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Full Paper

One-Pot Multi-Component Synthesis of 1,4-Dihydropyridines Using Zn^{2+}@KSF and Evaluating Their Antibacterial and Antioxidant Activities

Nosrat O. Mahmoodi, Sahar Ramzanpour, and Fateme Ghanbari Pirbasti

Department of Chemistry, Faculty of Science, University of Guilan, Rasht, Iran

New 5-aryl-10-(4-(4-methoxyphenyl)thiazole-2-yl)-9,10-dihydropyrido[2,3-d:5,6-d′]dipyrimidinone-2,4,6,8-(1*H*,3*H*,5*H*,7*H*)-tetraones **6a–d** were synthesized through one-pot four-component reaction of aldehydes, barbituric acid, and thiazole using Zn^{2+}@KSF under reflux condition. The key features of this reaction are: incorporating four heterocyclic rings, using a heterogeneous and efficient catalyst, high yield, and easy-to-setup reaction. The structure of the products was confirmed by FT-IR, ^{1}H NMR, and ^{13}C NMR spectra. The antibacterial activities of compounds **6a–d** were screened against *Escherichia coli*, *Micrococcus luteus*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* bacterial strains using the zone inhibition method. Also, the 2,2-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activities of compounds **6a–d** were evaluated. All compounds showed good antioxidant capacity in comparison to ascorbic acid. The IC_{50} values of the antioxidant activity were calculated. The proposed mechanism for antioxidant activity is discussed.

Keywords: Antibacterial / Antioxidant / Barbituric acid / 1,4-Dihydropyridines / Zn^{2+}@KSF

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Introduction

1,4-Dihydropyridines (1,4-DHPs) are used commercially such as diludine, felodipine, amlodipine, and nimodipin and also they possess various biological activities such as cardiovascular [1], HIV protease inhibition [2], antioxidant [3], anti-inflammatory [4], calcium channel blocker [5], analgesic [6], antitumor [7], antithrombotic [8], anticonvulsant [9], antimicrobial [10], and anticoagulant [11].

Thiazoles have been found to be associated with a wide variety of biological activities, such as antibacterial [12, 13], antifungal [14], anti-inflammatory [15], antimalarial [16], antioxidant [17], antitumor [18], antimicrotubule [19], and antihypertension [20].

Correspondence: Dr. Nosrat O. Mahmoodi, Department of Organic Chemistry, Faculty of Science, University of Guilan, PO Box 41335-1914, Rasht, Iran.
E-mail: mahmoodi@guilan.ac.ir, nosmahmoodi@gmail.com
Fax: +98-1313233262

Barbituric acid and its derivatives are found in many drugs [21–23]. These compounds are most important classes of drug molecules and were introduced for medical use in 1911 [24]. They have attracted much attention due to their antiviral [25], antibiotic [26], anti-inflammatory [27], and antitumor [28] activities. The biological activities and their ability to be functionalized made barbituric acids a useful starting material for synthesis of fused rings.

The scope of heterogeneous catalytic organic transformations is rapidly growing due to their well-documented advantages over homogeneous catalytic systems. Montmorillonite KSF has been used as catalysts in organic reactions and has represented several advantages over traditional acids. Such as the strong acidity, non-corrosive properties, mild reaction conditions, cheapness, high yields and selectivity, and the facility of setting and working-up. Recently, we used KSF as an efficient catalyst for synthesis of pyridazinones and phthalazinones [29–31], Schiff bases [32], 2-(thiazol-2-yl)-4,5-dihydropyridazin-3(2*H*)-one [33], and mono- and bis-indolylimidazole [34].

Following our prior efforts in the design and synthesis of heterocyclic compounds [35–40], and also regarding diverse

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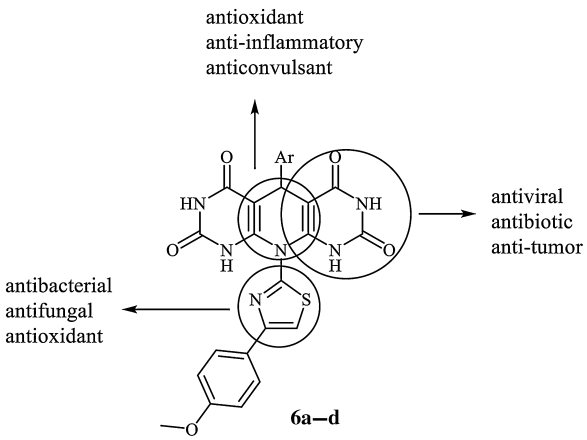


Figure 1. Structure of products **6a–d** and defining biological activities of each moiety.

biological activities of thiazoles and barbituric acids mentioned above, we report one-pot semi-four-component synthesis of novel 1,4-dihydropyridines bearing thiazole moiety using Zn^{2+}@KSF as a green catalyst (Fig. 1).

