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Synthesis and biological evaluation of some new heterocyclic derivatives from substituted thiopyrimidine

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Abstract: This study aimed at creation of a few new heterocyclic compounds that include sulfur and nitrogen atoms. Also, some chalcones, thiazolidine and Schiff base derivatives have been prepared. The spectroscopic data (IR, ^{1}H- and ^{13}C-NMR) have verified the structure of the produced molecules. Interesting findings were obtained when several synthetic substances were physiologically tested against a range of pathogenic Gram-positive and Gram-negative bacteria.

Keywords: thiazolidine; chalcones; Schiff bases; cyclization; pathogenic bacteria.

INTRODUCTION

Cyclic organic compounds, known as heterocyclic compounds, at least have one heteroatom other than carbon in the cyclic ring structure. The three most prevalent heteroatoms are oxygen, nitrogen and sulfur.[1] The most significant natural organic heterocyclic compounds are usually found in large quantities in the products of both plants and animals.[2] The use of heterocyclic compounds is widespread in the fields of agrochemical, pharmaceutical and veterinary applications.[3] Numerous heterocyclic substances are extremely beneficial and necessary for human life.[4] Hormones, vital amino acids, antibiotics, alkaloids, haemoglobin, vitamins, dyes and pigments are only a few examples of the many substances with heterocyclic structures.[5] Many pharmaceuticals and agrochemicals contain at least one heterocyclic unit; heterocycles play an important role in many natural products.[6] Important building blocks for novel materials with interesting electrical, mechanical or biological properties incorporate heterocyclic systems.[7]

Pyrimidine has two nitrogen atoms and a six-membered heterocyclic structure.[8] It is essential component of nucleic acid and widely distributed in nature in

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the form of N-substituted sugar derivatives (nucleosides).[9] Cytosine, thymine and uracil are pyrimidines that contribute to the distinctive three- dimensional structure of RNA and the double helix of DNA.[10] Pyrimidine and its derivatives are one of the most significant heterocyclic nitrogenous cycles .They are important enough to a variety of biological activities.[11] The ring system of pyrimidine is found in several vitamins, antibiotics, alkaloids and nucleic acids and their derivatives.[12]

Thiazolidine is a chemical compound found in many pharmaceutical drugs. It has been shown to have anti-inflammatory and antioxidant properties.[13] Thiazolidine has been studied for its potential use as a treatment for conditions such as arthritis and diabetes.[14] Also, it may help improve cognitive function and memory retention.[15] Its derivatives also exhibit anti-inflammatory and anti-tumor properties,[16] that make them promising candidates for treating chronic inflamematory and certain types of diseases.[17] After all, thiazolidine and its derivatives have shown great promise as a versatile class of drugs with diverse therapeutic applications.[18]

Chalcones are natural compounds found in plants and they have gained significant attention due to their diverse biological activities.[19] They have potential in reducing inflammation, treating cancer and managing diabetes.[20] These compounds employ their medicinal properties by affecting various signaling pathways and enzymes, leading to a wide range of therapeutic effects.[21] Interestingly, chalcones are also present in some food sources like green tea, apples and onions.[22] Some studies suggest that incorporating chalcones into our diet may offer health benefits like reducing the risk of cardiovascular diseases. Overall, chalcones hold promising prospects for developing new drugs and improving health outcomes.[23]

Schiff bases are a significant class of the most frequently used organic compounds. They have several uses in a wide range of industries.[24–26] A variety of enzymatic processes appear to use Schiff bases as significant intermediates.[27,28] Schiff bases, derived from heterocyclic compounds, are molecules of interest as their chemical and biological properties suggest such compounds as probable antibacterial candidates.

In this paper, we present synthesis of some novel heterocyclic compounds with new substituents as well as antibacterial activity for some compounds with different functional groups.

EXPERIMENTAL

General

The chemicals were obtained from two different commercial sources, BDH and Fluka without any further purification, while substituted thiopyrimidine (**1**)[29] was previously prepared and purified before usage. Melting points (MP) were calculated on the Electro-Thermal IA1900. IR (Shimadzu FT-IR-8400) spectrometer operating in the 4000–400 cm^{-1} range with

KBr disks were used. ^{1}H-NMR and ^{13}C-NMR spectrum were captured using a Varian Agilant USA 400 MHz, 100 MHz respectively, coupling constants (*J*) are provided in Hz, while chemical shifts (δ) are given in ppm. Spectrometer at the Laboret Centre, University of Theran. Thin layer chromatography (TLC) was used to monitor and confirm the compounds purity on TLC aluminium sheets.

