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Synthesis, characterization and anthelmintic activity evaluation of pyrimidine derivatives bearing carboxamide and sulphonamide moieties

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Abstract: Pyrimidines, sulphonamides and carboxamides have shown a large number of pharmacological properties against different types of diseases including helminthiasis. Seventeen new pyrimidine derivatives bearing sulphonamide and carboxamide were synthesized and investigated for their *in vitro* anthelmintic properties. Substituted benzenesulphonyl chlorides **15a**–**c** were treated with various amino acids (**16a**–**h**) to obtain benzenesulphonamide derivatives **17a**–**l**. Compounds **17a**–**f** were subsequently treated with benzoyl chloride to obtain the *N*-benzoylated derivatives **19a**–**f**. Further reactions of compounds **19a**–**f** and **17g**–**l** with 4- or 2-aminopyrimidine (**20**) using boric acid as a catalyst gave the required sulphonamide carboxamide derivatives **21a**–**q** in excellent yields. The compounds were isolated in their analytical grade and characterized using FTIR, ^{1}H-NMR, ^{13}C-NMR and HRMS. The *in vitro* anthelmintic studies showed that all the synthesized compounds possessed anthelmintic property. Compounds **21a**–**c**, **e**, **g**, **m** and **p** showed mean paralyzing times of 15, 19, 14, 18, 19, 19 and 18 min, respectively, at 100 mg mL^{-1} compared to 10 min for albendazole. Compounds **21a–c**, **g** and **m** had mean death times of 18, 24, 16, 20 and 25 min, respectively, at 100 mg mL^{-1} compared to 13 min for albendazole.

Keywords: catalysis; anthelmintics; synthesis; carboxamides; sulphonamides.

INTRODUCTION

Helminthiasis is causing untold misery to infected individuals. Anthelmintics are a group of anti-parasitic drugs that expel parasitic worms and other internal parasite from the body by either stunning or killing them without causing significant damage to the host.[1] Resistance to benzimidazoles (**1**) and closantel (**2**), Scheme 1, used to treat helminthiasis have been reported. There are genetic features in parasitic helminthes that favour the development of anthelmintic resis-

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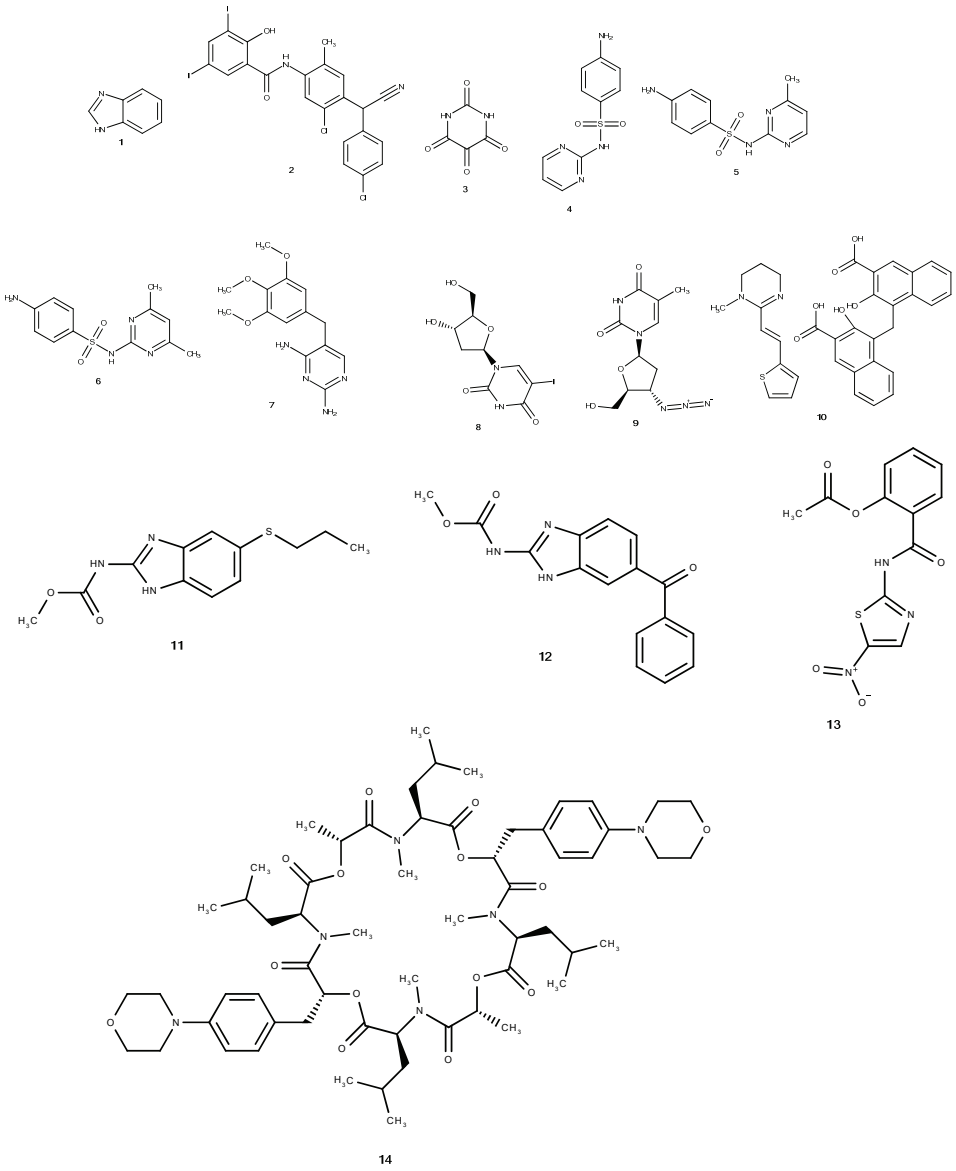


