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ORIGINAL PAPER

MgO nanoparticle-catalyzed, solvent-free Hantzsch synthesis and antibacterial evaluation of new substituted thiazoles

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Abstract In this study, some novel 4-thiazolylpyrazoles were synthesized by modified Hantzsch method, under solvent-free conditions and in the presence of MgO nanoparticles as catalyst. Excellent yields in shorter reaction times were achieved under the new general protocol. Also, the in vitro antibacterial effects of synthesized compounds were evaluated against 21 gram-positive and gram-negative pathogenic bacterial strains and compared to antibiotics such as ceftriaxone and penicillin. The results were reported as inhibition zone diameter, minimum inhibitory concentration (MIC), and minimum bactericidal concentration (MBC) values. The compounds showed moderate to good antibacterial activities. Among the newly synthesized thiazoles, compounds **7b**, **f** had inhibitory effects against eight pathogenic bacteria; besides, thioamide **6** with MIC and MBC values of 32 and 64 μg/mL against *Streptococcus agalactiae* was identified as the most effective antibacterial agent.

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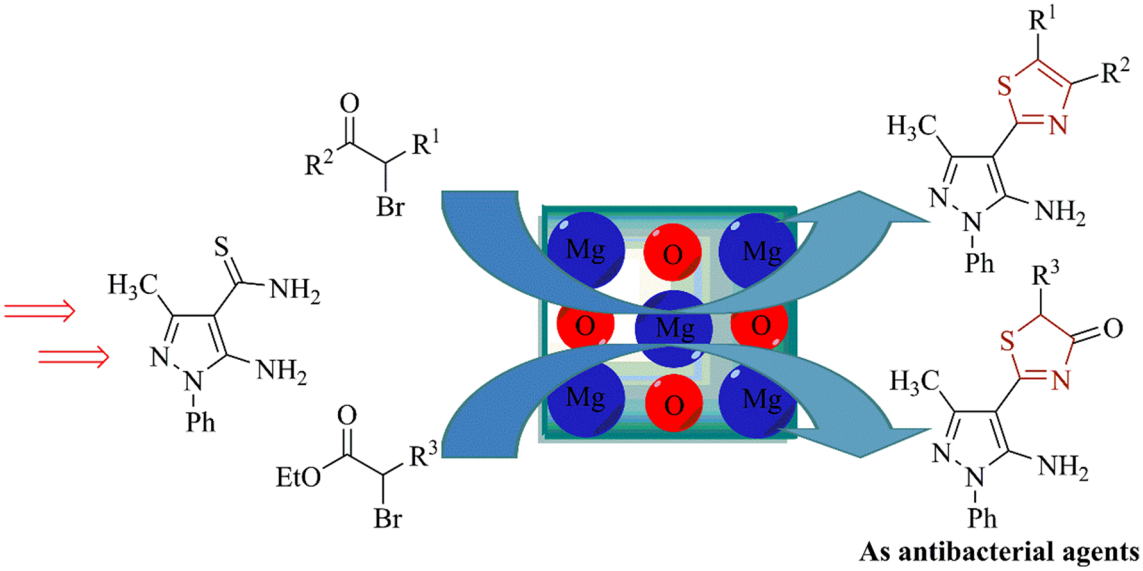
Graphical Abstract MgO nanoparticle was prepared and successfully used as an efficient recyclable catalyst for the Hantzsch thiazole synthesis; reaction times and product yields were significantly improved in the presence of nanocatalyst.



Keywords MgO nanocatalyst · Solvent-free condition · Thiazole · Hantzsch synthesis · Antibacterial activity

Introduction

Thiazoles belong to an important class of heterocyclic compounds that are found in many naturally occurring compounds and biologically active molecules [1]. Thiazole core can be found in compounds such as thiamine (vitamin B1), which plays a major role in the release of energy from carbohydrates and the function of nervous system, or luciferin, which is the main element in yellow light emission from fireflies [2]. Thiazole and its analogs are present in the chemical structure of various drugs such as meloxicam, ritonavir, sulfathiazole, tiazofurin, abafungin, bleomycine, niridazole, talipexole, riluzole, archazolid A, telomestatin and pramipexole which have known, respectively, as anti-inflammatory, antiretroviral, antimicrobial, antineoplastic, antifungal, anticancer, antischistosomal, antiparkinsonian, anticonvulsant, antiproliferative, telomerase-inhibiting and antidepressant agents [3–6]. Several methods have been developed for the synthesis of thiazole derivatives [7–26], of which Hantzsch approach is the most widely used method. Hantzsch synthesis involves cyclocondensation of primary thioamids with α-halocarbonyl compounds [27]. This method works nicely in preparation of simple thiazole ring systems; however, the reaction is not efficient when it applies to synthesis of polysubstituted thiazoles. Various developments were achieved in order to improve the reaction outcome such as the application of different catalysts [28] or reactants [29–33]. More improvements were observed when ionic liquids [34] and solvent-free conditions [35] as reaction media, and ultrasound [36] or microwave irradiations [37] as energy sources were used.

In recent years, nanoparticles have been widely used for various organic transformations. Shorter reaction times, higher yields, improved economy as well as the minimization of the amount of chemical wastes are just a few advantages of using nanocatalysts in organic synthesis [38]. These items were encouraged us to extend our experiences on the synthetic applications of MgO nanoparticles. To the best of our knowledge, there is no report in applying magnesium oxide nanoparticles to Hantzsch thiazole synthesis.