General procedure

*Synthesis of compound **2***.[30] A solution of 1-amino-4-methyl-6-phenylpyrimidine-2-(1*H*)-thione (**1**, 0.01 mol), in absolute ethanol (30 mL) and potassium hydroxide (8 g) was stirred for 35 min, then 0.01 mol of bromo ethyl acetate was gradually added. The reaction mixture was refluxed for 8 h, then, the progress of the reaction was monitored through TLC. After that, the mixture was mixed with crushed ice, ether was used to extract the product (4×30 mL) and after the solvent was evaporated at low pressure, column chromatography (5 petrol:1 EtOAc) was used to purify and to give the ester compound **2**.

*Synthesis of compound **3***.[31] To a solution of the ester compound **2** (0.01 mol) and 50 mL of absolute ethanol, 0.01 mol of hydrazine hydrate (85 %) was added. The mixture of the reaction was refluxed for 2 h, using a water bath. When TLC showed no ester was left, the mixture was cooled and the acid hydrazide was formed. Then, the resulting precipitate was filtered, washed with water and recrystallized from ethanol to give the compound **3**.

*Synthesis of compounds **4**–**6***.[32] The acid hydrazide **3** (0.01 mol) was dissolved in ethanol (30 mL), then *p*-nitrobenzaldehyde (0.01 mol) in ethanol (25 mL) was added and followed by few drops of acetic acid to get a clear solution. After refluxing the mixture for 4 h, the progress of the reaction was monitored through TLC, cooling the mixture resulted the precipitate which was filtered and purified using column chromatography (5 hexane:1 EtOAc) to give compound **4**. The above experiment was repeated, worked up and purified as mentioned above using 0.01 mol of acid hydrazide with 0.01 mol of 2,4-dimethoxybenzaldehyde and with 0.01 mol of 4-*N*,*N*-dimethylaminobenzaldehyde to give compounds **5** and **6**, respectively.

*Synthesis of substituted thiazolidines **7**–**9***.[33] In the presence of pyridine (20 mL), a mixture of compound **4** (0.01 mol) and thioglycolic acid (0.01 mol) was refluxed for 5 h. The TLC indicated that no starting materials were left, the mixture was cooled and concentrated. Purifying the crud product with column chromatography (10 hexane:2 EtOAc) gave the title compound **7**. The above experiment was repeated, worked upon and purified as above using 0.01 mol of thioglycolic acid each separately with 0.01 mol of compounds **5** and **6** to give compounds **8** and **9**, respectively.

*Synthesis of compound **10***.[34] A mixture of 1-amino-4-methyl-6-phenyl pyrimidine-2--(1*H*)thione (**1**, 0.01 mol) in 30 mL of ethanol and 0.01 mol of phenyl isothiocyanate was refluxed using the steam bath for 8 h. When TLC confirmed the reaction was completed, the mixture was cooled and stored overnight in the refrigerator. The filtration process was carried out and of the resulting solid was purified by column chromatography (5 petrol:1 EtOAc) to get compound **10**.

*Synthesis of compound **11***.[35] To a mixture of an equimolar of compound **10** (0.01 mol) and malonic acid (0.01 mol), 30 mL of acetyl chloride was added and then refluxed for 3 h. The progress of the reaction was monitored through TLC, then, the reaction mixture was cooled, filtered and the crude product was purified by column chromatography (5 hexane:1 EtOAc) to give compound **11**.

*Synthesis of chalcone **13***.[36] A solution of 1-amino-4-methyl-6-phenyl pyrimidine-2--(*1H*)thione (**1**, 0.01 mol) in THF (20 mL) was stirred while acetyl chloride (10 mL) was being added dropwise at 0 °C. The mixture was left to reach the room temperature, then it was

refluxed for 3 h. When the TLC revealed that the reaction was completed, crushed ice was added, then, an aqueous solution of (10 %) $NaHCO_3$ was used to neutralize the reaction mixture. The resulted precipitate was firstly filtered, washed with water and recrystallized from ethanol to produce compound **12**.

