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### Facile synthesis of tetrazolo[1,5-*a*]pyrimidine with the aid of an effective gallic

### acid nanomagnetic catalyst

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#### Abstract

The present work is the first report of nano-Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-gallic acid in multicomponent reactions as a catalyst. One-pot condensation of various aromatic aldehydes, β–ketoesters and 5-aminotetrazole to deliver the desired tetrazolo[1,5-*a*]pyrimidine derivatives is investigated. It involves successful surface modification of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH<sub>2</sub> as a potent magnetic support with a well-known natural acid which attracts considerable interests because of its applications in different sciences. This reusable magnetically separable nanocatalyst provides a convenient and reliable method for high yield tetrazole derivatives synthesis in short reaction times with wide variety range of the products and facile isolation. Acid grafting on the surface of amine-functionalized silica-coated magnetic nanoparticles confirmed by Fourier transform infrared (FT-IR) spectroscopy, thermogravimetric analysis (TGA) and energy-dispersive X-ray (EDX) analysis techniques. Structural characterization included scanning electron microscopy (SEM) images along with transmission electron microscopy (TEM) images and vibrating sample magnetometer (VSM) curve applied for morphology and magnetism type determination of the resulted nanocatalyst, respectively.

*Keywords*: Gallic acid; Green chemistry; Nanomagnetic catalyst; Multicomponent reactions; Tetrazolo[1,5-*a*]pyrimidine.

#### 1. Introduction

Azolo-annulated pyrimidines and 1,2,4-triazines have attracted continuing interest due primarily to their structural similarity to heterocyclic bases of DNA and RNA. As a consequence, these compounds can act as antimetabolites, being effective biologically active compounds. One of the categories which can be considerable as isosteres (structural analogues) of purine bases of DNA and RNA, such as hypoxanthine, adenine, and guanine is azolo[1,5-*a*]pyrimidines [1]. Substituted compounds of this valuable tetrazolo prymidines can be used as anti-HBV (hepatitis B virus) [2], anti-tumor [3] and anticancer [4] agents, besides antimicrobial and antioxidant properties of related metal complexes [5, 6].

Among the strategies used to construct the small molecule, multicomponent reactions (MCRs) are ideal synthetic tools to generate multiple molecular scaffolds from the same starting materials or intermediates because of their intrinsic convergence, complexity-generating power, as well as operational simplicity, resource and energy effectivity from the viewpoint of atom-economy and sustainable technology [7]. In addition, nature of applied catalyst can be playing a fundamental role in efficiency of procedure, green chemistry aspects and facility of that. With the rapid development in the field of catalytic chemistry, researchers have started to pay more attention to the detrimental effects of non-green processes to the environment. Recently, magnetic nanoparticles which can be separate magnetically after completion of a reaction, have gained recognition as potential environmentally benign replacement of the conventional Lewis acid and base catalysts in various organic synthetic processes [8, 9]. Furthermore, surface modification of nanoparticles can provide significant features likes stabilization of nanoparticles against agglomeration, make them compatible with another phase, enable their self-organization and

functionalization by the organic groups [10]. Wide range of catalytic protocols have been reported for heterocyclic compounds synthesis using nanomagnetic catalysts [11-17].

Gallic acid (3,4,5-trihydroxybenzoic acid) (GA) is a naturally occurring polyphenolic compound which is widely distributed across the plant kingdom such as leaves, roots and bark and also can be synthesized from phenylalanine via caffeic acid or trihydroxycinnamic acid [18] can be considered as a valuable acid for functionalizing the magnetic nanoparticles [19, 20].

Due to above mentioned reasons, in the present study, we attempt to design, prepare, characterize and investigate the application of nano-Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA as a heterogeneous catalyst in the synthesis of tetrazolo[1,5-*a*]pyrimidine derivatives (Scheme 1).



Scheme 1. (a) Preparation of  $Fe_3O_4@SiO_2-NH-GA$  and (b) synthesis of tetrazolo[1,5*a*]pyrimidine derivatives **4a–o** in the presence of  $Fe_3O_4@SiO_2-NH-GA$ .