In the present article, a three-step pathway for the synthesis of 4-thiazolylpyrazole derivatives using magnesium oxide nanoparticles as catalyst under solvent-free conditions has been described. A number of novel thiazole derivatives were synthesized under the optimized conditions. The results were compared to the classical Hantzsch method. The in vitro antimicrobial activities of synthesized compounds were evaluated against a variety of gram-positive and gram-negative pathogenic bacteria and reported as the minimum inhibitory concentration (MIC), the minimum bactericidal concentration (MBC), and inhibition zone diameter (IZD) values.

Experimental

Chemicals

All chemicals and solvents were obtained from Merck and Sigma-Aldrich and used without further purification. Antibiotics were purchased from Sigma-Aldrich. All yields were referred to isolated products. Melting points were recorded on a Kruss type KSP1 N melting point meter and uncorrected. Monitoring progress of the reactions and the purity of the products were affected by TLC on aluminum plates pre-coated by SiO_2 gel (60, Merck) using $CHCl_3$:CH_3OH (8:2, v/v) as mobile phase and visualized with iodine vapor. The IR spectra of the products were recorded on a Bruker Tensor 27 FT-IR spectrometer using KBr disks, and only noteworthy absorptions were listed as well. The ^{1}H and ^{13}C-NMR spectra of DMSO-d_6 solutions were recorded on a Bruker FT-NMR Ultra Shield-400 spectrometer (400 and 100 MHz, resp.). Elemental analyses were performed for C, H, N, and S on a Thermo Finnigan Flash EA microanalyzer. The concentration of bacterial suspensions was determined by using Jenway 6405 UV–Vis spectrophotometer. The X-ray diffraction (XRD) analysis was conducted by using a Bruker D8 X-ray diffractometer with cu-kα radiation (λ = 1.5418 Å) in the range of 10°–70° and the scanning rate of 1.5°/min. A scanning electron microscope (SEM) was applied to observe the surface morphology of nanoparticles using a Hitachi S4160 instrument.

Preparation of MgO nanoparticles

The MgO nanoparticles were prepared by wet chemical method according to the previously reported procedure [39], as follows: a suspension of starch (0.1 g) and magnesium nitrate (12.83 g, 0.1 mol) were mixed in 100 mL distilled water. Then, sodium hydroxide solution (25 mL, 0.008 M) was added slowly to the mixture while it was stirring vigorously over 2 h. The reaction mixture was left at room temperature for 24 h without stirring. The suspension was centrifuged at 10,000 rpm for 10 min. Centrifugate was washed three times using distilled water. The resulting magnesium hydroxide nanoparticles were placed in the furnace at 300 °C for 4 h to yield nanoparticles of MgO.

Preparation of 5-amino-3-methyl-1-phenyl-1*H*-pyrazole-4-carbonitrile (4)

Pyrazole **4** as the starting material was prepared according to the procedure reported by Allouche et al. [40] as follows: a solution of malononitrile (**1**) (2.18 g, 33 mmol), triethyl orthoacetate (**2**) (5.52 g, 34 mmol), phenylhydrazine (**3**) (3.57 g, 33 mmol) and few drops of acetic acid as catalyst in ethanol (30 mL) was refluxed for 12 h. The reaction mixture was cooled to room temperature, and the precipitates were filtered, washed with cold ethanol, and recrystallized from its ethanolic solution to give 6.54 g (83% yield) of the product **4** as white needles, m.p. 166–168 °C.

Preparation of 5-amino-3-methyl-1-phenyl-1*H*-pyrazole-4-carbothioamide (5)

The thioamide **5** was synthesized according to the literature procedure [41] with slight modification as follows: pyrazole **4** (1.98 g, 0.01 mol) was added to a solution of P_4S_{10} (4.44 g, 0.02 mol) in absolute ethanol (20 mL), and the resulting mixture was stirred at room temperature for 2 h. The precipitated solid was filtered out, washed with ethanol, and dried in an oven at 80 °C to afford compound **5** without the need for further purification. White to light yellow solid, m.p. 119–121 °C, yield 98%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.38 (3H, s, CH_3), 7.41 (2H, m, NH_2) 7.53 (5H, d, J = 4.3 Hz, Ph), 7.85, 8.94 (1H, s, 1H, s, $CSNH_2$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 174.70 (C=S), 165.60 (C-5 pyrazole), 145.52 (C=N), 143.97 (C-1 Ph), 129.05 (C-3,5 Ph), 128.17 (C-4 Ph), 126.87 (C-2,6 Ph), 101.17 (C-4 pyrazole), 14.49 (CH_3); IR (KBr) ν: 3317, 3268 (NH_2), 1620 (C=N), 1549 (C=C), 1392 (N–N), 1203 (C–N), 1086 (C=S) cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_4S$: C 56.87, H 5.21, N 24.12, S 13.80; found C 56.85, H 5.23, N 24.14, S 13.78.

General procedure for the synthesis of 4-thiazolylpyrazoles 7a–f

The classical Hantzsch conditions

A suspension of thioamide **5** (0.23 g, 1 mmol), the appropriate α-bromocarbonyl compounds (1 mmol) and sodium bicarbonate (0.08 g, 1 mmol) in DMF (1 mL) was stirred at room temperature for 24–46 h. Then, the mixture was poured gradually onto crashed ice; the solid obtained was filtered out, washed with water and ethanol, oven-dried, and finally purified by recrystallization from methanol to produce thiazoles **7a–f**.

The modified Hantzsch conditions (MgO-catalyzed process)

A few drop of DMF was added to a suspension of thioamide **5** (0.23 g, 1 mmol) and the appropriate α-bromocarbonyl compounds (1 mmol) in the presence of MgO nanoparticles (5% molar), and the reaction mixture was stirred at room temperature about 5 min before heating to 100 °C for 5–11 h. After the reaction was complete, acetone (5 mL) was added to the mixture at room temperature, and the

MgO nanocatalyst was filtered off. The recovered MgO was rinsed with more water and acetone and dried in an oven at 100 °C. The desired product was crashed out once. The filtrate was added to an ice-water mixture. The solid residue was filtered, oven-dried at 80 °C, and recrystallized from its methanolic solution to yield thiazoles **7a**–**f**.