Scheme 1. The structures of some anthelmintics.

tance.[2] Frequent usage of the same group of anthelmintic drugs, use of anthelmintics in sub-optimal doses, prophylactic mass treatment of domestic animals and continuous use of a single drug have contributed to the widespread development of anthelmintic resistance.[3] The spread of resistance to triclabendazole, the main drug used in the treatment of fluke infections, is of global concern.[4]

Pyrimidines have attracted attention as an important class of heterocyclic compound in chemotherapy. Alloxan (**3**), a diabetogenic agent,[5] sulfadiazine (**4**), sulfamerazine (**5**) and sulfadimidine (**6**), a potent agent against urinary tract infections and cerebrospinal meningitis[6] all contain the pyrimidine moiety. The biological importance of the pyrimidine ring was further highlighted by the reported use of sulphonamide–trimethoprim (**7**) combinations for the treatment of opportunistic infections in patients with AIDS,[7] 5-iododeoxyuridine (**8**), for the treatment of viral infections,[8] and zidovudine (**9**) as a potent inhibitor of *in vivo* replication and cytopathic effects of HIV.[9] The wide range of biological activities of pyrimidines are well reported in the literature.[10–19]

Hunziker[20] in 1967 reported pyrantel pamoate (**10**) as a depolarizing neuromuscular blocking agent that causes spastic paralysis in helminthes when employed in the treatment of infestations with pinworms and roundworms. This report suggests the possible use of pyrimidine derivatives as anthelmintic agents.

In addition to their traditional uses as antibacterial agents,[21] sulphonamides have also being widely used as diuretics,[22] anticonvulsant,[23] anticancer,[24] antiretroviral,[25] antihypertensive,[26] and antimalarial[27] agents amongst others. Mrozik and Matawan as early as 1976 patented the synthesis of substituted benzenesulphonamides that possessed anthelmintic properties.[28] Mohan *et al*.[29] reported the synthesis of some new methylpyrimidine sulphonamides that possessed anthelmintic activity comparable to that of piperazine citrate. Vijaya *et al*.[30] reported the synthesis of benzothiazole derived benzenesulphonamides that possessed anthelmintic activity comparable to that of albendazole. Kumar *et al*. reported some benzenesulphonamide derivatives that possessed mean paralyzing times comparable to that of mebendazole.[31] Babu and Selvakumar also reported some isoindole derivatives of benzenesulphonamide that could cause paralysis in 42 min at 10 mg per group.[32] These findings point to the fact that sulphonamide derivatives could play a leading role in the fight against helminthiasis.