### 2. Experimental

### 2.1. General

Reagents, chemicals and solvents, were all provided by Merck, Fluka and Aldrich. Melting points were measured with an Electrothermal 9100 apparatus. The FT-IR spectra were taken via Shimadzu IR-470 spectrometer. <sup>1</sup>H NMR spectra were recorded with a Bruker DRX-500 Avance spectrometer. SEM and TEM measurements were conducted using KYKY-EM3200 and Zeiss-EM10C electron microscopes at an acceleration voltage of 100 kV, respectively. Elemental analysis of the nanocatalyst was done by EDX analysis using Numerix DXP-X10P. Magnetic susceptibility measurements were performed by using a Lake Shore VSM 7410. TGA was recorded under air atmosphere by Bahr-STA 504 instrument.

### 2.2. Preparation of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA

On the basis of our previous work [21], the target nanocatalyst was synthesized by grafting of GA on the freshly prepared  $Fe_3O_4@SiO_2-NH_2$  nanoparticles. In this regard, 1.0 g of the  $Fe_3O_4@SiO_2-NH_2$  was dispersed in 5 mL of dry toluene. Then, the solution of dispersed GA (0.6 g in 10 mL of dry toluene) was added drop wise to the previously prepared mixture during 10 min under vigorous stirring for 1 h in presence of 10 mol% of ZrCl<sub>4</sub> as a co-catalyst for amidation of carboxylic acids [22]. After that, the obtained mixture was refluxed for 24 h. Finally, the catalyst was isolated by an external magnet, washed several times with ethanol and dried at room temperature.

#### 2.3. Typical procedure for synthesis of 5-aminotetrazole

5-Aminotetrazole as an active component for the present procedure of tetrazolo[1,5-a]pyrimidine derivatives synthesis was achieved by heating the mixture of 2-cyano-guanidine (84 mg, 1

mmol) and NaN<sub>3</sub> (71.5 mg, 1.1 mmol) in 2 mL of distilled water in the presence of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA (45 mg). Then, the nanocatalyst was separated from the reaction mixture by an external magnet. Next, washing the filtered precipitate with distilled water made it ready to use for intended purpose.

### 2.4. General procedure for the synthesis of tetrazolo[1,5-a]pyrimidine derivatives (4a-o)

Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA was added to a mixture of an aromatic aldehyde (1 mmol),  $\beta$ -ketoester (1 mmol), 5-aminotetrazole (93 mg, 1.1 mmol) in ethanol and refluxed for appropriate time. After completion of reaction (monitored by thin-layer chromatography, TLC (EtOAc/n-hexane 4:1), nanomagnetic catalyst was separated by an external magnet and rest of the reaction mixture was filtered, washed, dried and purified by recrystallization from ethanol to yield target products **4a**-**o**. Introducing a new tetrazolo[1,5-*a*]pyrimidine derivative (**4i**) could be considered as a noteworthy feature of present work (related spectral data is described as well). Other resulted products are known compounds and confirmed by melting points comparison with literature authentic samples.

### 2.5. Spectral data of the selected products

Methyl 7-(4-cyanophenyl)-5-methyl-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidine-6-carboxylate (**4i**): IR (potassium bromide): 3394, 3099, 2977, 2229, 1704, 1654, 1573, 1415, 1377, 1311, 1280, 1224, 1147, 1107, 1008, 838, 767, 698, 557. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta_{\rm H}$  (ppm) = 1.16 (t, J = 6.85 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.67 (s, 3H, 5-methyl-H), 2.66 (s, 3H, OCH<sub>3</sub>), 4.12 (q, 2H,

OCH<sub>2</sub>CH<sub>3</sub>), 6.78 (s, 1H, -CH), 7.5 (d, 2H, J = 7.6 Hz ArH), 7.67(d, 2H, J = 7.8 Hz ArH), 11.02 (s, 1H, NH).