3-Methyl-4-(4-methylthiazol-2-yl)-1-phenyl-1*H*-pyrazol-5-amine (**7a**): White crystals, m.p. 170–172 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.37 (3H, s, CH_3 pyrazole), 2.40 (3H, s, CH_3 thiazole), 6.71, 7.39 (1H, d, $J = 9.5$ Hz, 1H, m, NH_2), 7.04 (1H, s, CH thiazole), 7.54–7.56 (3H, m, H-3,4,5 Ph), 7.62 (2H, d, $J = 7.8$ Hz, H-2,6 Ph); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 161.92 (C-2 thiazole), 151.14 (C-4 thiazole), 146.52 (C-5 pyrazole), 146.32 (C-3 pyrazole), 138.79 (C-1 Ph), 129.84 (C-3,5 Ph), 127.21 (C-4 Ph), 123.29 (C-2,6 Ph), 109.14 (C-5 thiazole), 98.17 (C-4 pyrazole), 17.30 (CH_3 thiazole), 14.49 (CH_3 pyrazole); IR (KBr) ν: 3314, 3262 (NH_2), 1620 (C=N), 1556 (C=C), 1401 (N–N), 1200 (C–N), 641 (C–S) cm^{-1}. Anal. Calcd for $C_{14}H_{14}N_4S$: C 62.20, H 5.22, N 20.72, S 11.86; found C 62.23, H 5.23, N 20.70, S 11.84.

1-(2-(5-Amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-4-methylthiazol-5-yl)ethan-1-one (**7b**): Brown crystals, m.p. 118–120 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.38 (3H, s, CH_3 pyrazole), 2.54 (3H, s, $COCH_3$), 2.69 (3H, s, CH_3 thiazole), 6.97, 7.42 (1H, s, 1H, t, $J = 7.1$ Hz, NH_2), 7.54–7.61 (5H, m, Ph); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 164.57 (C=O), 161.92 (C-2 thiazole), 159.56 (C-4 thiazole), 147.70 (C-5 pyrazole), 147.08 (C-3 pyrazole), 138.36 (C-1 Ph), 129.88 (C-3,5 Ph), 127.58 (C-4 Ph), 123.66 (C-2,6 Ph), 115.33 (C-5 thiazole), 97.75 (C-4 pyrazole), 17.54 ($CO\underline{C}H_3$), 14.77 (CH_3 thiazole), 14.70 (CH_3 pyrazole); IR (KBr) ν: 3442, 3296 (NH_2), 1653 (C=O), 1617 (C=N), 1548 (C=C), 1397 (N–N), 1237 (C–N), 656 (C–S) cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_4OS$: C 61.52, H 5.16, N 17.94, S 10.26; found C 61.49, H 5.18, N 17.93, S 10.29.

Ethyl 2-(5-amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-4-methylthiazole-5-carboxylate (**7c**): Light yellow crystals, m.p. 144–146 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.31 (3H, t, $J = 7.1$ Hz, $CH_2C\underline{H}_3$), 2.38 (3H, s, CH_3 pyrazole), 2.67 (3H, s, CH_3 thiazole), 4.28 (2H, q, $J = 7.1$ Hz, $C\underline{H}_2CH_3$), 6.93, 7.42 (1H, d, $J = 7.3$ Hz, 1H, t, $J = 7.1$ Hz, NH_2), 7.54–7.61 (5H, m, Ph); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 192.23 (C=O), 183.80 (C-4 thiazole), 171.45 (C-2 thiazole), 150.11 (C-5 pyrazole), 149.70 (C-3 pyrazole), 137.50 (C-1 Ph), 130.01 (C-3,5 Ph), 128.28 (C-4 Ph), 124.18 (C-2,6 Ph), 123.28 (C-5 thiazole), 99.45 (C-4 pyrazole), 64.51 ($\underline{C}H_2CH_3$), 18.80 (CH_3 thiazole), 15.12 ($CH_2\underline{C}H_3$) 14.32 (CH_3 pyrazole); IR (KBr) ν: 3378, 3287 (NH_2), 1670 (C=O), 1619 (C=N), 1545 (C=C), 1396 (N–N), 1263 (C–N), 649 (C–S) cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_4O_2S$: C 59.63, H 5.30, N 16.36, S 9.36; found C 59.65, H 5.28, N 16.38, S 9.37.

Ethyl 2-(5-amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)thiazole-4-carboxylate (**7d**): Light yellow crystals, m.p. 165–167 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.33 (3H, t, $J = 7.1$ Hz, $CH_2C\underline{H}_3$), 2.40 (3H, s, CH_3 pyrazole), 4.33 (2H, q, $J = 7.1$ Hz, $C\underline{H}_2CH_3$), 6.85, 7.41 (1H, d, $J = 8.1$ Hz, 1H, t, $J = 7.2$ Hz, NH_2), 7.55 (3H, t, $J = 7.4$ Hz, H-3,4,5 Ph), 7.62 (2H, d, $J = 7.8$ Hz, H-2,6 Ph), 8.32 (1H, s, CH thiazole); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 162.95 (C=O), 161.17 (C-2 thiazole), 146.97 (C-4 thiazole), 146.52 (C-5 pyrazole), 145.26 (C-3 pyrazole), 138.56 (C-1 Ph), 129.86 (C-3,5 Ph), 127.40 (C-4 Ph), 123.45 (C-2,6 Ph), 123.96 (C-5 thiazole), 97.68 (C-4 pyrazole), 61.21 ($\underline{C}H_2CH_3$), 14.65 (CH_3 pyrazole, $CH_2\underline{C}H_3$); IR (KBr) ν: 3434, 3314 (NH_2), 1729 (C=O), 1602 (C=N), 1563 (C=C), 1394 (N–N), 1221 (C–N), 639 (C–S) cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_4O_2S$: C 58.52, H 4.91, N 17.06, S 9.76; found C 58.54, H 4.88, N 17.09, S 9.75.

