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Syntheses and antimicrobial activities of 1-(3-benzyl-4-oxo-3,4--dihydroquinazolin-2-yl)-4-(substituted) thiosemicarbazide derivatives

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Abstract: A series of 1-(3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)-4-(substituted) thiosemicarbazides (**AS1**–**AS10**) were obtained by the reaction of 3-benzyl-2-hydrazino-3*H*-quinazolin-4-one (**6**) with different dithiocarbamic acid methyl ester derivatives. The key intermediate, 3-benzyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**4**), was obtained by the reaction of benzyl amine (**1**) with carbon disulphide and sodium hydroxide in dimethyl sulphoxide to give sodium dithiocarbamate, which was methylated with dimethyl sulphate to yield the dithiocarbamic acid methyl ester **2** and condensation with methyl anthranilate (**3**) in ethanol yielded the desired compound (**4**) *via* the thiourea intermediate. The SH group of compound (**4**) was methylated in the favourable nucleophilic displacement reaction with hydrazine hydrate, which afforded 3-benzyl-2-hydrazino-3*H*-quinazolin-4-one (**6**). The IR, and ^{1}H- and ^{13}C-NMR spectra of these compounds showed the presence of peaks due to thiosemicarbazides, carbonyl (C=O), NH and aryl groups. The molecular ion peaks of the quinazolin-4-one moiety (*m*/*z* 144) were observed in all the mass spectra of the compounds **AS1**–**AS10**. Elemental (C, H, N) analysis satisfactorily confirmed purity and elemental composition of the synthesized compounds. All the synthesized compounds were screened for their antimicrobial activity against selective gram positive and gram negative bacteria by agar dilution method. In the present study, compounds **AS8** and **AS9** emerged as the most active compounds of the series.

Keywords: quinazolinone; substituted thiosemicarbazide; anti-bacterial; anti-tubercular activity.

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INTRODUCTION

Worldwide, tuberculosis (TB) is one of the leading causes of death. TB is an infection, primarily in the lungs (a pneumonia), caused by the bacteria *Mycobacterium tuberculosis*. Emergence of multi drug resistant tuberculosis (MDR-TB) makes the conditions most alarming.[1,2] Some of the MDR isolates are resistant to as many as seven of the commonly employed antimycobacterial drugs.[3] Quinazolines and condensed quinazolines have received the attention of medicinal chemists due to their potential biological activities. Among the biological activities exhibited by quinazolines, the antimicrobial activities of 2,3-disubstituted quinazolines are promising.[4] A literature survey indicated that the quinazolines nucleus substituted at the 2,3-positions (Fig. 1, **I** and **II**) showed significant antitubercular activity.[5,6] Pharmacophore such as thiosemicarbazides and thiosemicarbazones groups (Fig 1, **III** and **IV**) in different heterocyclic moieties were also found to exhibit antitubercular activity.[7–15] The present work is an extension of ongoing efforts towards developing effective antitubercular and antimicrobial agents by a hybrid approach using the quinazoline scaffold (Fig. 1). In this approach, two or more pharmacophores are merged into a single molecule. Therefore, with a single molecule containing more than one pharmacophore, each pharmacophore may address the active site of targets and offer the possibility of selectivity; further it can also reduce unwanted side effects.[16] In the present study, a substituted thiosemicarbazide moiety was placed at the C-2 position and a benzyl ring at the N-3 position of the quinazoline ring[17,18] and the antitubercular and antibacterial activities of the resulting compounds were studied against selected gram positive and negative bacteria.

