*Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 10145) and two Gram positive bacteria (*Bacillus subtillis* ATCC 11774 and *Staphylococcus aureus* subsp. *aureus* ATCC 11632) were used for the evaluation of antibacterial activity. Two filamentous fungal strains (*Aspergillus niger* (ATCC 6275) and *Fusarium oxysporum* (ATCC 7601)) and two yeast strains (*Candida albicans* ATCC 7754 and *Saccharomyces cerevisiae* (VTCC–Y–62)) were used for evaluating the antifungal properties of the synthesized compounds. Tetracycline and streptomycin (Sigma) were used as positive controls of the tests with Gram negative and Gram positive, respectively, and nystatin (Sigma) was used as positive control for the test of filamentous fungi and yeast. Pure DMSO was used as the negative control. The *MIC* value for a sample is expressed as the lowest concentration that inhibits the tested microbial growth.

RESULTS AND DISCUSSION

Chemistry

In the present strategy, the series of triarylpyrazoline sulfonamides contains a benzensulfonamide ring attached to a five-membered pyrazoline ring at position 1 and two aryl rings bearing varied functional groups attached to the pyrazoline ring at positions 3 and 5. These derivatives (**2a**–**i**) were synthesized in meth-

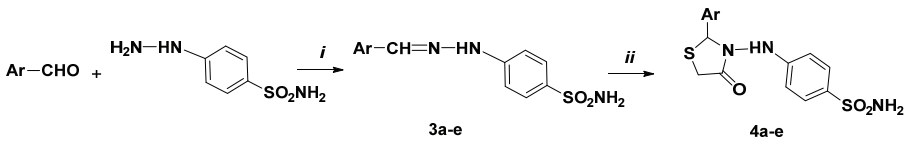
anol by cyclocondensation of 4-hydrazinylbenzenesulfonamide and the corresponding chalcones (**1a**–**i**), which were prepared from the appropriate aromatic aldehyde and the corresponding ketone in base catalyst/ethanol at room temperature for 5 h (Scheme 1). The present results showed that reaction time of the cyclocondensation (12 h) was much shorter than that of the previous report (36 h)[13] while the yields were similar (53–64 %).



Scheme 1. Synthesis of 1,3,5-triarylpyrazoline sulfonamides. Reagents: *i*) EtOH, KOH aq. (2 %), rt, 4 h; *ii*) 4-hydrazinylbenzenesulfonamide, MeOH, reflux, 12 h.

The structures of triarylpyrazolines were unambiguously characterized by IR, NMR and mass spectral data. The ^{1}H-NMR spectra showed characteristic singlet around 4.63–6.98 ppm for two protons of the $–SO_2NH_2$ moiety in the structures. In addition, signals belonging to the aliphatic protons of the pyrazoline ring, H_a, H_b and H_x appeared at around 3.15–3.27, 3.87–4.09 and 5.33–5.83 ppm, respectively. The other signals are in complete agreement with the assigned structures.

The synthetic route of 4-thiazolidinone sulfonamides is illustrated in Scheme 2. The hydrazone derivatives (**3a**–**e**) were prepared in good yields (63.0–74.0 %) *via* acid catalyzed condensation of the appropriate aromatic aldehyde and 4-hydrazinylbenzenesulfonamide in methanol for 4 h. Cyclocondensation of the appropriate phenylhydrazones (**3a**–**e**) with a large excess of mercaptoacetic acid afforded the respective 4-thiazolidinone sulfonamides (**4a**–**e**). The IR data of **4a**–**e** showed bands at around 3270 and 1700 cm^{-1} assigned to NH and CO stretching, respectively. In ^{1}H-NMR spectra, protons of amines including NH and NH_2 moieties are characterized by singlets at around 8.59–8.70 ppm and 7.04–7.06 ppm, respectively while the appearance of signals around 3.74–3.82, 3.84–3.95 and



a: Ar = C_6H_5; b: Ar = 4-MeC_6H_4; c: Ar = 4-$OMeC_6H_4$;
d: Ar = 2-OHC_6H_4, e: Ar = 4-ClC_6H_4

Scheme 2. Synthesis of 4-thiazolidinone sulfonamides. Reagents: *i*) CH_3COOH, methanol, reflux, 4 h; *ii*) $HSCH_2COOH$, reflux, 2 h.

5.83–5.90 ppm, confirmed aliphatic protons of 4-thiazolidinone ring (H_a, H_b and H_x, respectively).

Antimicrobial activity

The pyrazoline and 4-thiazolidinone derivatives were screened for their activity against four bacterial strains, including two Gram negative (*E. coli* and *P. aeruginosa*) and two Gram positive (*B. subtillis* and *S aureus*) bacteria, two filamentous fungal strains (*A. niger* and *F. oxysporum*) and two yeast strains (*C. albicans* and *S. cerevisiae*). The samples as the standard references including tetracycline and streptomycin were used for the tests of Gram negative and Gram positive bacteria, respectively while nystatin was used for test of fungi and yeast.

The data in average *MIC* values are given in Table I. It indicated that most of the pyrazoline sulfonamides exhibited high activity against three bacterial strains, *E. coli, B. subtillis* and *S. aureus*, both tested fungal strains and a yeast, *C. albicans*, whereas the 4-thiazolidinone derivatives did not show antimicrobial activity at the tested concentration (50 μg mL^{-1}).