2-(5-Amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)thiazol-4(5*H*)-one (**7e**): Light pink crystals, m.p. 238–240 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.42 (3H, s, CH_3), 4.01 (2H, s, CH_2), 7.46, 7.55 (1H, m, 1H, m, NH_2), 7.56–760 (5H, m, Ph); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 189.87 (C=O), 165.60 (C-2 thiazole), 149.92 (C-5 pyrazole), 149.70 (C-3 pyrazole), 137.48 (C-1 Ph), 130.07 (C-3,5 Ph), 128.36 (C-4 Ph), 124.23 (C-2,6 Ph), 99.45 (C-4 pyrazole), 36.31 (CH_2), 15.17 (CH_3); IR (KBr) ν: 3342, 3272 (NH_2), 1732 (C=O), 1627 (C=N), 1540 (C=C), 1402 (N–N), 1203 (C–N), 639 (C–S) cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_4OS$: C 57.34, H 4.44, N 20.57, S 11.77; found C 57.31, H 4.47, N 20.53, S 11.79.

2-(5-Amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-methylthiazol-4(5*H*)-one (**7f**): Yellow crystals, m.p. 137–139 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.55 (3H, d, $J = 7.2$ Hz, CH_3 thiazole), 2.41 (3H, s, CH_3), 3.85 (1H, m, CH), 7.46, 7.63 (1H, m, 1H, m, NH_2), 7.55–760 (5H, m, Ph); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 190.13 (C=O), 164.50 (C-2 thiazole), 147.78 (C-5 pyrazole), 147.15 (C-3 pyrazole), 138.53 (C-1 Ph), 129.86 (C-3,5 Ph), 127.54 (C-4 Ph), 123.61 (C-2,6 Ph), 97.85 (C-4 pyrazole), 65.17 (CH), 30.58 (CH_3 thiazole), 14.78 (CH_3 pyrazole); IR (KBr) ν: 3329, 3265 (NH_2), 1736 (C=O), 1629 (C=N), 1534 (C=C), 1396 (N–N), 1194 (C–N), 659 (C–S) cm^{-1}. Anal. Calcd for $C_{14}H_{14}N_4OS$: C 58.72, H 4.93, N 19.57, S 11.20; found C 58.73, H 4.96, N 19.55, S 11.17.

Antibacterial activity

The antibacterial activity of all newly synthesized compounds was evaluated against 21 pathogenic bacteria including gram-negative strains *Pseudomonas aeruginosa*

Scheme 1 Total synthesis of 4-thiazolylpyrazoles **7a–f**

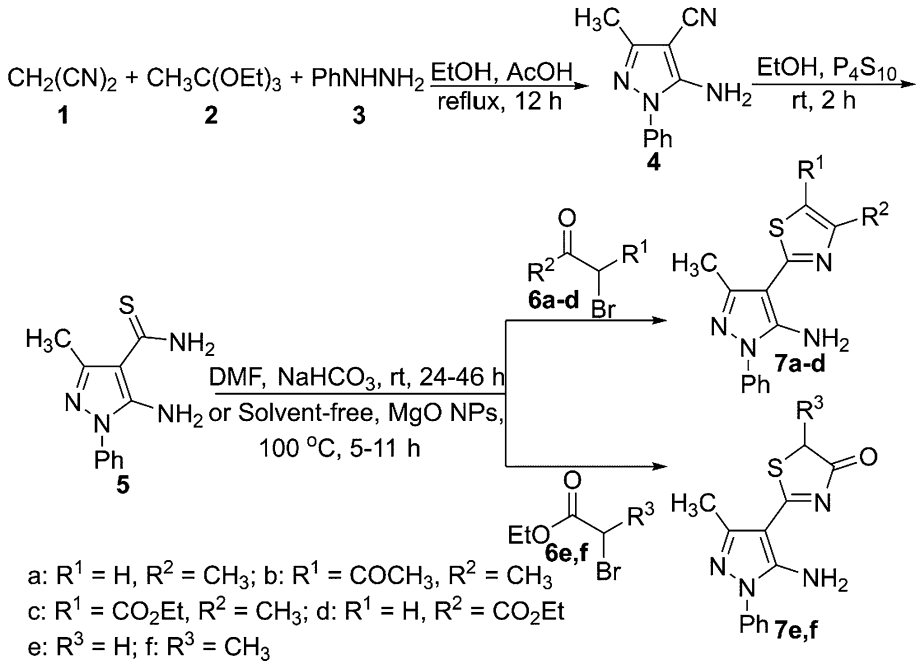


Table 1 Synthesis of Hantzsch thiazole derivatives under two different conditions

Thiazoles	α-Bromocarbonyls	Classical conditions		Modified conditions	
		Time (h)	Yield (%)	Time (h)	Yield (%)
7a	Bromoacetone	24	76	5	90
7b	3-Bromoacetylacetone	41	60	10	75
7c	Ethyl 2-bromoacetoacetate	41	77	10	91
7d	Ethyl bromopyruvate	46	52	11	68
7e	Ethyl bromoacetate	24	77	5	92
7f	Ethyl 2-bromopropionate	46	85	11	97