In order to prepare compound **13**, a flask with a magnetic stirrer was filled with 10 mL of 10 % sodium hydroxide solution along with 25 mL of ethanol, 0.01 mol of compound **12** and 0.01 mol of *p*-nitrobenzaldehyde. The mixture was stirred for 10 h at room temperature. The formed precipitate was then filtered, washed with cold water until it almost became neutral and dried before the crude product was purified using column chromatography (5 hexane:1 EtOAc) to give compound **13**.

*Synthesis of compound **14***.[36] Compound **13** (0.01 mol) and a nucleophilic reagent (thiourea, 0.01 mol) were dissolved in ethanol and sodium hydroxide was added (2 g NaOH and 10 mL ethanol). The mixture was stirred for 7–8 h. TLC proved that the reaction was complete. The produced solid was filtered off, totally dissolved in water and precipitated with HCl. The obtained precipitate was then filtered, washed with water, dried and recrystallized from ethanol/dioxan to obtain the target compound.

RESULTS AND DISCUSSION

Organic compounds based on substituted thiopyrimidines have many different applications in the field of synthetic organic chemistry. They are also significant in medicinal chemistry. The structures of the newly prepared compounds have been established after the target compounds were produced. The intermediates and final products were each characterized by FT-IR and ^{1}H-NMR and^{13}C--NMR. Compound **1** was used as starting material to obtain the target compounds.

In Fig. 1 esterification of compound **1** *via* reaction with CH_2BrCO_2Et in the presence of ethanol to give the corresponding ester **2** is presented. The structure was confirmed by ^{1}H-NMR which showed a quartet at δ 4.09 ppm and a triplet at δ 1.31 ppm related to methylene and methyl group for the ester **2**, respectively. In addition,^{13}C-NMR presented signal at δ 168.6 ppm due to C=O group and signal at 61.2 ppm refer to (CH_2 adjacent to O), IR spectrum presented the key band of carbonyl group at 1745 cm^{-1} for the ester. Treatment of an ester **2** with $N_2H_4{\cdot}H_2O$ in absolute ethanol was carried out successfully to synthesized acid hydrazide **3**. The obtained spectral data confirmed the formation of the desired product. The protons of amino group appeared as a doublet at 3.80 ppm in the acid hydrazide **3** demonstrating the elimination of the ester protons. The efficient reaction of substituted benzaldehydes with acid hydrazide **3** in ethanol gave the substituted hydrazones **4**–**6**, respectively. IR spectra revealed bands corresponding to the azomethine (CH=N) group and the other groups substituted on the aldehyde such as NO_2, OCH_3 and $N(CH_3)_2$ which confirm the coupling with aldehyde happened successfully. The ^{1}H-NMR for compound **4** presented a singlet at 8.44 ppm belonging to the proton of azomethine group, while for compound **5** it was a singlet at 3.79 ppm related to OCH_3 groups, also a singlet at 8.27 ppm belongs to

