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KF/CP NPs as an efficient nanocatalyst for the synthesis of 1,2,4-triazoles: the study of antioxidant and antimicrobial activity

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Abstract

In this research, a green procedure and conventional methodology have been developed for the synthesis of a series of 3-mercapto-1,2,4-triazole derivatives (**4a-f)** in the presence of KF/Clinoptilolite nanoparticles (KF/CP NPs) as catalyst in water at 80 °C. Also, diphenyl-picrylhydrazine (DPPH) radical trapping and ferric reduction activity potential (FRAP) assays are used for evaluation of antioxidant activity of some synthesized compounds (**4a-4d)**. Besides, the antimicrobial activity of some synthesized compounds was studied employing the disk diffusion test on Gram-positive bacteria and Gram-negative bacteria. This procedure has some advantages such as short time of reaction, simple and green procedure, using low-cost catalyst, excellent yield of product and employing different substrate.

Keywords: KF/Clinoptilolite nanoparticles; KF/CP NPs; green synthesis; diphenyl-picrylhydrazine (DPPH); antioxidant.

Introduction

Heterocyclic chemistry is the most challenging and amply rewarding field, and by far heterocycles are the largest class in organic chemistry. A majority of pharmaceuticals, biologically active agrochemicals, additives and modifiers used in industrial applications are heterocyclic by nature [1]. Synthetic organic chemists made significant progresses in discovering and developing wide range of heterocyclic compounds for the benefit of mankind. One remarkable structural feature and characteristic to heterocycles, which continue to be exploited, is their capability to accommodate the substituents around a central frame. Ever since their initial use in agriculture which began a century ago, the chemistry of nitrogen and sulfur containing heterocycles has made remarkable advances [2]. The pesticidal, fungicidal, antiviral and potential chemotherapeutic properties have been the inspiration for the overwhelming curiosity into the heterocyclic compounds in general, and the thiadiazoles, oxadiazoles, pyrazoles and triazoles in particular. Among the

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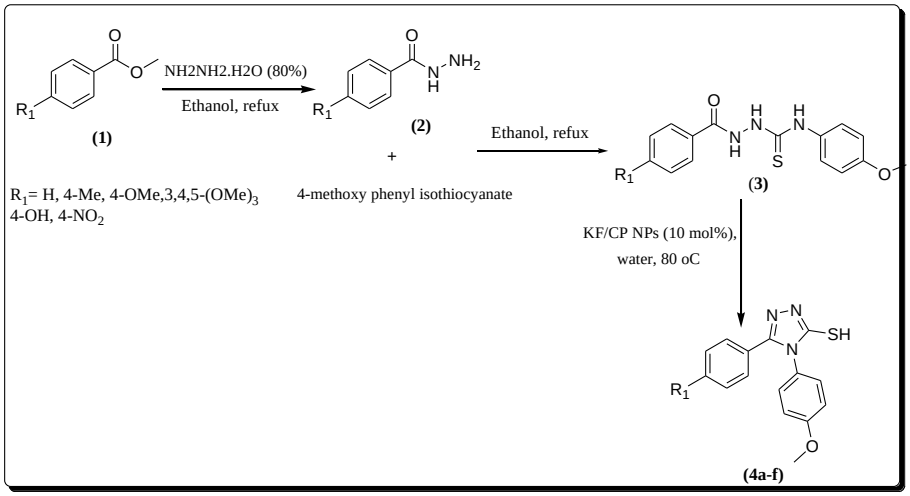
heterocyclic compounds, triazoles are one of the most key heterocycles exhibiting remarkable pharmacological activity as they are an essential constituent of all cells and living matter [3]. Triazole is a five-membered heterocyclic ring, which possesses three nitrogen atoms 1,2 and 4 positions. It is a much basic aromatic compound soluble in all organic solvents. The parent compound, triazole, was synthesized for the first time by Fischer in 1878. Over 0.2 million 1,2,4-triazole derivatives have been reported in the literature and this class of organic compounds has become extraordinarily important due to their wide-ranging biological, agrochemical and chemical properties. The advances in the synthesis and biological activity of 1,2,4-triazoles from time to time have also been reviewed [4-8]. 1,2,4-Triazoles have emerged as an important structural motif present in a large number of functionalized molecules with a broad range of biological activities, such as antibacterial [9], anti-inflammatory [10], antifungal [11], and antiviral [12]. Moreover, they are also found in valuable pharmaceuticals, including sitagliptin [13], maraviroc [14], trizaolam [15], deferasirox [16], and cefozopran [17, 18]. Owing to its broad spectrum of functions, the efficient methods for the synthesis of 1,2,4- triazoles have attracted much attention.