Results and discussion

Chemistry

A survey in literature showed that different 1,4-DHPs have been synthesized; however, 1,4-DHPs bearing thiazole moiety as N source of 1,4-DHPs ring of barbituric acid have not been reported yet.

Herein, we report an efficient method for regioselective synthesis of new 1,4-DHPs **6a–d** using premade thiazole **3** as amine part through one-pot 4 MCRs. 4-(4-Methoxyphenyl)-thiazole-2-amine **3** was prepared from reaction of 2-bromo-1-(4-methoxyphenyl)ethanone **1** with thiourea **2** in EtOH under reflux condition in high yield as a white powder [41] (Scheme 1).

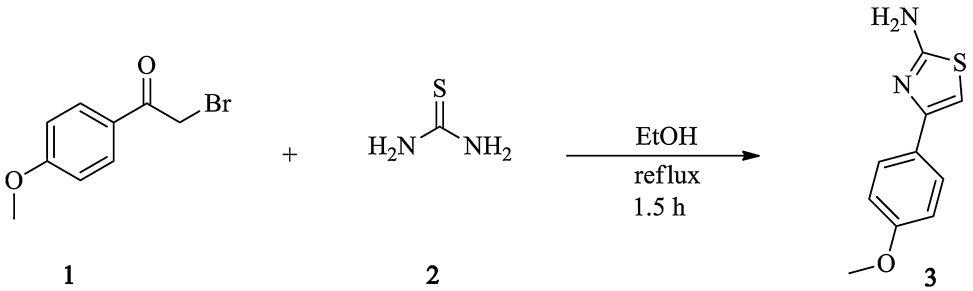
In this effort the reaction of 1 eq. of prepared thiazole **3**, 2 eq. barbituric acid **4**, and 1 eq. aldehydes **5a–d** in the presence of catalytic amount of Zn^{2+}@KSF under reflux condition led to preparation of 5-aryl-10-(4-(4-methoxyphenyl)thiazole-2-yl)-9,10-dihydropyrido[2,3-d:5,6-d′]dipyrimidinone-2,4,6,8-(1*H*,3*H*,5*H*,7*H*)-tetraones **6a–d** in reasonable yields (Scheme 2).

In order to establish the optimized reaction conditions, the reaction of thiazole **3** (1 mmol), barbituric acid **4** (2 mmol), and 4-nitrobenzaldehyde **5a** (1 mmol) under different conditions such as nature of solvent, type and amount of catalyst and reaction temperature were examined (Table 1). It was found that the reaction without any catalyst proceeded slowly with low yield after refluxing for 24 h (entry 1, Table 1). However, by using different catalysts under reflux condition in EtOH, the reaction yields increased; by using Zn^{2+}@KSF as catalyst in EtOH (78°C), the product obtained a higher yield and shorter reaction time (entry 5, Table 1). Also, the effect of different solvents such as ethylene glycol, EtOH, MeOH, AcOH, H_2O, DMF, and acetone was examined. When the reaction was carried out in EtOH the results showed that higher yields and shorter reaction times were obtained (entry 5, Table 1). Moreover, the amount of catalyst Zn^{2+}@KSF was investigated; by decreasing the amount of catalyst to 0.01 g (entry 6, Table 1), the yield decreased, on the other hand by increasing the amount of catalyst to 0.06 g (entry 7, Table 1), a slight increase in yield was observed. So, 0.03 g Zn^{2+}@KSF per 1 mmol substrate was efficient for the reaction. In the other efforts, the effect of temperature on the yield of product was studied.

Low yield of product was isolated at room temperature (entry 8, Table 1), by increasing the temperature from 78 to 120°C (entries 5, 9, 10, Table 1), a decrease of yield was observed. As a result, the optimized condition for synthesis of 1,4-DHPs **6a–d** was obtained in the presence of Zn^{2+}@KSF (0.03 g) in EtOH at 78°C.