### 3. Results and discussion

3.1. Characterization of the nanocomposite

#### 3.1.1. FT-IR Analysis

Comparative FT- IR spectra of Fe<sub>3</sub>O<sub>4</sub>, Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>, Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH<sub>2</sub> and Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA are shown in Fig. 1. All spectra have absorption peaks attributed to silica shell and magnetic core in common. Based on bands at 1607 and 1388 cm<sup>-1</sup> which are assigned to the C-C stretching and C-H bending vibrations, respectively, existence of aromatic ring in the synthesized nanocatalyst could be verified. Besides that, appeared bands at 1504 cm<sup>-1</sup> attributed to the N-H and C=O at 1680 cm<sup>-1</sup> corresponded to formation of amide group in final catalyst.



Fig. 1. Comparative FT-IR spectra of  $Fe_3O_4@SiO_2-NH-GA$  and its components manufacturing steps.

### 3.1.2. Energy-dispersive X-ray (EDX)

The elemental composition of the synthesized Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA was analysed using energy dispersive spectroscopy (EDX) in Fig 2. The results illustrated that Fe<sub>3</sub>O<sub>4</sub> was coated with silica shell and the inorganic compound functionalized surface of the catalyst successfully. Furthermore, higher intensity of the Si peak compared with the Fe ones indicates that nanomagnetic core was covered satisfyingly by silica layer and strong Si linkages were presented in intended catalyst.



3.1.3. Scanning electron microscopy (SEM)

With regards to SEM images of  $Fe_3O_4@SiO_2-NH-GA$ , formation of uniform spherical particles without any agglomeration was confirmed (Fig. 3). The calculated average diameter of 52 particles in chart c reveal that the catalyst was mostly made up of ~20 nm particles and nearly-uniform sized structure was obtained.





**Fig. 3**. a,b) SEM images of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA in different magnifications and c) related particle size distribution diagram.

3.1.4. Transmission electron microscopy (TEM)

As revealed by TEM image (Fig. 4) the silica shell is fully coated on the magnetic core through all particles uniformly. The magnetic core can be easily distinguished as dark regions from the shell according to different density and core-shell structure is clearly indicated.



Fig. 4. TEM image of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA.

### 3.1.5. Thermogravimetric analysis (TGA)

Thermal stability of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA was investigated by thermogravimetric analysis (TGA) (Fig. 5). Weight loss observed in the first area (at temperatures below 200 °C) can be attributed to water desorption from the surface of the silica layer, while weight loss above 600 °C is associated with the release of the structural water of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub> [23]. Furthermore, gallic

acid mass loss was occurred at temperature ~210-300 °C [24] and the other degradation took place at ~400-600 °C is due to organic part of 3-aminopropylsilica.



Fig. 5. TGA curve of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA.

#### 3.1.6. Vibrating sample magnetometer (VSM)

Magnetization curves of Fe<sub>3</sub>O<sub>4</sub>, Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>, Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH<sub>2</sub> and Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA are compared in Fig. 6. The saturation magnetization (Ms) of Fe<sub>3</sub>O<sub>4</sub>, Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>, Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA were measured 61.50, 40.28, 21.30 and 19.1 emu g<sup>-1</sup>, respectively. The observed decrease in saturation magnetization was most likely due to the existence of coated layers on the surface of the magnetic nanoparticles which formed during the nanocatalyst manufacturing process [25]. Facile separation of the nanocatalyst from final mixture could be resulted from high magnetic saturation character of resulted Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA.



Fig. 6. Study of magnetization behavior.

### 3.2.1. Optimizing the reaction conditions

In order to develop a better catalytic system, preliminary screening was performed on the reaction of benzaldehyde (106.1 mg, 1 mmol), ethyl acetoacetate (130.1 mg, 1 mmol) and 5-amino tetrazole (93.5 mg, 1.1 mmol) as a model reaction.