Green chemistry is a chemical procedure that decreases or removes the application and production of hazardous chemicals from the environment. Organic solvents that are needed for performing some organic reactions are often toxic and expensive. For this reason, elimination of these solvents is a suitable work for nature. Therefore, performing organic reactions in water as solvent has received wonderful notice in recent years [19].

Recently, organic chemists show a much attention to nanocatalysis. These compounds display an enhanced catalytic activity compared to their bulk sized types [20, 21]. Another topic in this work is investigation of the synthesized compounds power in terms of antioxidant activity. Usually, the compounds which have antioxidant activity, because of their reductive properties and chemical structure employed as transitional metals chelators and negative effect of free radicals, could be eliminated *via* these compounds. These compounds, in addition to its antioxidant activity, could prevent or reduce many diseases such as cardiovascular, inflammatory bowel syndrome, cancer, ageing, and Alzheimer [22-24]. In recent times, new and efficient synthetic antioxidant compounds for protective of humans against these diseases have been discovered and experimented by biologists, medicinal and food chemist. In continuation of our research on the new procedure for synthesis of important organic compounds with biological activity [25-29], we have synthesized compounds **4a-f** in the presence of KF/CP NPs as catalyst in water at room temperature in short time with 90-95% yields (Scheme 1). We have also investigated the DPPH radical trapping and FRAP assays for evaluation of antioxidant activity of the synthesized compounds (**4a-4d)** and compared the results with TBHQ and BHT as synthetic antioxidants. The antimicrobial activities of synthesized compounds were also studied employing the disk diffusion test on Gram-positive bacteria and Gram-negative bacteria.



Scheme 1. General procedure for synthesis of target compounds **4a-f**

Experimental

General

All chemicals employed in this research were purchased from Fluka and used without further purification. ^{1}H and ^{13}C NMR spectra were taken on a Bruker DRX-400 AVANCE spectrometer at 400 and 100 MHz, respectively in $CDCl_3$ using TMS as internal standard. Mass spectra (electron impact ionization) were given by a Finnigan MAT 8430 spectrometer operating at an ionization potential 70 eV. Elemental analyses were carried out employing a Heraeus CHN–O-Rapid analyzer. The morphology of nanostructure of KF/CP NPs was confirmed using scanning electron microscopy (SEM). X-ray diffraction (XRD) analysis was performed at room temperature employing a Holland Philips Xpert X-ray powder diffractometer with Cu Ka radiation (λ=0.15406 nm), over the 2θ collection range of 20–80°.

Preparation of nano KF/clinoptilolite

Nano sized natural clinoptilolite zeolite was prepared by grinding in a planetary ball mill using a zirconia vial set in dry conditions with a time period of about 20 min. Then, the KF/CP NPs catalyst was prepared according to previously reported procedure [29]. Thus, 1 g of KF was dissolved in distilled water (10 mL) and nano Clinoptilolite (9 g). The mixture was stirred for 50 min. Then, the water was evaporated at 60–70 °C under reduced pressure. Then, the impregnated clinoptilolite was dried at 70–80 °C in a vacuum drying oven for 30 h. The resulting material was powdered using a pestle and mortar. The obtained KF/CP NPs was taken care in a desiccator until required.

*General synthetic procedure for preparation of compounds **4a-f***

A mixture of different methyl benzoate (1 mmol) and hydrazine hydrate (0.75 g, 15 mmol, 80%) in 7 mL of ethanol was heated under reflux for 6 h. Excess ethanol was distilled and the contents were allowed to cool. The solid obtained product was filtered, washed with water, and dried to afford the corresponding benzohydrazide, which was used for the next reaction. Then, a solution of different benzohydrazides (1 mmol) and 4-methoxy phenyl isothiocyanate (1 mmol, 0.165 g) in ethanol (10 mL) was heated at reflux for 5 h and cooled down to room temperature gradually. The suspension was filtered, and the solid was washed with ethanol and dried to give the intermediate

hydrazinecarbothioamide as a white solid product. 0.05g of KF/CP NPs (10 mol%) was added to this solid in water media and the mixture was heated at 80 ^{o}C for 1 h. The resulting solution was cooled at room temperature and the precipitate was dissolved in ethyl acetate, and then the catalyst is separated by filtration. After evaporation of organic solvent, the precipitate was washed with water, and dried to obtain the title compounds as solid. Spectroscopic data for products listed below.

*4-(4-Methoxyphenyl)-5-phenyl-4H-1,2,4-triazole-3-thiol (**4a**)*
Yield: 92 %; m.p.; 110-112 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.79 (S, 3H, OMe), 7.00 (dd, 2H, *J*= 4.8 and 2.0 Hz, H-3′ and H-5′), 7.23 (dd, 2H, *J*= 4.8 and 2.0 Hz, H-2′ and H-6′), 7.30-7.35 (m, 3H, H-3, H-4 and H-5), 7.35-7.42 (m, 2H, H-2 and H-6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.37, 107.77, 119.48, 120.12, 129.55, 132.37, 134.10, 153.10, 166.60, 167.37. Anal. Calcd. for $C_{15}H_{13}N_3OS$:C, 63.58; H, 4.62; N, 14.83. Found: C, 63.83; H, 4.60; N, 14.88.