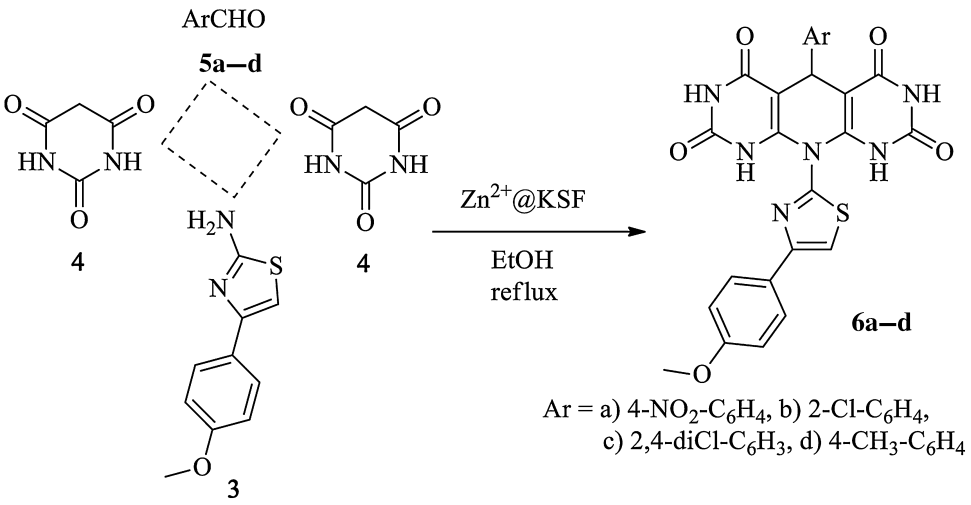
According to proposed mechanism (Scheme 3), nucleophilic addition of barbituric acid **4** to activated aldehyde **7** in the presence of catalyst led to intermediate **8** which becomes involved in the addition reaction with second molecule of **4** and subsequent addition of **3** to adduct **9** *via* **10** by losing water and finally further intramolecular cyclization led to **6a–d**.

The structure of products **6a–d** was characterized by FT-IR, ^{1}H NMR, and ^{13}C NMR spectra. The FT-IR spectra of compounds **6a–d** reveal the presence of two N–H stretching vibrations in 3450–3250 and 3280–3120 cm^{-1}, absorbance of C=O amide appeared in 1660–1700 cm^{-1}. In the ^{1}H NMR spectra of compounds **6a–d**, two singlets in 10.22–9.27 and 8.87–8.39 ppm are related to N–H of barbituric moiety, a sharp singlet in the 5.83–5.57 is due to C–H of 1,4-DHP and confirms the formation of 1,4-DHP ring.



1 2 3

Scheme 1. Preparation of 4-(4-metoxyphenyl)thiazole-2-amine **3**.



Scheme 2. Synthesis of 5-aryl-10-(4-(4-methoxyphenyl)thiazole-2-yl)-9,10-dihydropyrido[2,3-d:5,6-d′]dipyrimidinone-2,4,6,8-(1*H*,3*H*,5*H*,7*H*)-tetraones **6a**–**d**.

Sharp singlet in 5.99–5.87 ppm is related to C–H of the thiazole moiety, and methoxy group appeared in 3.77–3.76 ppm as a singlet. Aromatic protons appeared in the expected region 8.06–6.92 ppm. The ^{13}C NMR spectra of compounds **6a–d** reveal signal of 1,4-DHP carbons in 38.8–35.8 ppm which confirms the formation of 1,4-DHP ring, and methoxy group in 55.5–55.7 ppm. Other signal appeared in 86.8–169.4 ppm.

Antibacterial activity

Compounds **6a–d** were evaluated for their *in vitro* antibacterial activity against *Escherichia coli* (*E. coli*), *Micrococcus luteus* (*M. luteus*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Staphylococcus aureus* (*S. aureus*) by zone inhibition method. DMSO was used as negative control and penicillin G and cefixim were used as standard drugs. The concentration of compounds was 4000 μg/mL in DMSO as solvent. Results are summarized in Table 2. According to the results, compound **6a** had the most antibacterial activity against *E. coli* whereas it had the least antibacterial activity against *S. aureus*. Moreover, compound **6c** showed potent antibacterial activity against *S. aureus* and *M. luteus*. Recently, Lobo et al. [42] reported that the presence of NO_2 and Cl group has a positive effect against bacterial strains. Here, in our study, compound **6a** bearing nitro and compound **6c** bearing two Cl groups had good antibacterial activity. All the synthesized compounds showed weak antibacterial activity against *P. aeruginosa*.

Antioxidant assay

DPPH or 2,2-diphenyl-2-picrylhydrazyl is a stable free radical that can accept an electron or hydrogen radical and can be

Table 1. Optimization of the reaction conditions.