(PTCC 1310), *Klebsiella pneumoniae* (PTCC 1290), *Escherichia coli* (PTCC 1399), *Shigella flexneri* (PTCC 1234), *Shigella dysenteriae* (PTCC 1188), *Proteus mirabilis* (PTCC 1776), *Proteus vulgaris* (PTCC 1079), *Salmonella enterica* subsp. *enterica* (PTCC 1709), *Salmonella typhi* (PTCC 1609), *Enterococcus faecalis* (PTCC 1778) and gram-positive strains *Streptococcus pyogenes* (PTCC 1447), *Streptococcus agalactiae* (PTCC 1768), *Streptococcus equinus* (PTCC 1445), *Streptococcus pneumoniae* (PTCC 1240), *Listeria monocytogenes* (PTCC 1297), *Staphylococcus aureus* (PTCC 1189), *Staphylococcus epidermidis* (PTCC 1435), *Bacillus cereus* (PTCC 1665), *Bacillus subtilis* subsp. *spizizenii* (PTCC 1023), *Bacillus thuringiensis* subsp. *kurstaki* (PTCC 1494), and *Rhodococcus equi* (PTCC 1633) which were prepared from the Persian Type Culture Collection (PTCC), Tehran, Iran. Antibacterial activities were tested according to Clinical and Laboratory Standards Institute (CLSI) broth microdilution and disk diffusion methods described in guidelines M07-A9, M26-A and M02-A11 [42], repeated three times, and expressed as the average of three independent experiments.

Solution of all derivatives and antibiotics were prepared in DMSO and double-distilled water at initial concentrations of 9011 and 17.6 μg/mL, respectively, and these concentrations were also used to measure IZDs. In all tests, DMSO and antibiotics were used as negative and positive controls.

Results and discussion

Synthesis and spectroscopic characterization of thiazoles 7a–f

In this study, 4-thiazolylpyrazoles **7a–f** were synthesized in a three-step process (Scheme 1). Pyrazole **4** was prepared via an acid-catalyzed reaction of malononitrile (**1**),

triethyl orthoacetate (**2**), and phenylhydrazine (**3**). Thionation of pyrazole **4** by phosphorus pentasulfide (P_4S_{10}) was resulted in the formation of 5-amino-3-methyl-1-phenyl-1*H*-pyrazole-4-carbothioamide (**5**). Our efficient two-step synthesis of the desired compound (**5**) was resulted in higher yield than the four-step procedure reported by Giori et al. [43]. Finally, cyclocondensation of thioamide **5** with α-bromoketones **6a–f** formed 4-thiazolylpyrazoles **7a–f**. Through our optimization process, two different conditions were tested (classical Hantzsch vs. MgO-catalyzed reaction). Furthermore, we found that using MgO nanoparticles was resulted in higher yields and shorter reaction times as shown in Table 1.

Table 2 Optimization of the model reaction conditions

Entry	Solvent	*T* (°C)	Molar% MgO[a]	Time (h)	Yield (%)
1	DMF	rt	–	24	76
2	DMF	40	–	20	69
3	DMF	50	–	18	63
4	DMF	60	–	15	59
5	DMF	rt	1	22	78
6	DMF	rt	3	19	81
7	DMF	rt	4	17	84
8	DMF	rt	5	17	84
9	–	rt	–	19	46
10	–	40	–	16	53
11	–	60	–	14	61
12	–	80	–	12	70
13	–	90	–	12	70
14	–	rt	1	13	52
15	–	40	1	11	61
16	–	60	1	10	70
17	–	80	1	8	76
18	–	100	1	7	81
19	–	110	1	7	81
20	–	100	3	7	83
21	–	100	4	6	87
22	–	**100**	**5**	**5**	**90**
23	–	100	6	5	90

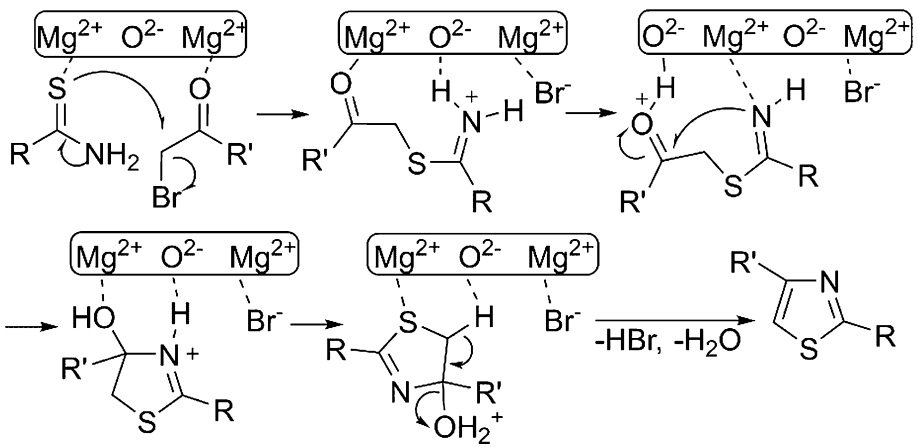
[a] In the form of nanoparticles

Similar thiazoles **7a–f** were synthesized using the classical Hantzsch protocol in order to compare with our novel procedure and demonstrated the generality of the new method. Thioamide **5** has been reacted with α-bromoketones **6a–f** in DMF at room temperature for 24–46 h under the classical Hantzsch protocol to form thiazoles **7a–f** in 52–85% yields. Besides, same products were obtained in higher yields (68–97%) under solvent-free conditions and shorter reaction times by using MgO nanocatalyst. The comparative results are shown in Table 1.