*4-(4-Methoxyphenyl)-5-p-tolyl-4H-1,2,4-triazole-3-thiol (**4b**)*
Yield: 91 %; m.p.; 122-124 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.05 (S, 3H, Me), 3.79 (S, 3H, OMe), 6.73 (d, 2H, *J*= 8.4 Hz, H-3′ and H-5′), 6.99 (d, 2H, *J*= 8.8 Hz, H-3 and H-5), 7.19 (d, 2H, *J*= 6.4 Hz, H-2′ and H-6′), 7.40 (d, 2H, *J*= 7.6 Hz, H-2 and H-6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.76, 55.67, 114.76, 122.66, 128.90, 129.47, 134.40, 138.08, 148.39, 157.31. Anal. Calcd. for $C_{16}H_{15}N_3OS$:C, 64.62; H, 5.08; N, 14.13. Found: C, 64.36; H, 5.100; N, 14.07.

*4,5-Bis(4-methoxyphenyl)-4H-1,2,4-triazole-3-thiol (**4c**)*
Yield: 89 %; m.p.; 128-130 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.70 (S, 3H, OMe), 3.78 (S, 3H, OMe), 6.80 (d, 2H, *J*= 8.8 Hz, H-3′ and H-5′), 6.93 (dd, 2H, *J*= 4.4 and 2.0 Hz, H-2′ and H-6′), 7.02 (d, 2H, *J*= 6.8 Hz, H-3 and H-5), 7.13 (d, 2H, *J*= 8.8 Hz, H-2 and H-6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.52, 55.70, 114.05, 114.17, 128.78, 130.16, 150.36, 158.59, 159.30, 169.13. Anal. Calcd. for $C_{16}H_{15}N_3O_2S$:C, 61.32; H, 4.82; N, 13.41. Found: C, 61.07; H, 4.83; N, 134.46.

*5-(3,4,5-Trimethoxyphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3-thiol (**4d**)*
Yield: 90 %; m.p; 134-136 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 3.73 (S, 3H, OMe), 3.83 (S, 6H, OMe), 7.23 (S, 2H, H-2 and H-6). 7.27 (d, 2H, *J*= 8.0 Hz, H-3 and H-5), 7.35 (d, 2H, *J*= 6.00 Hz, H-2 and H-6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.67, 56.37, 60.56, 106.97, 112.92, 118.38, 124.34, 126.35, 141.80, 153.10, 167.37. Anal. Calcd. for $C_{18}H_{19}N_3O_4S$: C, 57.89; H, 5.13; N, 11.25. Found: C, 58.12; H, 5.15; N, 11.20.

*4-(5-Mercapto-4-(4-methoxyphenyl)-4H-1,2,4-triazol-3-yl)phenol (**4e**)*
Yield: 89 %; m.p.; 121-123 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.78 (S, 3H, OMe), 6.73 (d, 2H, *J*= 8.4 Hz, H-3 and H-5), 6.93 (dd, 2H, *J*= 4.4 and 2.4 Hz, H-3' and H-5′), 7.02 (d, 2H, *J*= 6.8 Hz, H-2' and H-6′), 7.19 (d, 2H, *J*= 6.8 Hz, H-2 and H-6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.37, 107.77, 119.48, 102.12, 129.55, 132.37, 134.10, 153.10, 166.60, 167.37. Anal. Calcd. for $C_{15}H_{13}N_3O_2S$: C, 60.18; H, 4.38; N, 14.04; O, 10.69. Found: C, 59.93; H, 4.39; N, 13.98.

*4-(4-Methoxyphenyl)-5-(4-nitrophenyl)-4H-1,2,4-triazole-3-thiol (**4f**)*
Yield: 91 %; m.p.; 142-144 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.75 (S, 3H,

OMe), 6.90 (d, 2H, *J*= 8.8 Hz, H-3′ and H-5′), 7.27 (d, 2H, *J*= 8.0 Hz, H-2 and H-6), 8.17 (d, 2H, *J*= 8.8 Hz, H-2' and H-6'), 8.35 (dd, 2H, *J*= 5.2 and 2.0 Hz, H-3 and H-5). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.67, 109.77, 113.74, 120.06, 123.86, 128.90, 129.87, 132.40, 139.06, 141.19, 149.79, 157.30. Anal. Calcd. for $C_{15}H_{12}N_4O_3S$: C, 54.87; H, 3.68; N, 17.06; O, 14.62. Found: C, 54.65; H, 3.69; N, 16.99.