Entry	Solvent	Catalyst	Amount of catalyst (g)	Temperature (°C)	Time (h)	Yield (%)
1	EtOH	–	–	78	24	20
2	EtOH	*p*-TSA	0.03	78	6	72
3	EtOH	$ZnCl_2$	0.03	78	9	65
4	EtOH	KSF	0.03	78	4	50
5	EtOH	Zn^{2+}@KSF	0.03	78	2	84
6	EtOH	Zn^{2+}@KSF	0.01	78	2	55
7	EtOH	Zn^{2+}@KSF	0.06	78	2	86
8	EtOH	Zn^{2+}@KSF	0.03	rt	2	33
9	EtOH	Zn^{2+}@KSF	0.03	100	2	72
10	EtOH	Zn^{2+}@KSF	0.03	120	2	65
11	Ethylene glycol	Zn^{2+}@KSF	0.03	100	3	45
12	AcOH	Zn^{2+}@KSF	0.03	100	2.5	62
13	DMF	Zn^{2+}@KSF	0.03	100	3	51
14	MeOH	Zn^{2+}@KSF	0.03	65	2	82
15	H_2O	Zn^{2+}@KSF	0.03	100	4	60
16	Acetone	Zn^{2+}@KSF	0.03	50	3	60

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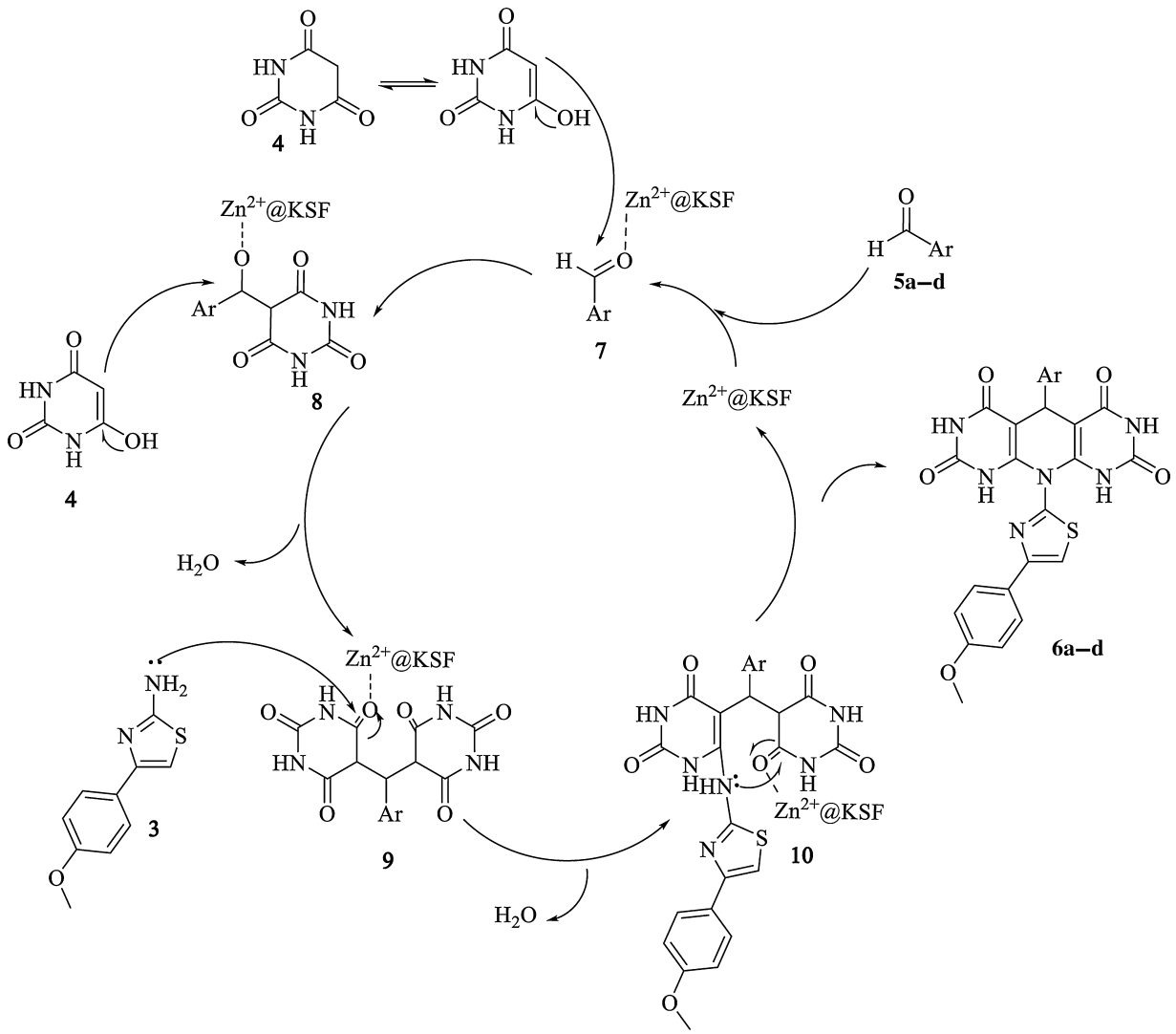

Scheme 3. Proposed mechanism for the formation of **6a–d**.