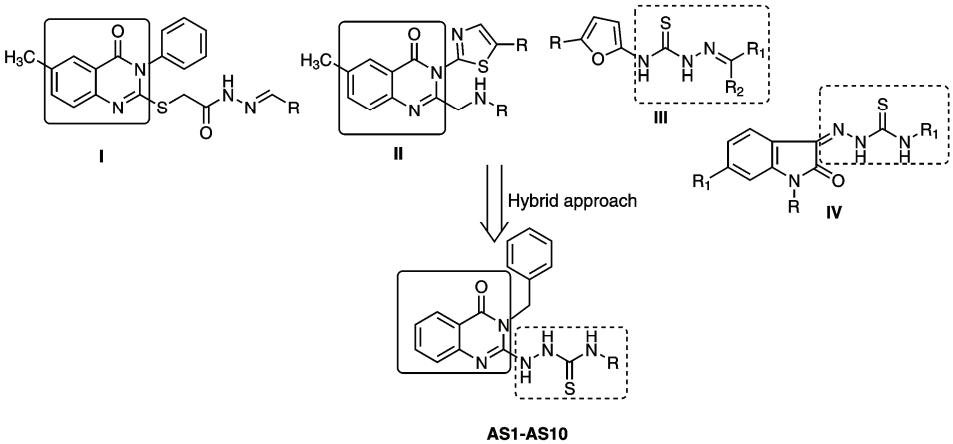


Fig. 1. Hybrid approach design of 1-[3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl]-4--[substituted] thiosemicarbazide analogues.

EXPERIMENTAL

Chemistry

Melting points (m.p.) were taken in open capillaries on a Thomas Hoover melting point apparatus (Thomas Hoover, USA) and are uncorrected. The IR spectra were recorded as films or in potassium bromide disks on a Perkin–Elmer 398 spectrometer (Perkin–Elmer). The ^{1}H-spectra were recorded on a DPX-300 MHz Bruker FT-NMR spectrometer (Bruker, USA). The chemical shifts are reported as parts per million (δ / ppm) with tetramethylsilane (TMS) as an internal standard. The mass spectra were obtained on a JEOL-SX-102 instrument (JEOL, Japan) using fast atom bombardment (FAB positive). The elemental analyses were realised on a Perkin–Elmer 2400 CHN analyzer (Perkin–Elmer) and the values were within acceptable limits of the calculated values (±0.4 %). The progress of the reactions were monitored on ready-made silica gel plates (Merck, Norway) using chloroform–methanol (9:1) as the solvent system. Iodine was used as the developing agent. All chemicals and reagents used in the synthesis were obtained from Aldrich (USA), Lancaster (USA) or Spectrochem (India) and were used without further purification.

The physical, analytical and spectral data for the compounds are given in the Supplementary material to this paper.

*3-Benzyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**4**)*

A solution of benzylamine **1** (0.02 mol) in dimethyl sulphoxide (10 ml) was stirred vigorously. To this mixture was added carbon disulphide (1.6 mL) and aqueous sodium hydroxide (1.2 mL, 20 M) dropwise during 30 min under stirring. Dimethyl sulphate (0.02 mol) was added gradually keeping the reaction mixture stirring in a freezing mixture for 2 h. The reaction mixture was then poured into ice water. The obtained solid **2** was filtered, washed with water, dried and recrystallised from ethanol. Methyl anthranilate (**3**, 0.01 mol) and the above prepared methyl *N*-(benzyl)carbamodithioate (**2**, 0.01 mol), were dissolved in ethanol (20 mL). To this, anhydrous potassium carbonate (100 mg) was added and the mixture refluxed for 22 h. The reaction mixture was cooled in ice and the solid that separated was filtered and purified by dissolving in 10 % alcoholic sodium hydroxide solution and re-precipitated by treating with dilute hydrochloric acid. The thus obtained solid was filtered, washed with water, dried and recrystallised from ethanol.

*3-Benzyl-2-(methylsulphanyl)-3*H*-quinazolin-4-one (**5**)*

3-Benzyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**4**, 0.01 mol) was dissolved in 40 mL of 2 % alcoholic sodium hydroxide solution. To this, dimethyl sulphate (0.01 mol) was added dropwise with stirring. After further stirring for 1 h, the reaction mixture was poured into ice water. The obtained solid was filtered, washed with water, dried and recrystallised from ethanol–chloroform (75:25) mixture.

*3-Benzyl-2-hydrazino-3*H*-quinazolin-4-one (**6**)*

3-Benzyl-2-(methylsulphanyl)-3*H*-quinazolin-4-one (**5**, 0.01 mol) was dissolved in ethanol (25 mL). To this, hydrazine hydrate (99 %, 0.1 mol) and anhydrous potassium carbonate (100 mg) were added and refluxed for 33 h. The reaction mixture was cooled and poured into ice–water. The so obtained solid was filtered, washed with water, dried and recrystallised from chloroform–benzene (25:75) mixture.