1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical trapping test

Radical trapping activity of **4a-4d** was calculated by DPPH (2, 2-diphenyl-1-picrylhydrazyl) radical trapping experiment according to the reported method by Shimada et al. [31]. Different concentrations of **4a-4d** (200–1000 ppm) were added to an equal volume of methanolic solution of DPPH (1 mmol/L). The mixtures were well shaken and then placed in a dark room. After 30 min at room temperature, the absorbance was recorded at 517 nm. In the control sample, **4a-4d** was exchanged with 3 mL methanol. Butylated hydroxytoluene (BHT) and 2-tertbutylhydroquinone (TBHQ) were employed as standard controls. The percentage inhibition of the DPPH radical was calculated according to the formula of Yen and Duh [32].

Reducing power experiment

The ability of compounds **4a-4d** to reduce iron (III) was evaluated by the method of Yildirim et al. [33]. Samples (1 mL) were mixed with 2.5 mL of phosphate buffer (0.2 mol/L, pH 6.6) and 2.5 mL of potassium ferricyanide ($K_3Fe(CN)_6$; 10g/L) and display for 30 min at 50 ^oC. Then, 2.5 mL of trichloroacetic acid (10% w/v) were added to the solution and centrifuged for 10 min. In the end, 2.5 mL of supernatant was mixed with 2.5 mL of distilled water and 0.5 mL $FeCl_3$ (1 g/L). The absorbance of samples was measured at 700 nm. Higher absorbance means higher reducing power.

Each measurement was performed in triplicate. The data were analyzed by running one-way analysis of variance (ANOVA) using SPSS software version 18.0. A one way ANOVA was used to estimate dissimilarity in the mean value of samples and control. All mean separations were carried out by Duncan multiple range test employing the importance level of 95% ($P < 0.05$).

Results and discussion

The heterocyclic compounds were synthesized by employing sequence outline following the procedure depicted in Scheme 1. Firstly, the methyl ester derivatives (1) were converted to the corresponding acid hydrazides (2) by treating hydrazine hydrate 80% in almost quantitative yield. After cooling the mixture to room temperature, the solid hydrazide product was washed with water and then dried. The reaction of different acid hydrazides (2) with 4-methoxy phenyl isothiocyanate resulted in carbothioamide salts (3) which then underwent intramolecular ring closure in the presence of KF/CP NPs (10 mol%) as base in refluxing water to generate the corresponding substituted 3-mercapto-1,2,4-triazole derivatives **4a-f**.

First of all, for confirming the morphology of KF/CP nanoparticles, scanning electron microscopy image (SEM) (Figure 1a) was carried out. Elemental analysis of the synthesized KF/CP NPs nanoparticles was performed using EDS technique (Figure 1b). As shown in Figure 1b, K and F peaks of KF/CP NPs nanoparticles indicate a successful synthesis. Also, the presence of peak carbon in the EDS spectrum indicates the presence of organic compounds at the nanoscale.

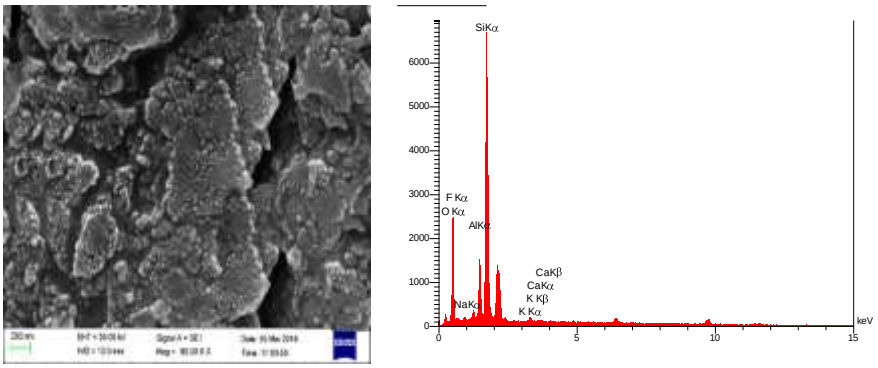


Figure 1. SEM image of KF/CP NPs (left) and EDS image of KF/CP NPs (right)

For calculating the crystallite size (D) of prepared KF/CP-NPs, X-ray diffraction patterns (XRD) were employed (Figure 2). The average crystallite size (D) for KF/CP-NPs was measured based on strongest intensity by employing the Debye–Scherrer's equation ($D=K\lambda/\beta cos\theta$); where D is the grain size, β is full-width at half-maximum or half-width (FWHM) in radians and h is the position of the maximum of diffraction peak, *K* is the so-called shape factor (0.89), θ is Bragg's diffraction angle and λ is the X-ray wavelength used (1.5406 A˚ for CuK_{α}). Particles size of KF/CP has been found to be 41 nm.