Carboxamides are ubiquitous functional groups in most drug molecules. Albendazole (**11**), mebendazole (**12**), nitazoxanide (**13**) and emodepside (14) are all carboxamide-containing molecules used as anthelmintic (Scheme 1). Kumar and Joshi[33] also reported carboxamide derivatives of 3*H*-1,5-benzodiazepine as promising anthelmintic with some derivatives possessing an activity better than that of piperazine citrate.

In view of the need for new anthelmintic agents,[2,4] in this work, the boric acid-catalysed syntheses of pyrimidine-derived carboxamides bearing a sulphonamide functionality are reported. The synergy arising from the successful incorporation of pyrimidine ring, carboxamide and sulphonamide pharmacophore was exploited in this research. It was expected that since the pharmacophores have individual anthelmintic activity, their successful incorporation in one molecule would improve the anthelmintic activity of the compound.

EXPERIMENTAL

All reactions requiring inert atmosphere were performed under a nitrogen atmosphere. Drying of solvents was achieved using molecular sieves for 48 h. All reagents were purchased from commercial suppliers, Aldrich, Merck, Fluka, Avra, SD fine and Alfa Aesar. Thin layer chromatography was performed using silica plates purchased from Avra. The plates were visualized under UV light (Popular India, India). The FT-IR spectra of the compounds were run in a Perkin–Elmer Spectrum version 10.03.06 and the bands are presented in wavenumbers. Proton and carbon-13 NMR spectroscopy were run in DMSO-d_6 and CD_3OD, unless otherwise stated on either Jeol 500 or 400 MHz instruments. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded at a frequency of 400 and 100 MHz, respectively, using the 400 MHz instrument and at 500 and 126 MHz, respectively, using the 500 MHz instrument. The chemical shifts are reported in ppm with reference to tetramethylsilane. Mass spectrometry was performed using micro-TOF electrospray time of flight (ESI-TOF) mass spectrometer, sodium formate was used as the calibrant. Some of the mass spectra were recorded in the negative mode and others in the positive mode. All experiments were realised at Prof. Sandeep Verma's Laboratory, Department of Chemistry, Indian Institute of Technology, Kanpur, India. Melting points were determined using a digital melting point apparatus and are uncorrected.

*General procedure for the synthesis of substituted benzenesulphonamides **17a–l***

Sodium carbonate (Na_2CO_3, 1.590 g, 15 mmol) was added to a solution of an amino acid (**16a**–**h**, 12.5 mmol) in water (15 mL) with continuous stirring until all the solutes had dissolved. The solution was cooled to –5 °C and the appropriate benzenesulphonyl chloride (**15a**–**c**, 15 mmol) was added in four portions over a period of 1 h. The slurry was further stirred at room temperature for about 4 h. The progress of the reaction was monitored using TLC (MeOH/DCM, 1:9). Upon completion of the reaction, the mixture was acidified using 20 % aqueous hydrochloric acid to pH 2. The crystals were filtered *via* suction and washed with pH 2.2 buffer. The pure products **17a**–**l** were dried over self-indicating fused silica gel in a desiccator.

General procedure for the synthesis of N*-benzoyl derivatives of benzenesulphonamides **19a–f***

The appropriate benzenesulphonamide (**17a**–**f**, 1.0 mmol) was dissolved in NaOH (10 %, 10 mL) in a 50 mL round bottom flask. Benzoyl chloride (**18**, 1.1 mmol, 0.2 mL) was transferred into the solution of the appropriate benzenesulphonamide and stirred at room temperature. The reaction progress was monitored by TLC (3 % MeOH in DCM) to the disappearance of the benzenesulphonamide spot. Upon completion of the reaction, the solution was transferred into a beaker containing crushed ice and then acidified to a pH of 3 with concentrated hydrochloric acid. The solid was collected *via* suction filtration and transferred into a beaker containing CCl_4 (10 mL), covered with a watch glass and boiled for 10 min. The mixture was allowed to cool slightly and then filtered. The obtained product **19a**–**f** was washed with 10––20 mL of CCl_4 and dried over fused self-indicating silica gel in a desiccator.