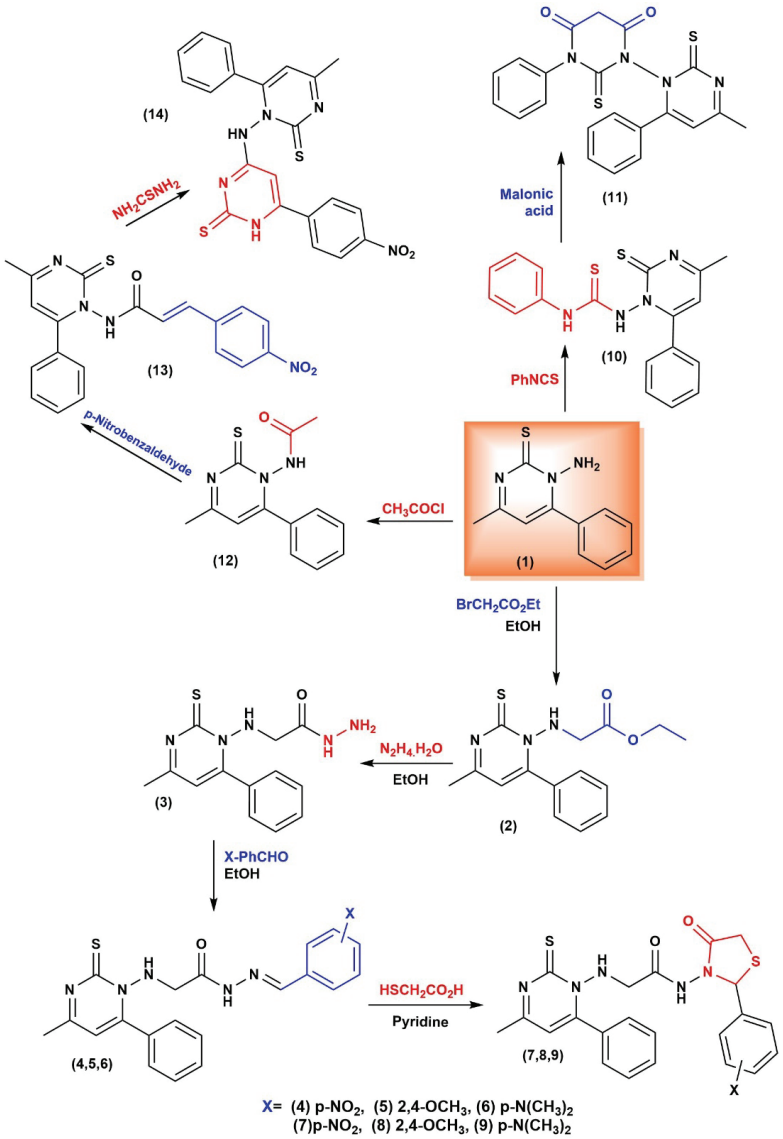

Fig. 1. Synthesis of compounds **2**–**14**.

the proton of CH=N group. For compound **6**, the ^{1}H-NMR data showed a singlet at 2.89 ppm referring to 6 protons of two methyl groups (*N*,*N*-dimethyl group) and a singlet at 8.40 ppm for CH=N proton. Also, ^{13}C-NMR showed signals at δ 148.6 and 41.9 ppm related to CH=N and two CH_3 groups, respectively. On the other hand, a new five membered heterocyclic compounds were formed by refluxing substituted hydrazones **4**–**6** with thioglycolic acid in pyridine again the

resulting compounds were verified by ^{1}H-, ^{13}C-NMR and IR. Compound **7** showed two doublets at 3.38 and 3.34 ppm for methylene group within the thiazolidine ring. The IR spectrum also confirmed the structure of **7** by showing an asymmetric and symmetric stretching for NO_2 group at 1518 and 1345 cm^{-1}, respectively. Also, compounds **8** and **9** were confirmed by ^{1}H-, ^{13}C-NMR and IR spectra which showed the essentially required peaks as presented in compound **7**. The second line consisted of two steps, the first one was formation of compound **10** by the reaction of compound **1** with phenyl isothiocyanate in ethanol. IR showed band at 1485 cm^{-1} belonging to C=S, ^{13}C-NMR also confirmed the formation of **10** with a signal at δ 180.5 ppm that refer to carbon in C=S group. Treatment of equimolar of **10** and malonic acid in the presence of acetyl chloride gave the target compound **11** which offered two bands for two carbonyl groups at 1734 and 1676 cm^{-1}, respectively. Similarly, ^{13}C-NMR showed two signals at δ 164.4 and 161.5 ppm due to two (C=O) groups, ^{1}H-NMR gave a singlet at 2.97 ppm that belongs to CH_2 adjacent to C=O group. The last line included three steps, the first step was the synthesis of **12** through the reaction of compound **1** with acetyl chloride, ^{1}H-NMR showed a singlet at 2.01 ppm for acetyl protons, ^{13}C-NMR gave signal at 166.4 ppm belonging to C=O and 20.5 ppm for CH_3 adjacent to C=O. IR spectrum showed band at 1735 cm^{-1} for carbonyl group. Secondly, the reaction between compound **12** and *p*-nitrobenzaldehyde produced compound **13**. Again, the structure of the resulted compound was confirmed by ^{1}H-NMR spectrum which showed two doublets at 7.79 and 7.03 ppm belonging to the α and β protons, respectively. In addition, ^{13}C-NMR indicate the formation of structure by signal for C=O at 166.1 and 122.2, 146.7 ppm of α and β carbon, respectively. IR revealed a band at 1703 cm^{-1} due to the carbonyl group. Finally, the cyclization of chalcone **13** *via* adding thiourea to give new substituted six membered heterocyclic ring compound **14** was carried out successfully. ^{1}H-NMR spectrum showed a singlet at 9.02 ppm for the proton in the new-formed substituted thiopyrimidine ring.