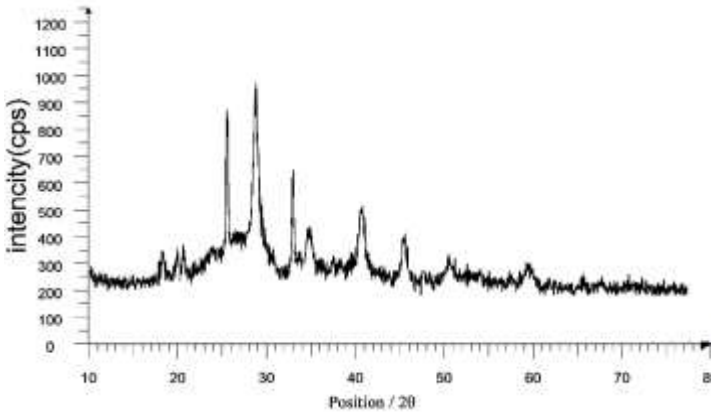


Figure 2. XRD spectra of KF/CP NPs

For choosing the best of reaction conditions in the last step, carbothioamide salts (3) were chosen as a sample reaction. It was discovered that the yield of this reaction without catalyst is very low (Table 1, Entries 1-6). By adding a catalyst to the mixture of reaction, the yield of 4a is raised. A number of catalysts such as CM-ZnO, CuO-NPs, ZnO-NPs, Fe_3O_4-MNPs, TiO_2-NPs, and also KF/CP NPs were experimented for finding efficient catalyst (Table 1). Also, some solvents such as CH_2Cl_2, CH_3CN, H_2O and toluene and various temperatures were considered for the model reaction and the outcomes are exhibited in Table 1.

As shown in Table 1, water is the best solvent for this reaction because of excellent yield of product. The yield of reaction in CH_3CN and toluene is similar to water but both of two solvents are toxic and organic. The KF/CP NPs are

selected as the best catalyst for these reactions.

Table 1. Determination of best outcome for compound **4a**

Entry	Catalyst	Solvent	Temp.	Yield[a] (%)
1	-----	H_2O	r.t.	25
2	-----	H_2O	80	25
3	-----	CH_3CN	80	15
4	-----	Toluene	r.t.	5
5	-----	Toluene	80	5
6	------	Solvent-free	80	----
7	KF/CP (NPs)	H_2O	r.t.	92
8	KF/CP (NPs)	CH_3CN	r.t.	68
9	ZnO-NPs	H_2O	r.t.	45
10	TiO_2-NPs	H_2O	r.t.	65
11	Fe_3O_4-MNPs	H_2O	r.t.	78
12	Fe_3O_4-MNPs	CH_3CN	r.t.	80
13	CuO-NPs	H_2O	r.t.	63
14	CuO-NPs	CH_3CN	r.t.	75

[a]Isolated yield.

The amount of catalyst was determined by raising it from 10 to 25 mol %. When the amount of catalyst is enlarged, the yield of reaction didn't display any significant growth. As a result, the optimum amount of KF/CP-NPs as catalyst is 10 mol%. Thus, 10 mol% KF/CP-NPs as a catalyst, 80 ^oC temperature and water as solvent are optimum condition for generation of compound **4a**. These conditions are experimented for other reactions that are exhibited in Scheme 1.

For reusing the catalyst, after completion of reaction and filtration, it was washed with ethyl acetate, dried in air and used exactly under the similar conditions with no further purification. It was displayed that the catalyst could be employed for four times with no substantial falling in the yield of product and its catalytic activity (Table 2).

Table 2. Reuse of KF/CP-NPs for the synthesis of **4a**

	Cycle				
	1	2	3	4	5
Yield (%)	92	92	91	**90**	90

Study of antioxidant activity employing diphenyl-2-picrylhydrazyl (DPPH)

For determination of antioxidant activity of some synthezied compounds and their antioxidant property in foods and biological systems [34,35] as well as power of compounds to take free radicals, diphenyl-2-picrylhydrazyl (DPPH) radical trapping experiment is widely used. In these experiment, the DPPH radical takes the hydrogen atom (or one electron) of synthezied compounds **4a-4d** and gives an evaluation of antioxidant activity basis of free radical trapping. The absorption of DPPH radical was observed area 517 nm, but when DPPH radical is reduced by an antioxidant or a radical species, its absorption decreases. As found from the results, free radical trapping activity of compounds **4a-4d** is excellent but weaker than to BHT and TBHQ. Therefore, concentration and structure were key factor on the DPPH trapping activity (P<0.05) (Figure 3). Normally, the DPPH scavenging ability of these compounds was attained TBHQ>BHT>**4c**>**4a**>**4b**>**4d**

respectively. The free radical trapping power had been enhanced from 200 to 1000 ppm. So, by rising concentration in all samples, the free radical activity was raised. For instance, compound 4b with a concentration of 1000 ppm had 67.40% inhibition while a concentration of 200 ppm of compound 4b was exhibited 15.20% free radical inhibition.