*General procedure for the synthesis of the novel pyrimidine derivatives **21a–q***

To a suspension of *N*-benzoyl substituted benzenesulphonamide (**19a**–**f**) or substituted benzenesulphonamide (**17g**–**l**, 1.0 mmol) in dry toluene (40 mL), in a flask equipped with a Dean–Stark apparatus for azeotropic removal of water, was added 4- or 2-aminopyrimidine (**20**, 1.0 mmol) and boric acid (0.1 mmol) at room temperature and then refluxed for 8 h. On completion of the reaction, as monitored by TLC, the reaction mixture was precipitated to amides by the addition of about 40 mL *n*-hexane.[34] The pyrimidine derivative was obtained

via suction filtration, washed with *n*-hexane and dried over fused silica gel or concentrated using a rotary evaporator and dried over vacuum in the case of the oily products. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded at a frequency of 400 and 100 MHz, respectively, using the 400 MHz instrument and at 500 and 126 MHz, respectively, using the 500 MHz instrument.

Anthelmintics studies

The anthelmintic activity studies were performed against *Giardia duodenalis* at 2 mg mL^{-1} concentration using the Garg and Atal method.[35] Suspensions of the samples were prepared by triturating the synthesized compounds (100 mg) with Tween 80 (0.5 %) and distilled water and the resulting mixtures were stirred using a mechanical stirrer for 30 min. The suspensions were diluted to contain 0.2 % of the test samples. A suspension of the reference drug, albendazole, was prepared at the same concentration in a similar way. Three sets of *G. duodenalis* of almost similar sizes (2 inch in length) were placed in Petri plates of 4″ diameter containing 50 mL of a suspension of a test sample or the reference drug at room temperature. Another set of *G. duodenalis* was kept as control in 50 mL suspension of distilled water and Tween 80 (0.5 %). The paralyzing and death times were noted and their mean was calculated for triplicate sets. The death time was ascertained by placing the earthworms in warm water (50 °C), which stimulated the movement if the worm was alive.

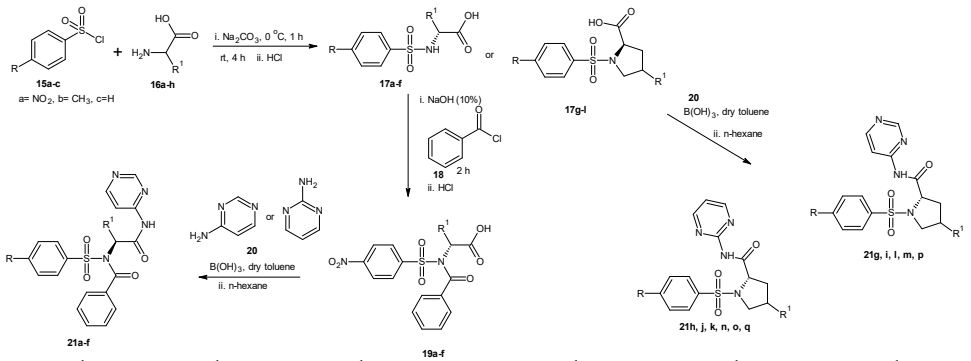
RESULTS AND DISCUSSION

The reaction of substituted benzenesulphonyl chloride (**15a**–**c**) with various amino acids (**16a**–**h**) in the presence of sodium carbonate gave various benzenesulphonamides (**17a**–**k**). Further reactions of compounds **17a**–**f** with benzoyl chloride (**18**) in the presence of sodium hydroxide gave *N*-benzoyl derivatives (**19a**–**f**). The boric acid catalysed reaction of compounds **19a**–**f** and **17g**–**l** with 4- and 2-aminopyrimidine (**20**) gave new pyrimidine derivatives (**21a**–**q**), as shown in Scheme 2.

The analytical and spectral data of the synthesized compounds are given in the Supplementary material to this paper. The spectral characterizations are in agreement with the structures.

In the FTIR spectra, the diagnostic bands at 3412–3217 cm^{-1} were assigned to NH stretching vibrations. The bands between 1700–1661 cm^{-1} (two bands per molecule), 1623–1601 cm^{-1} (two bands per molecule) and 1586–1456 cm^{-1} (two bands per molecule) were assigned to C=O, C=N and NO_2 stretching, respectively. Compound **21c** showed two bands at the NH region which were assigned to the NH of pyrimidine and of the indole ring. Among the hydroxyl derivatives, the bands between 3312–3203 cm^{-1} were assigned to the OH group. In the proline derivatives **21j**–**q**, the OH band disappeared. In both the 4-hydroxyproline and proline derivatives **21g**–**q**, there was only one C=O band between 1749–1659 cm^{-1}.