As solvent has impressive effect in these reactions, solvent screening was carried out (Table 1, entries 2-6) in which EtOH and CH<sub>3</sub>CN afforded good yields. By considering green and safe aspects, EtOH was chosen as suitable solvent (Table 1, entry 2). Experiments on catalyst amount affirmed that 45 mg of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA should be selected as minimum required catalyst amount to achieve high expected yield (Table 1, entry 13). Besides that, in case of catalyst-free condition, the reaction did not proceed (Table 1, entry 7). The results reported in Table 1

revealed that in comparison with prolonged reaction times of some reported procedures (Table 1, entries 15-17), present study can be considered as a time-saving, environmentally friendly and efficacious approach to tetrazolo[1,5-a]pyrimidine derivatives synthesis.

Entry	Catalyst	Temp.	Time	Solvent	Yield (%)
		(°C)	(min)	0	
1	Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> -NH-GA	r.t.	15	EtOH	65
2	Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> -NH-GA	Reflux	15	EtOH	90
3	Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> -NH-GA	Reflux	15	H <sub>2</sub> O	76
4	Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> -NH-GA	Reflux	15	CH <sub>3</sub> CN	85
5	Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> -NH-GA	Reflux	15	PEG-400	83
6	Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> -NH-GA	Reflux	15	CH <sub>2</sub> Cl <sub>2</sub>	30
7	-	Reflux	120	EtOH	Trace
8	Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> -NH-GA (5 mg)	Reflux	15	EtOH	35
9	Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> -NH-GA (10 mg)	Reflux	15	EtOH	49
10	Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> -NH-GA (20 mg)	Reflux	15	EtOH	60
11	Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> -NH-GA (30 mg)	Reflux	15	EtOH	73
12	Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> -NH-GA (40 mg)	Reflux	15	EtOH	81
13	Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> -NH-GA (45 mg)	Reflux	15	EtOH	90
14	Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> -NH-GA (50 mg)	Reflux	14	EtOH	90
15	Sulfamic acid	85	420	Solvent-free	85 [26]
16	FeCl <sub>3</sub> .6H <sub>2</sub> O	85	540	Solvent-free	46 [26]

Table 1. Screening of reaction condition and catalyst efficiency investigation.

17	Concentrated HCl	Reflux	120	EtOH	60.9 [27]
18	GA	45	15	EtOH	66

<sup>a</sup> Isolated yields.

### 3.2.2. Study the scope of present catalytic reaction

Various aromatic aldehydes were employed to study the generality of optimized conditions. The results were summarized in Table 2. The results revealed efficiency of the procedure against both electron-withdrawing and donating groups substituted aromatic aldehydes. Furthermore, the reaction was extended to di- and tri-substituted aromatic aldehydes and related tetrazolo[1,5-*a*]pyrimidine derivatives were generated in excellent yields. On the other hand, reliability of the present study was increased via successful synthesis of a new derivative (Table 2, Entry 9).

Table	2.	Green	synthesis	of	5-methyl-7-aryl-4,7-dihydrotetrazolo[1,5-a]pyrimidine-6-
carbox	ylic	ester d	erivatives	4a-	o in the presence of 5 mol% of Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub> -NH-GA.

Entry	$\mathbb{R}^1$	R <sup>2</sup>	Product	Time (min)	Yield <sup>a</sup> (%)	Mp (°C)	
						Found	Reported
1	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	<b>4</b> a	15	90 <sup>b</sup>	202-204	204-205 [28]
2	4- $NO_2C_6H_4$	$C_2H_5$	<b>4</b> b	20	82	226-228	225-227 [29]
3	3- NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	$C_2H_5$	<b>4</b> c	15	84	204-206	203-208 [30]
4	3,4,5-(CH <sub>3</sub> O) <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	$C_2H_5$	4d	20	80	200-202	199-201 [26]
5	2,4- Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	$C_2H_5$	<b>4</b> e	20	83	256-258	252-256 [28]
6	4- $BrC_6H_4$	$C_2H_5$	<b>4</b> f	20	82	220-223	221-223 [28]
7	3- ClC <sub>6</sub> H <sub>3</sub>	$C_2H_5$	4g	15	90	182-184	180-185 [30]
8	$4-FC_6H_4$	$C_2H_5$	4h	15	88	196-198	197-198 [26]
9	4-CNC <sub>6</sub> H <sub>4</sub>	$C_2H_5$	<b>4</b> i	15	90	238	This work
10	3,4,5-(CH <sub>3</sub> O) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	CH <sub>3</sub>	<b>4</b> j	20	81	217-218	200-202[26]
11	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	4k	15	89	190-191	196-198 [31]
12	3-NO <sub>2</sub> -4-HOC <sub>6</sub> H <sub>3</sub>	CH <sub>3</sub>	<b>4</b> i	15	86	250-251	248-250 [30]
13	3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH <sub>3</sub>	<b>4</b> m	20	85	219-220	210-212 [26]
14	4- $MeC_6H_4$	CH <sub>3</sub>	4n	15	88	192-195	209-211 [32]
15	$2,4-Cl_2C_6H_3$	CH <sub>3</sub>	40	15	89	256-258	257-259 [26]