*General procedure for synthesis of 1-(3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)-4--(substituted) thiosemicarbazides (**AS1**–**AS10**)*

A solution of primary alkyl/aryl amine (0.02 mol) in dimethyl sulphoxide (10 mL) was stirred vigorously. To this, simultaneously, carbon disulphide (1.6 mL) and aqueous sodium hydroxide 1.2 mL (20 M) were added dropwise during 30 min with stirring. Dimethyl sulphate (0.02 mol) was added gradually to the stirred reaction mixture in a freezing mixture and the stirring was continued for further 2 h. The reaction mixture was then poured into ice water and the obtained solid was filtered, washed with water, dried and recrystallised from ethanol to afford methyl *N*-(substituted) dithiocarbamates (**7**).

3-Benzyl-2-hydrazino-3*H*-quinazolin-4-one (**6**, 2.32 g, 0.01 mol) and methyl *N*-(substituted) dithiocarbamate (**7**, 0.01 mol) were dissolved in ethanol and refluxed for 22–30 h (until the evolution of methanethiol ceased). After completion of the reaction, the reaction mixture was cooled to room temperature. The obtained solid was filtered, dried and recrystallised from ethanol. By adapting the above procedure, the compounds **AS1–AS10** were prepared. It should be noted that the synthesis of compounds **AS1**–**AS3**, **AS5** and **AS6** were previously reported.[19-21] However, none of these compounds has been examined for their antitubercular activities.

Pharmacology

Antibacterial activity. Evaluation of antibacterial activity was realized using the agar dilution method.[10,11] The standard strains were procured from the American Type Culture Collection (ATCC), Rockville, MD, USA, and the pathological strains were procured from the Department of Microbiology, MNR Medical College, Sangareddy, India. The antibacterial activity of the synthesized compounds was screened against the following bacterial strains: *Proteus vulgaris* ATCC 9484, *Salmonella enterica* subsp. *enterica* sarovar Typhimurium ATCC 33068, *Klebsiella pneumoniae* ATCC 13883, *Edwardsiella tarda*, *Pseudomonas aeruginosa* ATCC 27853, *Bacillus subtilis* ATCC 6051 and *Salmonella enterica* subsp. *enterica* sarovar Paratyphi. All bacteria were grown on Muller–Hinton Agar (Hi-media) plates (37 °C, 24 h) and the minimum inhibitory concentration (*MIC*) was considered to be the lowest concentration that completely inhibited the growth on agar plates, disregarding a single colony or faint haze caused by the inoculums.[22,23] The *MIC* values of the test compounds were compared with those the reference drug ciprofloxacin. The data given in Table I were calculated from at least three different experiments in duplicate.

Antitubercular activity. Ten-fold serial dilutions of each test compound/drug were incurporated into Middlebrook 7H11 agar slants with OADC growth supplement. Inoculums of *Mycobacterium tuberculosis* $H37R_V$ were prepared from fresh Middlebrook 7H11 agar slants with OADC Growth Supplement adjusted to 1 mg mL^{-1} in Tween 80 (0.05 %, *w*/*V*) saline diluted to 10^{-2} to give a concentrate of approximately 107 CFU mL^{-1}. A 5 μL amount of bacterial suspension was spotted into 7H11 agar tubes containing 10-fold serial dilutions of the drugs per mL. The tubes were incubated at 37 °C, and final readings were recorded after 28 days. Tubes having the compounds were compared with control tubes in which medium alone were incubated with $H37R_V$. The concentration at which complete inhibition of colonies occurred was taken as the active concentration of test compound. The *MIC* is defined as the minimum concentration of compound required to give complete inhibition of bacterial growth.[24-26] The *MIC* values of the test compounds were compared with that of the reference drug gatifloxacin.