Higher yields, shorter reaction times as well as using an eco-friendly procedure are some benefits of our new procedure. It is important to notice that the MgO nanoparticles can be recycled at least three times with almost no loss of reactivity.

The reaction of thioamide **4** with bromoacetone (**6a**) in a 1:1 molar ratio was selected in order to roll out the effect of parameters such as temperature, presence or absence of solvent, and the amount of the catalyst (Table 2).

It was observed that a slightly increase in the reaction temperature decreased the product yield drastically under the classical conditions. Based on the Le Chatelier's principle, this might happen due to the increase in the solubility of the product in DMF at higher temperatures which in turn decreased the conversion of the reactants to the desired products (Entries 1–4). The yield was improved when MgO nanoparticles were added to the reaction mixture in DMF at room temperature (Entries 5–8). Under solvent- and catalyst-free conditions, an increase in the temperature to 80 °C led to increase in the yield and decrease in the reaction time (Entries 9–13). It was shown that eliminating the solvent and increasing the reaction temperature in the presence of 1 mol% of the catalyst improved the yield and shortened the reaction time as well (Entries 14–19). Further increase



Scheme 2 A proposed mechanism for the Hantzsch thiazole synthesis in the presence of MgO nanoparticles

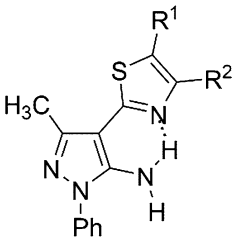


Fig. 1 Formation of intramolecular hydrogen bonding in thiozoles

in the reaction temperature as well as the amount of the catalyst improved the yield to 90% (Entry 22). The highest yield with the shortest time was obtained under solvent-free conditions and in the presence of 5 molar% MgO nanoparticles at 100 °C and considered as the optimal condition.

The role of the MgO nanoparticle in this reaction has been illustrated by a plausible mechanism in Scheme 2. The dual nature of acidic and basic MgO has helped to catalyze different stages of this reaction.

The chemical structures of compounds **6** and **7a–f** were confirmed based on their ^{1}H, ^{13}C-NMR, and other analytical data. Methyl and phenolic proton signals of pyrazole ring system in compounds **7a–f** were, respectively, appeared within δ = 2.37–2.42 and 7.54–7.80 ppm. The two hydrogens of the amino group (NH_2) were appeared in different chemical shifts probably due to intramolecular hydrogen bonding with nitrogen of thiazole ring as shown in Fig. 1. The ^{13}C-NMR spectra of these products were exhibited signals within δ = 14.32–15.17, 123.29–138.79, 97.68–99.45, 145.26–149.70, 146.52–150.11 ppm which attributed, respectively, to methyl, phenyl, 4-, 3-, and 5-carbons of pyrazole ring system. Also, signals within δ = 161.17–185.41 ppm were assigned to the 2-carbons of thiazole ring

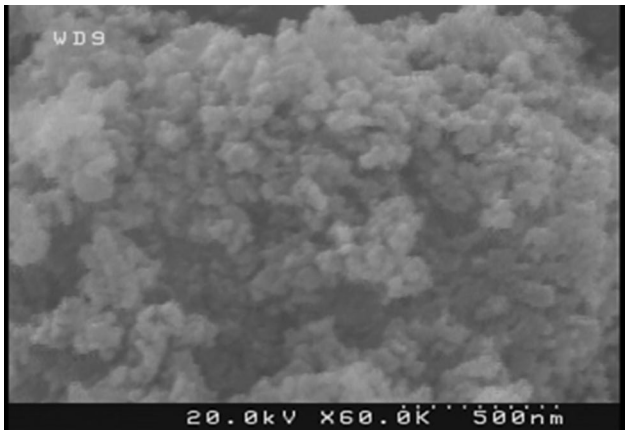


Fig. 3 SEM image of prepared MgO nanoparticles

system. In the FT-IR spectra of thiazole derivatives, absorption bands within ν = 3262–3314 and 3314–3442 cm^{-1} were determined to correspond to symmetric and asymmetric stretching vibrations of the amino groups. The microanalytical data also confirmed the purity of all products.

Structure of applied MgO nanoparticles was characterized using XRD and SEM techniques and illustrated in Figs. 2 and 3, respectively. In XRD pattern, the sharp and intense main peaks were found around 2θ values of 42.7 and 62.06 with (110) and (200) crystal planes, confirmed crystalline structure of MgO [39]. The average crystallite size of nanoparticles is estimated from Scherrer equation as to be 23.7 and 25.7 nm. The morphology of the synthesized nanocrystals was determined by SEM and their particle size found to be in the range 30–50 nm. Dense flakes form of nanoparticles is also obvious in Fig. 3.