In the ^{1}H-NMR spectra, the peaks at 8.71–8.55 ppm appearing as a doublet were assigned to the 2H of the pyrimidine ring. The lone hydrogen of the pyrimidine appeared at 8.45–8.30 ppm as a singlet. In compound **21c,** the NH proton of indole appeared at 10.66 ppm. In the 4-hydroxyproline derivatives, the singlet at 8.35–8.28 ppm was assigned to the 1H of the pyrimidine ring; while the doublet at



16a: R^1=H; **16b**: R^1=Bn; **16c**: R^1=2-indolyl; **16d**: R^1=*i*-Bu; **16e**: R^1=*s*-Bu; **16f**: R^1=*i*-Pr; **16g**=L-4-hydroxyproline and **16h**= L-proline; **17a–f**: R=NO_2; **17a**: R^1=H; **17b**: R^1=C_8H_9; **17c**: R^1=2-indolyl; **17d**: R^1=*i*-Bu; **17e**: R^1=*s*-Bu; **17f**: R^1=*i*-Pr; **17g**: R=NO_2, R^1=OH; **17h**: R= NO_2, R^1=H; **17i**: R=CH_3, R^1=OH; **17j**: R=CH_3, R^1=H; **17k**: R=H, R^1=OH; **17l**: R=H, R^1=H; **19a–f**: R=NO_2; **19a**: R^1=H; **19b**: R^1=Bn; **19c**: R^1=2-indolyl; **19d**: R^1=*i*-Bu; **19e**: R^1=*s*-Bu; **19f**: R^1=*i*-Pr; **21a–f**: R=NO_2; **21a**: R^1=H; **21b**: R^1=Bn; **21c**: R^1=2-indolyl; **21d**: R^1=*i*-Bu; **21e**: R^1=*s*-Bu; **21f**: R^1=*i*-Pr; **21g**: R=NO_2, R^1=OH; **21i**: R=CH_3, R^1=OH; **21l**: R=H, R^1=OH; **21m**: R=NO_2, R^1=H; **21p**: R=H, R^1=H; **21h**: R=NO_2, R^1=OH; **21j**: R=CH_3, R^1=OH; **21k**: R=H, R^1=OH; **21n**: R=NO_2, R^1=H; **21o**: R=CH_3, R^1=H; **21q**: R=H, R^1=H

Scheme 2. Synthetic route to the pyrimidine derivatives.

8.25–8.08 ppm were assigned to the 2H of the pyrimidine. In the 2-aminopyrimidine derivatives, the pyrimidine rings appeared as a triplet and two doublets between 8.76–8.08 ppm. The OH peak appeared as a singlet at 4.31–4.17 ppm. ^{13}C-NMR spectra of the derivatives, excepting the proline and 4-hydroxyproline derivatives **21g–q**, showed two peaks between 174.99–163.88 ppm assigned to the C=O carbons. The peaks at 158.24–152.02 ppm were assigned to C=N carbons. The C–OH peak of the 4-hydroxypyrimidine derivatives appeared at 69.31–68.91 ppm.

The results of the anthelmintic activity are presented in Table I. The anthelmintic activities increased as the concentration increased. All the synthesized compounds possessed anthelmintic activity with a mean paralyzing time ranging from 25–75, 18–60 and 14–41 min at 25, 50 and 100 mg mL^{-1}, respectively, compared to 28, 20 and 10 min for albendazole. The mean death time ranged from 30–109, 20–97 and 16–63 min, compared to 35, 25 and 13 min for albendazole at 25, 50 and 100 mg mL^{-1}, respectively. Compounds **21a** and **c** had comparable anthelmintic activity to that of albendazole. Among the 4-hydroxyproline derivatives **21g–l**, the trend of activities showed that 4-hydroxy-1-[(4--nitrophenyl)sulfonyl]-*N*-(pyrimidin-4-yl)pyrrolidine-2-carboxamide (**21g**) was the most active. The results showed that with the exception of the 4-aminopyrimidine derivative **21g**, which was more active than the 2-aminopyrimidine