Cytotoxicity profile of the tested compounds. For cytotoxic assay with HeLa, approximately 10,000 cells were seeded with 0.1 mL RPMI 1640 culture medium per well of 96-well

micro-plates. HeLa cells were pre-incubated for 48 h without the test substances. The solutions of the compounds of the corresponding concentrations were applied carefully on the monolayers of HeLa cells after the pre-incubation time. The monolayers of the adherent HeLa cells were fixed by glutaraldehyde and stained with a 0.05 % solution of methylene blue for 15 min. After gently washing, the stain was eluted by 0.2 mL of 0.33 M HCl in the wells. The optical densities were measured at 630 nm in a micro plate reader. In general, the compounds showed no significant cytotoxic effect at the tested concentration.[27]

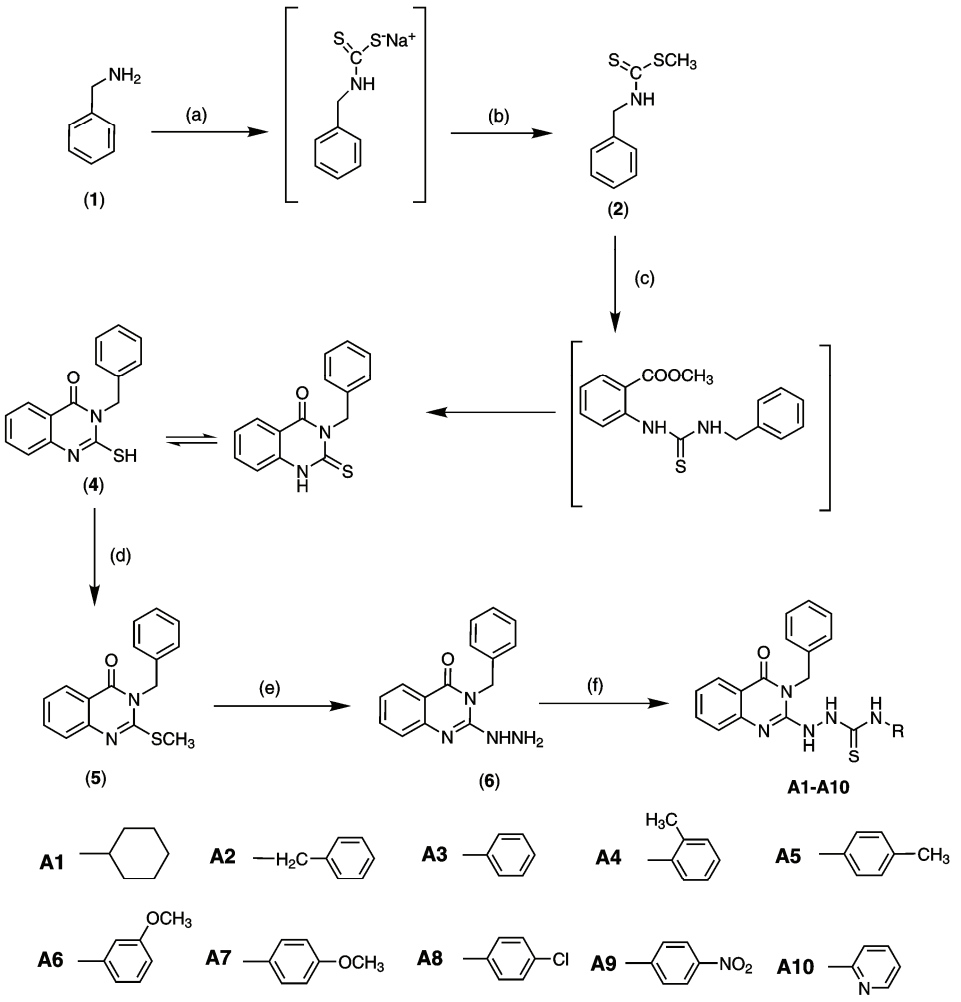
RESULTS AND DISCUSSION

Chemistry

Synthetic route depicted in Scheme 1 outlines the chemistry part of the present work. The key intermediate 3-benzyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4--one (**4**) was obtained by reacting aniline (**1**) with carbon disulphide and sodium hydroxide in dimethyl sulphoxide to give sodium dithiocarbamate, which was methylated with dimethyl sulphate to afford the dithiocarbamic acid methyl ester **2**. Compound **2** on reflux with methyl anthranilate (**3**) in ethanol yielded the desired 3-benzyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**4**) *via* the thiourea intermediate in good yield (80 %). The obtained product was cyclic and not an open chain thiourea **3a**. The 3-benzyl-2-(methylsulphanyl)-3*H*-quinazolin-4-one (**5**) was obtained by dissolving **4** in 2 % alcoholic sodium hydroxide solution and methylating with dimethyl sulphate under stirring at room temperature. Nucleophilic displacement of the methylthio group of **5** with hydrazine hydrate was performed using ethanol as solvent to afford 3-benzyl-2-hydrazino-3*H*-quinazolin-4--one (**6**). The required long duration of the reaction (33 h) might be due to the presence of the bulky aromatic ring at position 3, which might have reduced the reactivity of quinazoline ring system at the C-2 position. The title compounds 1-(3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)-4-(substituted) thiosemicarbazides (**AS1**–**AS10**) were obtained by the condensation of the amino group of 3-benzyl--2-hydrazino-3*H*-quinazolin-4-one (**6**) with a variety of methyl ester of dithiocarbamic esters. The formation of title products was indicated by the disappearance of peak due to NH, NH_2 of the starting material in IR and ^{1}H-NMR spectra of all the compounds **AS1**–**AS10**. The IR and ^{1}H-NMR spectra of these compounds showed the presence of peaks due to thiosemicarbazides, carbonyl (C=O), NH and aryl groups. The mass spectra of the title compounds showed molecular ion peaks corresponding to their molecular formulae. In the mass spectrum of compounds **AS1–AS10**, a common peak at *m*/*z* 144 corresponding to the quinazolin-4-one moiety appeared. Elemental (C, H, N) analysis satisfactorily confirmed the elemental composition and purity of the synthesized compounds.

Antitubercular activity

The synthesized compounds were screened for their *in vitro* antimycobacterial activity against *M. tuberculosis* strain $H37R_V$. The results are expressed in



Scheme 1. Synthesis of 1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)-4-(substituted) thiosemicarbazides. Reagents and conditions: a) CS_2, NaOH, DMSO, 30 min; b) dimethyl sulphate, 2 h; c) methyl anthranilate, anhydrous K_2CO_3, EtOH reflux, 22 h; the product is **3a**; d) 2 % alcoholic NaOH, dimethyl suphate, 1 h; e) hydrazine hydrate, anhydrous K_2CO_3, EtOH reflux, 33 h; f) methyl N-(substituted) carbamodithioate, EtOH reflux, 22–30 h; notation "**A**" in the Scheme replaces notation "**AS**" from the text.

terms of minimum inhibitory concentration (*MIC*). The results of antimycobacterial activity depicted in Table I, indicate that the test compounds inhibited the growth of *Mycobacterium* to varying degree. Compounds with aliphatic substituents showed lower antitubercular activity over the aryl and heteroaryl substituents. The compounds with electron withdrawing substituent on the aryl ring showed better activity over the unsubstituted or electron donating substituent on

the aryl ring. Among the test compounds, 2-(3-benzyl-4-oxo-3,4-dihydroquinazolin-2-yl)-*N*-(4-chlorophenyl)hydrazinecarbothioamide (**AS8**) and 1-(3-benzyl--4-oxo-3,5-dihydroquinazolin-2-yl)-4-(4-nitrophenyl)hydrazinecarbothioamide (**AS9**) exhibited antitubercular activity at the minimum microgram concentration (3 μg mL^{-1}).

TABLE I. Antitubercular and antibacterial activity of the synthesized compounds **AS1**–**AS10**; (*MIC* in μg mL^{-1}); na – no activity

Microorganism	Test Compound										Standard[a]
	AS1	**AS2**	**AS3**	**AS4**	**AS5**	**AS6**	**AS7**	**AS8**	**AS9**	**AS10**	
M. tuberculosis	125	63	63	6	13	13	6	3	3	6	1
S. enterica serovar Typhimurium	66	63	63	63	63	125	63	8	8	16	4
P. vulgaris	63	63	125	125	63	63	63	8	16	32	1
K. pneumoniae	63	125	125	32	63	125	63	16	16	63	1
B. subtilis	63	125	63	125	63	32	32	8	8	16	1
P. aeruginosa	125	125	16	63	32	32	63	16	8	32	1
E. tarda	na	na	na	na	na	na	na	na	na	na	na