Table 2. **Antibacterial activity of newly synthesized compounds 6a–d as zone of inhibition (mm).**

Compound	Antibacterial activity (mean ± SD)			
	S. aureus	*M. luteus*	*E. coli*	*P. aeruginosa*
6a	6.66 ± 0.57	9.50 ± 2.12	18.33 ± 2.08	8.33 ± 1.15
6b	7.50 ± 0.70	6.50 ± 0.70	7.66 ± 1.52	7.33 ± 0.57
6c	11.66 ± 0.57	13.00 ± 1.41	8.66 ± 1.52	7.33 ± 0.57
6d	6.50 ± 0.70	9.00 ± 1.41	8.00 ± 1.00	–
DMSO[a)]	–	–	–	–
Penicillin G[b)]	23	55	45	24
Cefixim[b)]	38	35	39	30

[a)] Negative control.
[b)] Positive control.

converted to a stable molecule. DPPH has a strong absorption band at 517 nm, when DPPH radical accepts an electron from other compound, its absorption band will decrease. The decrease in absorption band depends on the tested compounds antioxidant capacity. Higher antioxidant capacity of the tested compound led to more decrease of absorption band. Radical scavenging activity of compounds **6a–d** was determined in concentrations 2000–62.5 μg/mL in methanol. Also, their IC_{50} values were reported which is the concentration of tested compound required to scavenge 50% of the DPPH radical concentration (6.25×10^{-6} M). The experiments were conducted in triplicate. All compounds showed antioxidant activity. According to Fig. 2 radical scavenging activity was dose dependent and increased with concentration of the compounds **6a–d**. Compound **6d** exhibited the highest DPPH radical scavenging whereas compound **6b** had the lowest DPPH radical scavenging capacity. The IC_{50} values were calculated according to line equations and are reported in Table 3. The IC_{50} values were between 1.28 and 0.33 mg/mL. Compound **6d** had the lowest IC_{50} value (0.33 mg/mL) in comparison to ascorbic acid (0.38 mg/mL).

The good antioxidant activity of compounds **6a–d** can be due to N–H groups of barbituric acid component which can donate H radical to DPPH and then conjugate through system. Also, C–H bond on the DHP ring can release H radical to DPPH. The highest antioxidant capacity of compound **6d** in comparison to other derivatives can be due to methyl group on aromatic ring which can donate H radical and can be converted to a stable benzyl radical which can resonate in molecule and stabilize the radical through the whole compound. The proposed radical molecules for compound **6d** are depicted in Scheme 4.

Conclusion

In conclusion, a convenient, efficient, high yield, simple setup, and work-up, one-pot, semi-four-component procedure for synthesis of novel 5-aryl-10-(4-(4-methoxyphenyl)thiazole-2-yl)-9,10-dihydropyrido[2,3-d:5,6-d′]dipyrimidinone-2,4,6,8-(1*H*,3*H*,5*H*,7*H*)-tetraones **6a–d** bearing four heterocyclic moiety was reported. The synthesis was performed by the reaction of barbituric acid, aldehydes, and 4-(4-methoxyphenyl)thiazole-2-amine in the presence of Zn^{2+}@KSF as an efficient catalyst. Compound **6c** showed good antibacterial activity against *S. aureus* and *M. luteus*, whereas compound **6a** exhibited good antibacterial activity against *E. coli.* All compounds showed good and reasonable DPPH radical scavenging activity, compound **6d** exhibited very high antioxidant capacity in comparison to ascorbic acid.

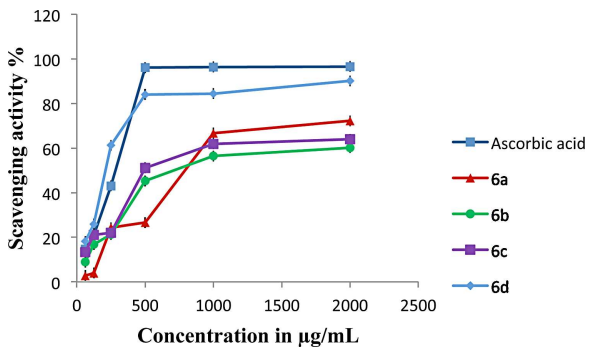

Figure 2. DPPH radical scavenging activity of compounds **6a–d**.