derivative **21h**, the 2-aminopyrimidines were more active than the 4-aminopyrimidine derivatives in the 4-hydroxyproline series. Among the proline derivatives, the 4-aminopyrimidines were more active than the 2-aminopyrimidines. Considering the substitution in the benzene ring, the *p*-nitro derivatives were the most active. The trend among the 4-aminopyrimidines was NO_2>CH_3>H, while that of the 2-aminopyrimidines was H>NO_2>CH_3. The trend of the activities imply that substitution at the *para* position of the benzene ring improved activity among the 4-aminopyrimidine derivatives, whereas the unsubstituted derivatives had better activity among the 2-aminopyrimidine derivatives. Compounds **21a, 21c, 21g** and **21m** are worthy of further development as anthelmintic agents given their similar anthelmintic activities to that of albendazole.

TABLE I. *In vitro* anthelmintic activities of the new derivatives

Sample	Mean paralyzing time, min			Mean death time, min		
	c / mg mL^{-1}					
	25	50	100	25	50	100
21a	25	22	15	36	25	18
21b	39	29	19	64	44	24
21c	22	18	14	30	20	16
21d	47	41	28	79	67	42
21e	47	34	18	79	68	42
21f	46	38	20	73	49	27
21g	37	26	19	59	34	20
21h	48	38	21	83	65	30
21i	55	40	23	89	77	45
21j	49	44	22	74	56	29
21k	48	36	20	76	61	28
21l	56	42	24	92	75	49
21m	39	31	19	63	39	25
21n	48	40	26	90	78	42
21o	75	62	41	109	95	59
21p	39	31	18	63	52	29
21q	75	60	41	103	97	63
Albendazole	28	20	10	35	25	13

CONCLUSIONS

In conclusion, novel pyrimidine derivatives bearing sulphonamide and carboxamide moieties were successfully synthesized through boric acid catalysed direct amidation of various benzenesulphonamides and 4- and 2-aminopyrimidine in good to excellent yield. This synthetic approach provided further highlights into the utility of boric acid in direct amidation reactions of unactivated carboxylic acids. The procedure reported herein is simple, economical, efficient and environmentally friendly. Additionally, the derivatives were precipitated in their analytical grade without the necessity for chromatographic purification. Four of

the seventeen new derivatives had comparable anthelmintic activity to that of albendazole and as such could be further developed as alternative anthelmintic agents to combat the resistance that will certainly follow the use of monotherapy in helminthiasis.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of the synthesized compounds are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

ИЗВОД

СИНТЕЗА, КАРАКТЕРИЗАЦИЈА И ИСПИТИВАЊЕ АНТИХЕЛМИНТИЧКЕ АКТИВНОСТИ ДЕРИВАТА ПИРИМИДИНА КОЈИ САДРЖЕ КАРБОКСАМИДНЕ И СУЛФОНАМИДНЕ ФУНКЦИОНАЛНЕ ГРУПЕ

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Пиримидини, сулфонамиди и карбоксамиди показују велики број фармаколошких особина према различитим узрочницима болести, међу којима су и глисте. Синтетисано је седамнаест нових деривата пиримидина, који садрже сулфонамидне и карбоксамидне функционалне групе, и испитана је њихова *in vitro* активност према црвима. Супституисани бензенсулфонил хлориди **15a**–**c** у реакцији са различитим амино-киселинама (**16a**–**h**) дају бензенсулфонамидне деривате **17a**–**l**. Једињења **17a**–**f** су у реакцији са бензоил-хлоридом дали *N*-бензоиловане деривате **19a**–**f**. У наставку, добијени деривати **19a**–**f** и **17g**–**l** са 4- или 2-аминопиримидином (**20**), у присуству борне киселине као катализатора, као производе дају сулфонамидне и карбоксамидне деривате **21a**–**q**, у одличном приносу. Једињења су изолована и окарактерисана помоћу FTIR, ^{1}H-NMR, ^{13}C-NMR и HRMS. Испитивањем *in vitro* активности према црвима показано је да су сва једињења активна. Једињења **21a**–**c**, **e**, **g**, **m** и **p** показују средње време изазивања парализе 15, 19, 14, 18, 19, 19 и 18 min при 100 mg mL^{-1} редом, што је блиско активности коју показује албендазол (10 min). Једињења **21a**–**c**, **g** и **m** показују средње време парализе 18, 24, 16, 20, односно 25 min при 100 mg mL^{-1}.

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