[a]Gatifloxacin was used as a reference standard against *M. tuberculosis*, whereas ciprofloxacin was used as a reference standard for the other bacteria

Antibacterial activity

Among the different substituents, aryl and heteroaryl substituents exhibited better activity over the aliphatic cyclic substituents. Compounds with electron withdrawing substituents, such as –Cl and $–NO_2$ showed better activity over the unsubstituted and electron donating substituents. Compounds **AS8** and **AS9** emerged as the most active compounds of the series. Compound **AS8** showed the most potent activity against *E. coli*, *P. vulgaris*, *B. subtilis* and *S. enterica* subsp. *enterica* serovar Typhimurium, while compound **AS9** showed the most potent activity against *E. coli*, *B. subtilis*, *P. aeruginosa* and *S. enterica* subsp. *enterica* serovar Typhimurium.

CONCLUSIONS

In summary, the syntheses of a new series of 1-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)-4-(substituted) thiosemicarbazides was described. These derivatives exhibited significant antibacterial activity against various Gram-positive and Gram-negative bacteria, including *M. tuberculosis.* Among the series, compound **AS8** showed the most potent activity against *E. coli*, *P. vulgaris*, *B. subtilis* and *S. enterica* subsp. *enterica* serovar Typhimurium, while compound **AS9** showed the most potent activity against *E. coli*, *B. subtilis*, *P. aeruginosa* and *S. enterica* subsp. *enterica* serovar Typhimurium. The test compounds **AS8** and **AS9** exhibited antitubercular activity at the minimum microgram concentration

(3 μg mL^{-1}) and show potential for further optimization and development to new antitubercular agents.

SUPPLEMENTARY MATERIAL

The physical, analytical and spectral data for the compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

Acknowledgements. The authors gratefully acknowledge the Central Instrumentation Facility, IIT Chennai, India for the spectral analysis of the compounds synthesised in this study and Dr. D. Sriram, Birla Institute of Technology & Sciences, Hyderabad Campus for performing the antitubercular screening of the test compounds.

ИЗВОД

СИНТЕЗА И АНТИМИКРОБНА АКТИВНОСТ 1-(3-БЕНЗИЛ-4-ОКСО-3,4-ДИХИДРОКИНАЗОЛИН-2-ИЛ)-4-СУПСТИТУИСАНИХ ДЕРИВАТА ТИОСЕМИКАРБАЗИДА

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Синтетисана је серија 1-(3-бензил-4-оксо-3,4-дихидрокиназолин-2-ил)-4-супституисаних деривата тиосемикарбазида (**AS1**–**AS10**), реакцијом 3-бензил-2-хидразино-3*H*-хиназолин-4-она (**6**) и различитих деривата метил-естара дитиокарбаминске киселине. Главни интермедијер 3-бензил-2-тиоксо-2,3-дихидро-1*H*-хиназолин-4-он (**4**) добијен је после секвенције у којој је реакцијом бензиламина (**1**) са угљен-дисулфидом и натријум-хидроксидом у диметил-сулфоксиду добијен дитиокарбамат, који је метилован диметил-сулфатом при чему је добијен метил-естар дитиокарбаминске киселине **2** и који је кондензацијом са метил-антранилатом (**3**) у етанолу дао жељени производ **4** преко тиоуреидног интермедијера. Тиол-група у једињењу **4** метилована је да би била извршена нуклеофилна замена помоћу хидразин хидрата, чиме је добијен 3-бензил-2-хидразинохиназолин-4-он (**6**). IR, ^{1}H- и ^{13}C-NMR спектри једињења показују присуство сигнала тиосемикарбазидних, карбонилних (C=O), NH и арил-група. У свим масеним спектрима деривата **AS1–AS10** присутан је сигнал хиназолин-4-он јона (m/z 144). Елементална анализа (C, H, N) је показала добру чистоћу једињења. Испитана је антимикробна активност свих синтетисаних једињења према одабраним грам-позитивним и грам-негативним бактеријама. Деривати **AS8** и **AS9** показују најбоље активности у овој серији испитаних једињења.

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