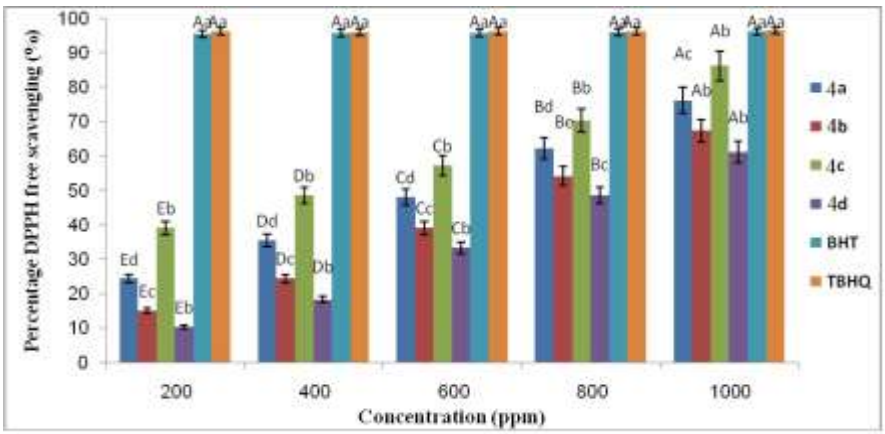


Figure 3. Radical trapping activity (RSA) of compounds 4a-4d

Ferric ions (Fe^{3+}) reducing potential (FRAP)

Reducing power of the synthesized compounds was determined by calculating the exchange amount of Fe^{3+}/ferricyanide complex to the Fe^{2+}/ferrous form at 700 nm [33]. The reducing power of compounds **4a-4d** compared with synthetic antioxidants (BHT and TBHQ) are showed in Figure 4. The bigger reducing power means higher absorbance of the compounds. The reducing activity order of compounds **4a-4d** was as following: TBHQ>BHT>**4c**>**4a**>**4b**>**4d** (Figure 4). In all of them, the increasing concentration was enhanced ferric ions reducing power. Compounds **4c** show very good reducing activity compared to standards (BHT and TBHQ).

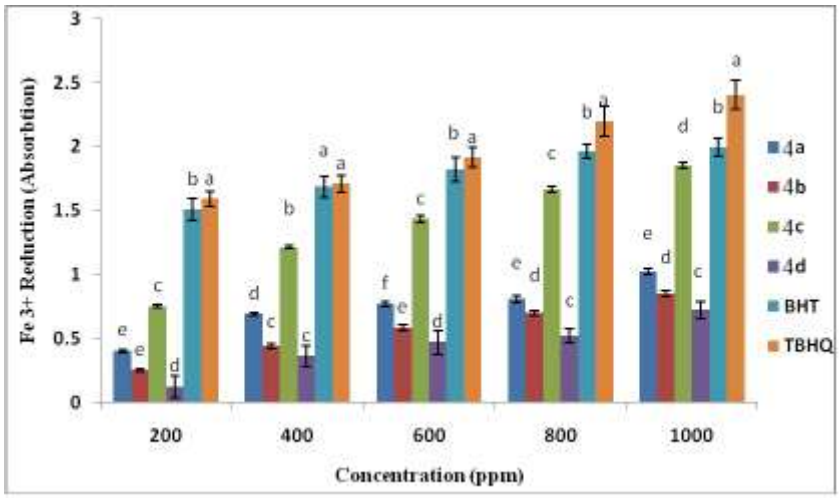


Figure 4. Ferric ions (Fe^{3+}) reducing antioxidant power (FRAP) of compounds **4a-4d**

Analysis of the antibacterial activity of synthesized compounds

Also, a comparison between the activity of our synthesized compounds with Streptomycin and Gentamicin as standard drug was discussed. The results of the antimicrobial activity of some synthezized compounds on bacterial species are shown in Table 3. The present study indicated that the type of bacteria and concentration of compounds are effective on the diameter of the inhibition zone. It is apparent from the data listed in Table 3, the antimicrobial activity of the most synthesized compounds **4a**, **4d** and **4f** were good active against Gram positive bacteria and Gram negative bacteria so that the diameter of the inhibition zone of compounds has the maximum effect on *Escherichia coli.*

Table 3. The antibacterial activity of the tested compounds

Compounds	Staphylococcus aureus (+)	Bacillus cereus (+)	Pseudomonas aurignosa (-)	Escherichia coli(-)
4a	17	18	16	22
4b	7	10	--	7
4c	6	----	---	7
4d	16	15	15	19
4e	5	5	5	10
4f	15	18	17	18
Streptomycin	18	21	19	25
Gentamicin	20	23	19	20