Table 3. IC_{50} for DPPH assay of compounds 6a–d and comparison to ascorbic acid.

Compound	DPPH assay IC_{50} (mg/mL)
6a	1.11
6b	1.28
6c	1.12
6d	0.33
Ascorbic acid	0.38

Experimental

Chemistry

Zn^{2+}@KSF was prepared according to the literature procedure [43]. The ^{1}H NMR spectra were obtained on a Bruker Avance 400 MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker 100 MHz instrument. DMSO-d_6 was used as solvent. FT-IR spectra were measured with a Shimadzu IR-470 spectrophotometer. Melting points are uncorrected and were determined using a MettlerFp5 apparatus. DPPH radical scavenging activity was recorded on UNICO 1200 spectrophotometer. All chemicals were purchased from Aldrich, Merck, and Fluka.

General procedure for the synthesis of 5-aryl-10-(4-(4-methoxyphenyl)thiazole-2-yl)-9,10-dihydropyrido[2,3-d:5,6-d′]dipyrimidinone-2,4,6,8-(1H,3H,5H,7H)-tetraones ***6a–d***

Thiazole **3** (1 mmol), barbituric acid **4** (2 mmol), aldehydes **5a–d** (1 mmol), and 0.03 g Zn^{2+}@KSF were dissolved in EtOH (10 mL), the mixture was refluxed for the required time (2 h). The progress of the reaction was controlled by TLC (*n*-hexane/EtOAc 6:3). After completion of the reaction, the hot mixture was filtered to remove the catalyst, then cooled down, and the solid filtered off and washed with hot water for purification.

*10-(4-(4-Methoxyphenyl)thiazole-2-yl)-5-(4-nitrophenyl)-9,10-dihydropyrido[2,3-d:5,6-d′]dipyrimidone-2,4,6,8-(1H,3H,5H,7H)-tetraone (**6a**)*

Cream solid, yield 84%; m.p. 320–323°C; FT-IR (KBr, ν cm^{-1}): 3340, 3200, 2850, 1710, 1680, 1600, 1510, 1540, 1340, 1460, 1250, 1010, 830, 780, 660. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 10.22 (s, br. 2H, H_f, NH), 8.87 (s, br. 2H, H_e, NH), 8.06 (d,

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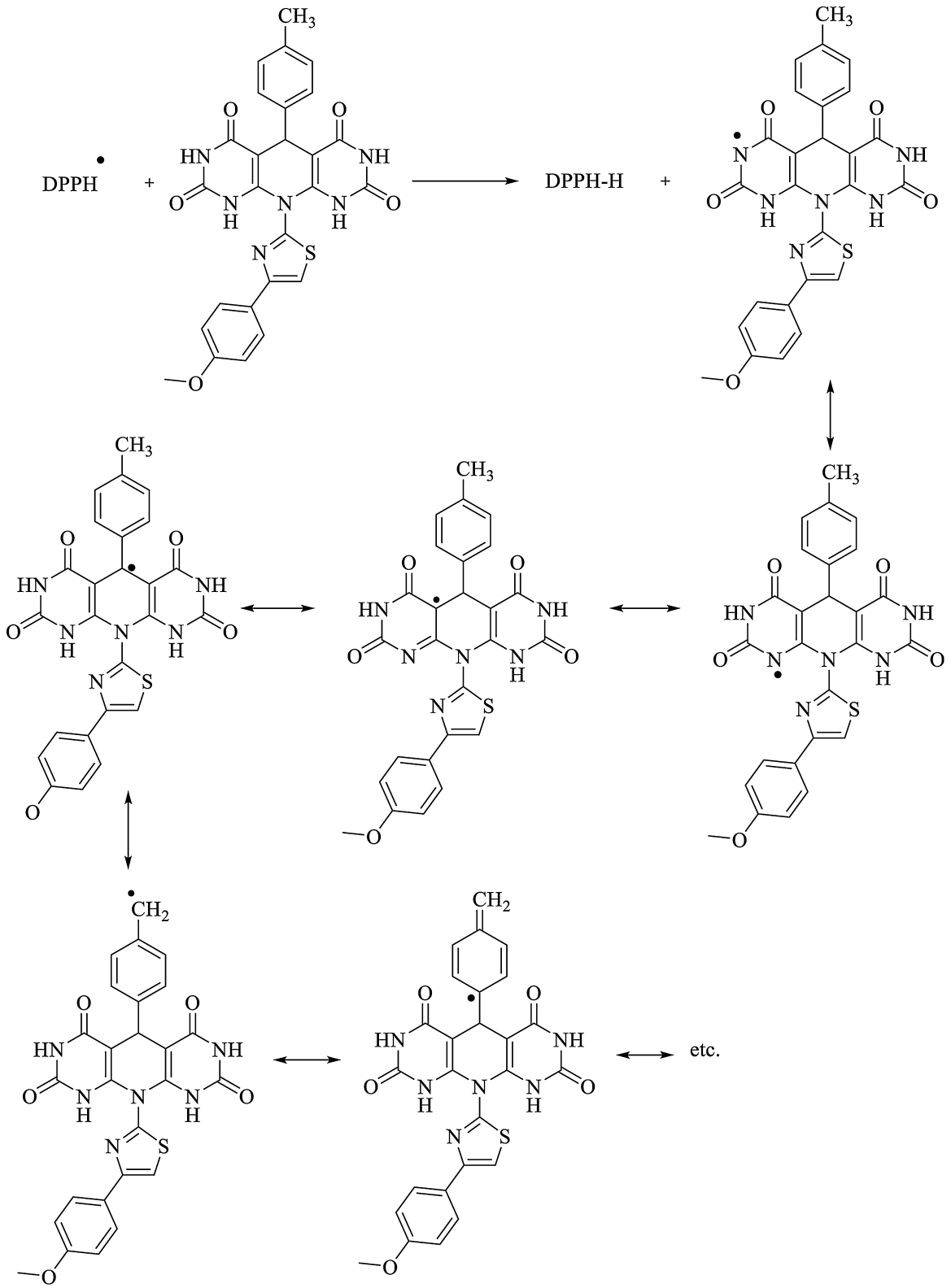