The biological study

The disc diffusion method was used to test the antibacterial efficacy of some synthesized compounds against two bacterial strains, *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative). DMSO was used as a solvent for both the control and the selected samples. For the initial assessment of the invitro antibacterial activity, a total of five compounds were carefully chosen from Fig. 1, taking into consideration the structural properties of the compounds obtained, namely compounds **11** and **14**. These compounds were deemed to be the final products. In addition, compounds **2**, **6** and **8** were also included in the selection process due to their involvement as either intermediate or final products in the various transformation steps outlined in the scheme. These five compounds

showed significant activities and could largely inhibit the bacteria growth. According to the results shown in Table I, five different concentrations have been taken (12.5, 25, 50, 100 and 200 mg/mL) to determine the optimal dose or therapeutic rang of the screened compounds.

TABLE I. Biological activity of some prepared compounds

Compound	Concentration, g/L	Bacteria	
		S. aureus	*E. coli*
14	200	12	24
	100	8	19
	50	0	16
	25	0	14
	12.5	0	5
2	200	21	20
	100	19	18
	50	17	14
	25	13	12
	12.5	9	5
6	200	9	18
	100	0	16
	50	0	12
	25	0	10
	12.5	9	5
11	200	10	23
	100	8	19
	50	0	17
	25	0	12
	12.5	0	7
8	200	23	25
	100	21	20
	50	15	17
	25	13	14
	12.5	6	8
Amikacin (amk)	20 mg/disc	21	20

At 200 mg/mL for compound **8** (23 mm) and compound **2** (21 mm), *S. aureus* was inhibited, whereas compounds **14**, **11** and **6** (12, 10 and 9 mm, respectively) at 200 mg/mL of concentration *E. coli* was inhibited. Compounds **8**, **14** and **11** had inhibition zones of 25, 24 and 23 mm, while compounds **2** and **6** at 200 mg/mL have 20 and 18 mm, respectively. It is thought to be that those compounds exhibiting high activity are attributed to the multi-functional groups (highly containing of nitrogen and sulfur) and the structure possessed by these particular compounds.[37]

Chemically, it has been observed that antimicrobial activity can be enhanced by introducing different constituents at different positions of the heterocyclic ring

(thiazolidinone (**8**), pyrimidine thion (**14**)).[38,39] Several studies indicated that the bacterial death could occurr via either inhibiting DNA gyrase which is mainly responsible for bacterial chromosome replication and transcription[40] or likely by inhibition of Mur ligases action which is responsible for peptidoglycan biosynthesis, a crucial molecule that is giving the shape and rigidity to the cell wall envelope 1.[41]

CONCLUSION

Synthesizing heterocyclic compounds containing multi-functional groups with interesting biological activity could help develop new medicinal compounds for treatment of complex infections and diseases. New heterocyclic compounds have been successfully synthesized using substituted thiopyrimidine as a starting material. The initial biological screening of some synthesized compounds (**2**, **6**, **8**, **11** and **14**) against two pathogenic bacteria namely, *S. aureus* and *E. coli* showed interesting biological properties. Compounds **8** and **14** presented the highest inhibition activity compared to control. The reason behind that antibacterial activity of these compounds could be related to inhibition of the essential enzymes (DNA gyrase or Mur ligases) for the bacterial growth. In addition, the type and position of substituents on the hetero-ring play a significant role in the activity. Spectral data have been used to elucidate and confirm the structure of the prepared compounds. Biological screening for some prepared compounds has been evaluated. The outcomes revealed that the bioactivity of some synthesized molecules could be employed in the field of pharmaceutical chemistry.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12544, or from the corresponding author on request.

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И З В О Д

СИНТЕЗА И ИСПИТИВАЊЕ БИОЛОШКЕ АКТИВНОСТИ НЕКИХ ХЕТЕРОЦИКЛИЧНИХ ДЕРИВАТА СУПСТИТУИСАНИХ ТИОПИРИМИДИНА

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Током овог истраживања осмишљено је неколико нових хетероцикличних једињења који садрже атоме азота и сумпора. Такође, синтетисано је и неколико деривата халкона, тиазолидина и Шифових база. Спектроскопским подацима (IC, ^{1}H- и ^{13}C-NMR) поврђена је структура добијених молекула. Интересантни резултати су добијени из биолошких тестова према палети патогених Грам-позитивних и Грам-негативних бактерија.

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