Conclusion

In summary, the procedure described here provides a suitable method for the preparation of 1,2,4-triazole derivatives in good yield in the presence of KF/Clinoptilolite nanoparticles (KF/CP-NPs) as catalyst in water at reflux conditions in short time. Also, compound **4c** showed a very good radical trapping activity and reducing activity relative to standards (BHT and TBHQ) by investigation of antioxidant activity. Moreover, the antimicrobial activity of some synthesized compounds was proved employing the disk diffusion test on Gram-positive bacteria and Gram-negative bacteria. The obtained results of disk diffusion test showed that compounds **4a**, **4d** and **4f** prevented the bacterial growth. Moreover, easy workup of catalyst and product, performing reactions in water and reusability of catalyst makes this method as an interesting option compared to other approaches.

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References

[1] (a) A.R. Katritzky, C.W. Ress, E.F.V. Scriven, *Comprehensive heterocyclic chemistry II*., Eds. Pergamon: Oxford, U.K., **1996**, 1-9; (b) S. Sadegh-Malvajerd, Z. Arzehgar, F. Nikpour, *Zeitschrift für Naturforschung* B, **2014**, *68*, 182-186; (c) S. Sajjadifar, Z. Arzehgar, A. Ghayuri, *J. Chin. Chem. Soc.* **2017**, *65*, 205-211.

[2] A.R. Katritzky, C.A. Ramsden, E.F.V. Scriven, R.J.K. Taylor, *Comprehensive heterocyclic chemistry III*., Eds. Pergamon: Oxford, U.K., **2008**, 1-13.

[3] H.P. Michael, J.C. Philip, V.H. Søren, C.J. Nykola, R.H. Ashley, L.L.

Dennis, *J. Chem. Phys*. **2012**, *136*, 10-21.
[4] K.T. Potts, *Chem. Rev*., **1961**, *61*, 87-127.
[5] V.F. Ferreira, D.R. Da Rocha, F.R. Da Silva, F.G. Ferreira, N.A. Boechat, J.L. Magalhães, *Expert.Opin. Therapeut. Patents*, **2013**, *23*, 319-331.
[6] S.C. Holm, B.F. Straub, *Org. Preparat. Proce. Internat*., **2011**, *43*, 319–347.
[7] D.S. Bele1, I. Singhvi, *Asian. J. Biochem. Pharma. Res*., **2011**, *2*, 38-58.
[8] A.H. Kaplaushenko, *Medichna Khimiya*. **2007**, *9*, 65-69.
[9] (a) A.R. Bhat, G.V. Bhat, G.G. Shenoy, *J. Pharm. Pharmacol*. **2001**, *53*, 267−272. (b) K. Colanceska-Ragenovic, D. Vesna, K. Vlado, G.M. Dora, B. Aleksandra, *Molecules* **2001**, 6, 815−824. (c) B. Shivarama Holla, K.N. Poorjary, B.S. Rao, M.K. Shivananda, *Eur. J. Med. Chem.* **2002**, *37*, 511−517. (d) T. Yamanaka, H. Ohki, M. Ohgaki, S. Okuda, A. Toda, K. Kawabata, S. Inoue, K. Misumi, K. Itoh, K. Satoh, U. S. Patent US 2005004094A1, 2005.
[10] (a) O. Bekircan, N. Gumurkcuoglu, *Indian J. Chem.* **2005**, *44B*, 2107−2113. (b) A. A. Siddiqui, A. Arora, N. Siddiqui, A. Misra, *Indian J. Chem*. **2005**, *44B*, 838−841. (c) D.H. Boschelli, D.T. Connor, U. S. Patent US 2005114958A, 2005.
[11] a) Collin, X.; Sauleau, A.; Coulon, J. *Bioorg. Med. Chem. Lett.* **2003**, 13, 2601−2605. (b) Lamrence, E.K.U.S. Patent 4, 263, 312, **1981**. (c) Rollas, S.; Kalyoncuoglu, N.; Sur-Altiner, D.; Yegenoglu, Y. *Pharmazie* **1993**, 48, 308−309.
[12] (a) E. De Clercq, J. *Clin. Virol.* **2004**, *30*, 115−133. (b) I. Kucukguzel, E. Tatar, S.G. Kucukguzel, S. Rollas, E. Clercq, De. *Eur. J. Med. Chem.* **2008**, *43*, 381−392.
[13] Y. Bo, C. Lin, F. Ruiying, G. Zhiping, *Eur. J. Pharmacol.* **1999**, *380*, 145−152.
[14] N. Mulakayala, Ch. Upendar Reddy, J. Iqbal, M. Pal, *Tetrahedron* **2010**, *66*, 4919−4938.
[15] C.S. Li, C.Y. An, X.M. Li, S.S. Gao, C.M. Cui, H.F. Sun, B.G. Wang, *J. Nat. Prod.* **2011**, *74*, 1331−1334.
[16] E. Nisbet-Brown, N.F. Olivieri, P.J. Giardina, R.W. Grady, E.J. Neufeld, R. Sechaud, A.J. Krebs-Brown, J.R. Anderson, D. Alberti, K.C.; Sizer, D.G. Nathan, *Lancet* **2003**, *361*, 1597−1602.
[17] Y. Iizawa, K. Okonogi, R. Hayashi, T. Iwahi, T. Yamazaki, A. Imada, *Antimicrob. Agents Chemother.* **1993**, *37*, 100−105.
[18] (a) M.M. Heravi, H. Hamidi, V. Zadsirjan, *Current Organic Synthesis*, **2014**, *11(5)*, 647-675; (b) M.M. Heravi, H. Hamidi, V. Zadsirjan, *Current Org. Syn*. **2014**, *11*, 647-675. (c) M. Shiri, M.M. Heravi, H. Hamidi, M.A. Zolfigol, Z. Tanbakouchian, A. Nejatinezhad-Arani, N.A. Koorbanally, *J. Iranian Chem. Soc.* **2016**, *13*, 2239-2246.
[19] (a) J. Tao, R. J. Kazlauskas, Biocatalysis for Green Chemistry and Chemical Process Development, John Wiley & Sons, **2011**; (b) S. Sajjadifar, S. Rezayati, *International Journal of ChemTech Research*, **2013**, 5, 1964-1968.
[20] S. Rostamizadeh, M. Nojavan, R. Aryan, E. Isapoor, M. Azad, *J. Mol. Catal. A: Chem.* **2013**, *374–375*, 102-110.
[21] (a) D. Beydoun, R. Amal, G. Low, S. McEvoy, J. *Nanopart. Res.* **1999**, *1*, 439–458; (b) M.M. Heravi, H.A. Oskooie, N. Karimi, H. Hamidi, *Chin. Chem. Lett*. **2011**, *22*, 1059-1062.
[22] (a) B. Halliwell, *Free Radical Res.* **1999**, *31*, 261–272; (b) F. Ahmadi, M. Kadivar, M. Shahedi, *Food Chem.* **2007**, *105*, 57–64.