Scheme 4. DPPH radical scavenging with DHP **6d**.

$J = 8.8$ Hz, 2H, H_i), 7.38 (d, $J = 8.4$ Hz, 2H, H_c), 7.29 (d, $J = 8.4$ Hz, 2H, H_h), 7.01 (d, $J = 8.8$ Hz, 2H, H_b), 5.99 (s, 1H, H_d), 5.57 (s, 1H, H_g), 3.76 (s, 3H, H_a). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 169.4, 165.1, 160.6, 154.0, 150.9, 146.79, 145.5, 130.9, 128.3, 123.3, 121.1, 114.6, 97.9, 88.8, 55.7, 38.8. Anal. calcd. for $C_{25}H_{17}N_7O_7S$: C, 53.66; H, 3.05; N, 17.54. Found: C, 53.68; H, 3.07; N, 17.51%.

10-(4-(4-Methoxyphenyl)thiazole-2-yl)-5-(2-chlorophenyl)-9,10-dihydropyrido[2,3-d:5,6-d′]-dipyrimidone-2,4,6,8-(1H,3H,5H,7H)-tetraone ***(6b)***
White solid, yield 82%; m.p. 322–324°C; FT-IR (KBr, ν cm^{-1}): 3250, 3150, 3050, 2950, 2820, 1700, 1660, 1600, 1570, 1510, 1470, 1350, 1260, 1030, 1090. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 9.35 (s, br. 2H, H_f, NH), 8.39 (s, br. 2H, H_e, NH), 7.63 (d, $J = 7.2$ Hz, 1H, H_k), 7.32 (d, $J = 8$ Hz, 2H, H_c), 7.25–7.10 (m, 3H, H_h, H_i, H_j), 6.92 (d, $J = 8.8$ Hz, 2H, H_b), 5.87 (s, 1H, H_d), 5.67 (s, 1H, H_g), 3.77 (s, 3H, H_a). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 168.5, 163.9, 159.9, 152.1, 151.1, 150.0, 142.0, 133.0, 131.4, 130.2, 129.3, 127.3, 126.5, 123.9, 114.3, 99.8, 86.8, 55.6, 36.2. Anal. calcd. for $C_{25}H_{17}ClN_6O_5S$: C, 54.69; H, 3.13; N, 15.29. Found: C, 54.72; H, 3.15; N, 15.31%.