Fig. 2 XRD spectrum of the chemically synthesized MgO nanoparticles

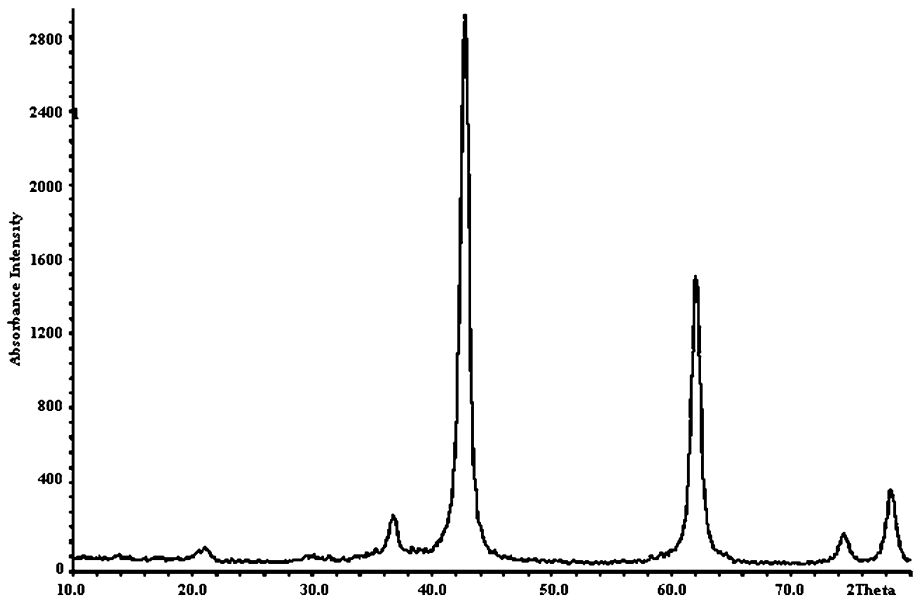


Table 3 Screening of IZD, MIC, and MBC of the newly synthesized derivatives and antibiotics against some gram-positive and gram-negative bacteria

Bacteria	Products/Antibiotics								
	6	**7a**	**7b**	**7c**	**7d**	**7e**	**7f**	Ceftriaxone	Penicillin
1310									
IZD	12.23	19.16	11.57	18.25	15.61	18.34	16.27	16.2	–
MIC	1024	1024	512	1024	1024	1024	1024	0.5	–
MBC	2048	2048	1024	2048	2048	2048	2048	1	–
1665									
IZD	–	8.78	9.40	–	–	–	11.08	–	–
MIC	–	1024	1024	–	–	–	512	–	–
MBC	–	4096	2048	–	–	–	2048	–	–
1079									
IZD	–	–	18.33	–	–	–	–	–	12.82
MIC	–	–	1024	–	–	–	–	–	8
MBC	–	–	1024	–	–	–	–	–	32
1399									
IZD	–	–	–	–	–	–	10.92	31.49	–
MIC	–	–	–	–	–	–	1024	8	–
MBC	–	–	–	–	–	–	2048	8	–
1240									
IZD	–	12.85	15.39	13.47	17.03	16.26	15.09	–	12.20
MIC	–	128	512	256	2048	256	256	–	8
MBC	–	256	512	512	4096	512	512	–	16
1189									
IZD	–	–	18.06	13.54	10.28	–	18.62	15.36	18.32
MIC	–	–	1024	2048	2048	–	256	4	8
MBC	–	–	2048	4096	4096	–	512	16	32
1778									
IZD	–	–	8.93	10.65	–	–	–	18.38	23.64
MIC	–	–	512	512	–	–	–	1	8
MBC	–	–	1024	1024	–	–	–	2	16
1297									
IZD	10.48	–	–	4.74	–	–	–	8.27	22.11
MIC	1024	–	–	2048	–	–	–	8	8
MBC	2048	–	–	4096	–	–	–	8	16
1768									
IZD	13.89	11.29	11.57	20.14	8.06	7.73	16.37	–	–
MIC	32	64	1024	512	512	256	128	–	–
MBC	64	64	2048	1024	4096	1024	256	–	–
1435									
IZD	12.86	7.58	10.06	16.43	8.18	–	9.64	18.54	23.58
MIC	512	256	256	256	512	–	1024	0.5	0.5
MBC	1024	512	512	512	1024	–	1024	2	1
1445									
IZD	8.74	7.86	–	–	–	7.82	10.22	8.09	13.61
MIC	1024	256	–	–	–	512	1024	8	8
MBC	2048	512	–	–	–	2048	2048	16	32

IZD (mm), MIC (μg/mL), MBC (μg/mL)

–, no noticeable antibacterial effect at selected highest concentration

Antibacterial evaluation of the newly synthesized compounds

The in vitro antibacterial effects of the newly synthesized derivatives in comparison to antibiotics such as ceftriaxone and penicillin were evaluated and presented as IZD, MIC, and MBC values in Table 3. Since the synthesized derivatives at the initial concentrations were ineffective against some bacteria, their data has not been given in this table.

The derivatives had an inhibitory activity against various bacterial families of both gram-positive and gram-negative strains. All 4-thiazolylpyrazoles **7a–f** showed inhibitory properties toward *P. aeruginosa*, *S. pneumoniae,* and *S. agalactiae*. Thiazoles **7b**, **f** in comparison to others were effective on eight pathogenic bacteria, as the result they came out as the most broad-spectrum agents. The inhibitory effects against *P. vulgaris* were only observed from thiazole **7b** and penicillin. Thiazole **7f** and ceftriaxone were also identified to be the only effective compounds against *E. coli*. The best inhibitory effect was observed in thioamide **6** with MIC and MBC values of 32 and 64 μg/mL, respectively, against *S. agalactiae.*

Conclusion

Some new thiazole derivatives were synthesized using modified Hantzsch method in the presence of MgO nanocatalyst under solvent-free conditions. The present protocol has the benefits such as greater efficiency, shorter reaction time, and higher product yield over the classical condition. Finally, the in vitro antibacterial activities of the newly synthesized compounds were examined against a variety of pathogenic bacteria. Moderate to good activities were observed for all derivatives. The inhibitory effects of all synthesized compounds against *S. agalactiae* were successfully demonstrated, while antibiotics such as ceftriaxone and penicillin were ineffective on this pathogen.