<sup>a</sup> Isolated yield.

#### 3.2.3. Mechanism evaluation

A suggested mechanism for the formation of tetrazolopyrimidines using Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA is shown in Scheme 2. Initially, activated aldehyde by nanomagnetic catalyst may participate in Knoevenagel condensation with elimination of water and forms intermediate A. In the next step, intermediate B forms by consequent imine-enamine tautomerization of 5-aminotertrazole and intermediate A. Intermolecular cyclization of intermediate B and release a H<sub>2</sub>O molecule leads to desired products [4a-o].



Scheme 2. Plausible mechanism for the synthesis of tetrazolo[1,5-a]pyrimidines using Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA.

#### Reusability of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA magnetic nanocatalyst

Owing to the magnetic properties of synthesized  $Fe_3O_4@SiO_2-NH-GA$  and accordingly facile separation from the crude reaction, impel us to persist in green aspects of present work. The recovered catalyst from reaction mixture was washed with EtOH and dried to be ready for later run. Six subsequent runs were investigated by recovered nanomagnetic catalyst. Slight decrease was observed in obtained yields after 6 time reuse of magnetic catalyst (Fig. 7).



Fig. 7. Reusability studies of the nanocatalyst for the model reaction.

#### 4. Conclusions

The main goal of the present study was to extend the application domain of gallic acid by proving the catalytic potency of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA in multicomponent and cycloaddition reactions, excellent performance of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-GA as catalyst makes it worthy to apply in other MCRs. Surface modifying of nanomagnetic particles by a significant natural phenolic acid is a remarkable feature of this work. TGA results exhibited that the nanocomposite was stable at least until ~210-300 °C without considerable mass loss and gallic acid successfully incorporated into the structure. EDX analysis showed the presence of Si, C, N, O and Fe elements. According to the collected data, by adding an extra layer to the core shell system the magnetic power was substantially declined which was confirmed by VSM analysis. The obtained results indicated that the current vigorous acid-modified nanomagnetic catalyst has superparamagnetic properties and monotonous structure with an average particle diameter of around 20 nm. Besides that, core-shell structure and uniform coat of silica layer inferred from TEM analysis. To the best of our knowledge in comparison with the long time, hard reaction conditions previously reported procedures, this simple protocol offers several advantages including one-pot multicomponent synthesis, outstanding catalytic performance in terms of yields, brief time period of the reactions, lack of hazardous catalyst or solvent, facile work-up procedure, ease of separation, broad substrates scope, recyclability of the magnetic catalyst at least for 7-times, carrying out reactions with approximately low loading of the catalyst (0.045 g) and good accordance with some of the green chemistry principles.

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#### **Supplementary Information**

Additional supporting information including spectroscopic characterization data of some products can be found in the online version of this article at the publisher's web site. Accepter

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### Abstract

The first report of nano-Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-NH-gallic acid in multicomponent reactions as a reusable magnetically separable nanocatalyst for one-pot condensation of various aromatic aldehydes, ß-.id ketoesters and 5-aminotetrazole to deliver the desired tetrazolo[1,5-a]pyrimidine derivatives is