10-(4-(4-Methoxyphenyl)thiazole-2-yl)-5-(2,4-dichlorophenyl)-9,10-dihydropyrido[2,3-d:5,6-d′]-dipyrimidone-2,4,6,8-(1H,3H,5H,7H)-tetraone ***(6c)***
White solid, yield 80%; m.p. 321–323°C; FT-IR (KBr, ν cm^{-1}): 3450, 3280, 3120, 2950, 2820, 1700, 1660, 1600, 1580, 1510, 1460, 1370, 1250, 1030, 1100. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 9.48 (s, br. 2H, H_f, NH), 8.53 (s, br. 2H, H_e, NH), 7.62 (d, $J = 8.8$ Hz, 1H, H_i), 7.37 (s, 1H, H_j), 7.28 (d, $J = 8$ Hz, 2H, H_c), 7.15 (d, $J = 8.8$ Hz, 1H, H_h), 6.94 (d, $J = 8$ Hz, 2H, H_b), 5.87 (s, 1H, H_d), 5.83 (s, 1H, H_g), 3.76 (s, 3H, H_a). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 168.7, 163.9, 160.9, 152.1, 151.1, 142.1, 141.0, 133.7, 132.8, 131.9, 131.4, 130.3, 130.2, 127.3, 126.6, 126.1, 114.3, 99.9, 86.8, 55.5, 35.8. Anal. calcd. for $C_{25}H_{16}Cl_2N_6O_5S$: C, 51.48; H, 2.76; N, 14.39. Found: C, 51.50; H, 2.74; N, 14.41%.

10-(4-(4-Methoxyphenyl)thiazole-2-yl)-5-(paratolyl)-9,10-dihydropyrido[2,3-d:5,6-d′]dipyrimidone-2,4,6,8-(1H,3H,5H,7H)-tetraone ***(6d)***
Cream solid, yield 84%; m.p. 327–329°C; FT-IR (KBr, ν cm^{-1}): 3400, 3120, 2920, 2820, 1680, 1650, 1570, 1510, 1460, 1250, 1020, 840, 780, 620. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 9.27 (s, br. 2H, H_f, NH), 8.51 (s, br. 2H, H_e, NH), 7.53 (d, $J = 6.8$ Hz, 2H, H_c), 7.08–6.88 (m, 6H, H_b, H_h, H_i), 5.88 (s, 1H, H_d), 5.59 (s, 1H, H_g), 3.76 (s, 3H, H_a), 2.50 (s, 3H, H_j). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): 169.3, 168.5, 164.2, 155.4, 152.2, 151.1, 134.4, 130.8, 129.3, 128.6, 127.1, 114.3, 99.8, 86.8, 55.6, 37.0, 20.9. Anal. calcd. for $C_{26}H_{20}N_6O_5S$: C, 59.08; H, 3.82; N, 15.89. Found: C, 59.06; H, 3.84; N, 15.91%.

Pharmacology

Antibacterial assay
The antibacterial activity of compounds was evaluated biologically using the Agar well-diffusion method. First, nutrient agar plates were prepared according to manufactures' instructions and incubated at 37°C. After cooling at room temperature, a suspension of 30 μL bacteria was added to nutrient agar plates. Cups (5 mm in diameter) were cut in the agar using sterilized glass tube. Each well received 30 μL of the 4 mg/mL solution of the test compounds dissolved in DMSO. Then, plates were incubated at 37°C and after 24 h, the inhibition zones were measured and value expressed in millimeters. The experiments were performed in triplicate. The results are reported as mean ± standard deviation of zone of inhibition in millimeter. Activity of each compound was compared with penicillin G and cefixim as standard drugs. DMSO was used as negative control.

DPPH radical-scavenging activity
DPPH radical-scavenging activity of compounds **6a–d** was evaluated according to Jin [44] method. The 2,2-diphenyl-2-picrylhydrazyl (DPPH) solution was prepared by dissolving an appropriate amount of DPPH in MeOH to give a concentration of 6.25×10^{-5} M. Then, 3.9 mL of this solution was added to 0.1 mL of sample solution in different concentrations (2000, 1000, 500, 250, 125, 62.5 μg/mL in MeOH). The samples were shaken vigorously and were kept in dark for 30 min, then the decrease in the absorbance of the resulting solution was measured at 517 nm. MeOH was used as blank and a sample of 3.9 mL DPPH containing 0.1 mL of MeOH instead of sample was used as control. Inhibition of free radical DPPH in percentage was calculated as follows:

$$\text{Radical scavenging activity} = \left(\frac{A_{\text{blank}} - A_{\text{sample}}}{A_{\text{blank}}}\right) \times 100$$

where A_{blank} is the absorbance of negative control (containing all reagents except test compounds) and A_{sample} is the absorbance of the test compounds and all the reagents. IC_{50} of the samples was calculated by plotting the radical scavenging percentage against sample concentration.

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The authors have declared no conflict of interest.

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