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References

1. A. Ayati, S. Emami, A. Asadipour, A. Shafiee, A. Foroumadi, Eur. J. Med. Chem. **97**, 699 (2015)
2. Z. Xu, T. Ye, in Heterocycles, in *Natural Product Synthesis*, ed. by K.C. Majumdar, S.K. Chattopadhyay (Wiley-VCH, Weinheim, 2011), pp. 459–505
3. V. Gupta, V. Kant, Sci. Int. **1**, 253 (2013)
4. F. Sasse, H. Steinmetz, G. Höfle, H. Reichenbach, J. Antibiot. **56**, 520 (2003)
5. M.Y. Kim, H. Vankayalapati, K. Shin-Ya, K. Wierzba, L.H. Hurley, J. Am. Chem. Soc. **124**, 2098 (2002)
6. C.B. Mishra, S. Kumari, M. Tiwari, Eur. J. Med. Chem. **92**, 1 (2015)
7. P.W. Sheldrake, M. Matteucci, E. McDonald, Synlett **2006**, 460 (2006)
8. G.S. Lingaraju, T.R. Swaroop, A.C. Vinayaka, K.S.S. Kumar, M.P. Sadashiva, K.S. Rangappa, Synthesis **44**, 1373 (2012)
9. D. Castagnolo, M. Pagano, M. Bernardini, M. Botta, Synlett **2009**, 2093 (2009)
10. J.F. Sanz-Cervera, R. Blasco, J. Piera, M. Cynamon, I. Ibáñez, M. Murguía, S. Fustero, J. Org. Chem. **74**, 8988 (2009)
11. M. Narender, M.S. Reddy, V.P. Kumar, B. Srinivas, R. Sridhar, Y.V.D. Nageswar, K.R. Rao, Synthesis **2007**, 3469 (2007)
12. Y. Ishiwata, H. Togo, Synlett **2008**, 2637 (2008)
13. U. Kazmaier, S. Ackermann, Org. Biomol. Chem. **3**, 3184 (2005)
14. P.B. Gorepatil, Y.D. Mane, V.S. Ingle, Synlett **24**, 2241 (2013)
15. Y. Sun, H. Jiang, W. Wu, W. Zeng, X. Wu, Org. Lett. **15**, 1598 (2013)
16. T.B. Nguyen, L. Ermolenko, W.A. Dean, A. Al-Mourabit, Org. Lett. **14**, 5948 (2012)
17. T. Guntreddi, R. Vanjari, K.N. Singh, Org. Lett. **17**, 976 (2015)
18. X. Zhang, W. Zeng, Y. Yang, H. Huang, Y. Liang, Org. Lett. **16**, 876 (2014)
19. H. Zheng, Y.J. Mei, K. Du, X.T. Cao, P.F. Zhang, Molecules **18**, 13425 (2013)
20. M. Kodomari, T. Aoyama, Y. Suzuki, Tetrahedron Lett. **43**, 1717 (2002)
21. S.L. You, J.W. Kelly, Tetrahedron **61**, 241 (2005)
22. J. Hämmerle, M. Spina, M. Schnürch, M.D. Mihovilovic, P. Stanetty, Synthesis **2008**, 3099 (2008)
23. H. Beyzaei, R. Aryan, H. Moghadas, J. Serbian Chem. Soc. **80**, 453 (2015)
24. F.L. Chubb, J.T. Edward, Can. J. Chem. **59**, 2724 (1981)
25. S.M. Al-Mousawi, M.S. Moustafa, M.H. Elnagdi, Arkivoc **2010**, 224 (2010)
26. M. Suresh, P. Lavanya, C.V. Rao, Arab. J. Chem. **9**, 136 (2016)
27. J. Banothu, K. Vaarla, R. Bavantula, P.A. Crooks, Chin. Chem. Lett. **25**, 172 (2014)
28. A. Safari, Z. Abedi-Jazini, Z. Zarnegar, M. Sadeghi, J. Nanoparticle Res. **17**, 495 (2015)
29. M.W. Bredenkamp, C.W. Holzapfel, W.J. van Zyl, Syn. Commun. **20**, 2235 (1990)
30. V.E. Bhingolikar, S.R. Mahalle, S.P. Bondge, R.A. Mane, Indian J. Chem. **44B**, 2589 (2005)
31. A.S. Shahvelayati, I. Yavari, A.S. Delbari, Chin. Chem. Lett. **25**, 119 (2014)
32. I. Yavari, A. Malekafzali, S. Seyfi, J. Iran. Chem. Soc. **11**, 285 (2014)
33. H. Zali-Boeini, S.G. Mansouri, J. Iran. Chem. Soc. **13**, 1571 (2016)
34. T.M. Potewar, S.A. Ingale, K.V. Srinivasan, Tetrahedron **63**, 11066 (2007)
35. B.S. Dawane, S.G. Konda, V.T. Kamble, S.A. Chavan, R.B. Bhosale, B.M. Shaikh, Eur. J. Chem. **6**, 358 (2009)
36. S.M. Gomha, K.D. Khalil, Molecules **17**, 9335 (2012)
37. P.S. Shisode, P.P. Mahulikar, J. Chem. Pharm. Res. **2**, 576 (2010)
38. L. Zeng, K. Li, F. Huang, X. Zhu, H. Li, Chin. J. Catal. **37**, 908 (2016)
39. M. Sundrarajan, J. Suresh, R. Gandhi, Dig. J. Nanomater. Biostruct. **7**, 983 (2012)
40. F. Allouche, F. Chabchoub, F. Carta, C.T. Supuran, J. Enzyme Inhib. Med. Chem. **28**, 343 (2013)
41. B. Kaboudin, D. Elhamifar, Synthesis **2006**, 224 (2006)
42. M. Balouiri, M. Sadiki, S.K. Ibnsouda, J. Pharm. Anal. **6**, 71 (2016)
43. P. Giori, A.C. Veronese, C.B. Vicentini, M. Guarneri, J. Heterocycl. Chem. **22**, 1093 (1985)