TABLE I. Antimicrobial activity (*MIC* / μg mL^{-1}) of sulfonamide derivatives; T – tetracycline; S – streptomycin; N – nystatin

Compd.	Microorganism							
	Bacterial Gram (–)		Bacterial Gram (+)		Fungi		Yeast	
	E. coli	*P. aerugi-nosa*	*B. sub-tillis*	*S. aur-eus*	*A. niger*	*F. oxyspo-rum*	*S. cere-visiae*	*C. albi-cans*
2a	>50	>50	>50	25	25	25	>50	>50
2b	>50	>50	12.5	12.5	12.5	50	>50	>50
2c	50	>50	25	25	>50	>50	>50	25
2d	>50	>50	>50	>50	>50	>50	>50	>50
2e	25	>50	25	25	>50	>50	>50	50
2f	>50	>50	50	25	>50	>50	>50	>50
2g	>50	>50	>50	>50	25	>50	>50	>50
2h	>50	>50	>50	>50	25	>50	>50	>50
2i	>50	>50	>50	>50	>50	>50	>50	>50
4a	>50	>50	>50	>50	>50	>50	>50	>50
4b	>50	>50	>50	>50	>50	>50	>50	>50
4c	>50	>50	>50	>50	>50	>50	>50	>50
4d	>50	>50	>50	>50	>50	>50	>50	>50
4e	>50	>50	>50	>50	>50	>50	>50	>50
T	5.5	11.0	–	–	–	–	–	–
S	–	–	7.2	11.4	–	–	–	–
N	–	–	–	–	23.1	11.6	5.8	11.6

Amongst the synthesized pyrazolines, compound **2b** having 2-hydroxy substitution on benzene ring exhibited similar antibacterial activity to both Gram positive bacteria (*MIC* values at 12.5 μg mL^{-1}) in comparison with streptomycin and superior antifungal activity to *A. niger* (*MIC* value at 12.5 μg mL^{-1}) in res-

pect to nystatin (*MIC* value at 23.1 μg mL^{-1}). It is noteworthy that only derivatives **2c** and **2e** containing 4-tolyl substitut attached to the pyrazoline ring at position 5 showed activity against *E. coli* (*MIC* values at 50 and 25 μg mL^{-1}, respectively) and yeast, *C. albicans* (*MIC* values at 25 and 50 μg mL^{-1}, respectively) while three pyrazoline compounds **2g**, **2h** and **2i** bearing 4-methoxyphenyl substituent at position 3 did not show antibacterial activity at the tested concentration. The results reveal that substituents in the structure of triarylpyrazoline sulfonamides have important effects on the antimicrobial activity. In general, a 4-methylphenyl substituent attached to pyrazoline ring exhibited activity over the 4-methoxyphenyl substituent and the pyrazolines containing hydroxy group can be important antibacterial agents. It is essential for the next research to prepare new antimicrobial triarylpyrazoline sulfonamides with excellent activity.

CONCLUSIONS

In summary, 1,3,5-triarylpyrazoline and 4-thiazolidinone sulfonamides were prepared from 4-hydrazinylbenzenesulfonamide in good yields. All the synthesized sulfonamides including novel compounds **2f**, **2h**, **4c** and **4d**, were well characterized by spectral analyses and investigated for their antimicrobial activity. Seven pyrazoline sulfonamides **2a**–**c** and **2e**–**h** exhibited high activity against the different strains, whereas the 4-thiazolidinone derivatives did not display antimicrobial activity at the tested concentration. Among them, compound **2b** was found to be a potential antibacterial and antifungal agent compared with the references, streptomycin and nystatin, respectively.

SUPPLEMENTARY MATERIAL

Experimental data for synthesis of compounds **1a**–**i** and **3a**–**e**, NMR and HRMS spectra of compounds **2** and **4** are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА НОВИХ ДЕРИВАТА СУЛФОНАМИДА КОЈИ САДРЖЕ 1,3,5-ТРИАРИЛПИРАЗОЛИНСКЕ И 4-ТИАЗОЛИДИНОНСКЕ СТРУКТУРНЕ ДЕЛОВЕ, КАО АНТИМИКРОБНИХ АГЕНАСА

THI-DAN THACH[1,2], THI TUONG-VI LE[1], HUU THIEN-AN NGUYEN[2-4], CHI-HIEN DANG[2,4], VAN-SU DANG[5] и THANH-DANH NGUYEN[3,4]

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Две серије сулфонамида су синтетисане полазећи од 4-хидразинилбензенсулфонамида као полазног једињења. 1,3,5-Триарилпиразолин-сулфонамиди (**2a**–**i**) добијени су реакцијом

циклокондензације различитих халкона у приносу 53–64 %, док су 4-тиазолидинонски деривати (**4a**–**e**) добијени реакцијом циклокондензације 2-меркаптосирћетне киселине са различитим фенилхидразонима у приносу 43–62 %. Синтетисана једињења су окарактерисана FTIR, ^{1}H- и ^{13}C-NMR и масеним спектрима. Испитана је *in vitro* антимикробна активност према четири бактерије (*E. coli*, *P. aeruginosa, B. subtillis* и *S. aureus*), два филаментна соја гљивица (*A. niger* и *F. oxysporum*) и два соја квасца (*C. albicans* и *S. cerevisiae*). Седам пиразолина **2a**–**c** и **2e**–**h** показују значајну инхибицију различитих микробних сојева. Од њих, једињење **2b** показује добру антифунгалну активност према гљивици *A. niger* (*MIC* 12,5 μg mL^{-1}), у поређењу са референтним леком.

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