[23] M.A. Babizhayev, A.I. Deyev, V.N. Yermakovea, I.V. Brikman, J. Bours, *Drugs R. D.* **2004**, *5*, 125–139.
[24] L. Liu, M. Meydani, *Nutr. Rev.* **2002**, *60*, 368–371.
[25] M. Rajabi, Z. Hossaini, M.A. Khalilzadeh, S. Datta, M. Halder, S.A. Mousa, *J. Photochem. Photobiol. B.* **2015**, *148*, 66-72.
[26] F. Khaleghi, I. Jantan, L.B. Din, W.A. Yaacob, M.A. Khalilzadeh, S.N.A. Bukhari, *J. Nat. Med.* **2014**, *68*. 351-357.
[27] F. Tavakolinia, T. Baghipour, M.A. Khalilzadeh, Z. Hossaini, M. Rajabi, *Nucleic Acid Ther.* **2012**, *22*, 265-270.
[28] M. Rajabi, M.A. Khalilzadeh, J. Mehrzad, *DNA Cell Bio*l. **2012**, *31*, 128-134.
[29] M. Rajabi, M.A, Khalilzadeh, F. Tavakolinia, P. Signorelli, R. Ghidoni, E. Santaniello, DNA. *DNA Cell Biol.*, **2012**, *31*, 783-789.
[30] a) M.A. Khalilzadeh, A. Hosseini, A. Pilevar, *Eur. J. Org. Chem.* **2011**, *8*, 1587 b) S. Salmanpour, M.A. Khalilzadeh, A. Hosseini, *Comb. Chem. High Throughput Screen.*, **2013**, *16*, 339 c) M.A. Khalilzadeh, H. Keipour, A. Hosseini, D. Zareyee, *New J Chem.*, **2014**, *38*, 42.
[31] K. Shimada, K. Fujikawa, N.T. Yahara, *J. Agri. Food Chem.*, **1992**, *40*, 945.
[32] G.C. Yen, P.D. Duh, *J. Agri. Food Chem.*, **1994**, *42*, 629.
[33] A. Yildirim, A. Mavi, A.A. Kara, *J. Agri. Food Chem.*, **2001**, *49*, 4083.
[34] A.R. Saundane, M.K. Nandibeoor, *Monatsh Chem.*, **2015**, *146*, 1751.
[35] A.M. Bidchol, *Food and Bioprocess Tech*., **2011**, *4*, 1137.

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