KCC-1-NH₂-DPA: an efficient heterogeneous recyclable nanocomposite for the catalytic synthesis of tetrahydrodipyrazolopyridines as a well-known organic scaffold in various bioactive derivatives

Sajjad Azizi, Nasrin Shadjoub and Mohammad Hasanzadeh

ABSTRACT

In this study, a novel approach has been used for the efficient synthesis of tetrahydrodipyrazolopyridine derivatives (5a–m) via a four-component one-pot condensation reaction of aromatic aldehydes, hydrazinehydrate, ethyl acetoacetate, and ammonium acetate in the presence of KCC-1-npr-NH₂-DPA as an advanced nano-catalyst in ethanol under reflux conditions at 30 min. For this purpose, mesoporous fibrous nano-silica functionalized by dipenicillamine as a novel nanocatalyst (KCC-1-npr-NH₂-DPA) was synthesized using a hydrothermal protocol. KCC-1-npr-NH₂-DPA nano-catalyst is easily recyclable eight times without the considerable loss of catalytic activity. Other remarkable features include the short reaction time, simple work-up procedure and providing excellent yields (89–98%) of the products under mild reaction conditions. Furthermore, the effects of solvent, concentration of catalyst, time and temperature for the synthesis of tetrahydrodipyrazolopyridine (5a) were studied.

1. Introduction

Pyrazolopyridines represent a well-known organic scaffold in various bioactive derivatives and have various pharmacological properties. These compounds exhibit significant biological properties, including anti-bacterial [1,2], anti-microbial [3,4], anti-fungal [5], anti-tumor [6], anti-virus [7], anti-Leishmania [8], HIF 1-α-prolyl hydroxylase inhibitors [9], B-RafV600E inhibitors [10], protein kinase inhibitors [11], PDE4B inhibitors [12], dopaminergic properties [13] and cancer cell lines growth inhabitation activities [14]. The main problems for the synthesis of pyrazolopyridine compounds are long reaction times, utilization of non-reusable and toxic catalyst and use of particular conditions. Therefore, looking for simple and efficient methods for the synthesis of pyrazolopyridines is essential. For these reasons, multicomponent reactions (MCRs) are specially well suited for variety-oriented synthesis [15]. MCRs provide suitable conditions with high demand in advanced organic synthesis. It is especially accurate in case of heterocycle compounds [16] as those reactions comfort formation of various bonds in one-pot operation [17]. Development of several synthetic methodologies to achieve various diversities of pyrazolopyridines derivatives, exhibits the growing...
interests into these compounds [18]. MCRs have also be widely utilized for synthesis of functional poly- 
mers and polymeric composites with great potential for biomedical and environmental applications 
[19–22]. Thus, the synthesis of pyrazolopyridines by 
MCRs with a suitable catalyst could enhance their 
efficiency from an ecological points of view. 

Several kinds of catalysts have been used to 
advance the reactions using MCRs, such as acetic 
acid [23], carbonaceous material (C-SO$_3$H) [24], p-
TSA [25] and L-proline [26]. In recent years, the use 
of nanocatalysts has increased quickly and caused in 
the advancement of several active and capable nano-
catalyst for various procedures [27–30]. These mate-
rials have several advantages over formal catalysts, 
such as excellent activity and high stability. In add-
ition, metal nanoparticles with a superior support 
provides a large area for the discovery of novel and 
highly active nanocatalyst for significant reactions, 
which also promises the advantage of recycling. 
Recently, surface functionalized mesoporous systems 
have appeared as one of the most significant 
research areas in the concerning of advanced func-
tional materials [28,31,32]. Particularly, researchers 
reported synthesis of fibrous nano-silica (KCC-1), as 
a new nano-silica with high surface area (typically 
$>700$ m$^2$ g$^{-1}$), broad pore size distribution, large 
pore sizes [33], ease of surface modification, low 
density, suitable stability, and low toxicity with good 
biocompatibility [9,11,12]. Also, this dendritic 
fibrous nanosilica showed special activities in vast 
fields such as heterogeneous catalysis [34], gas capture, 
solar energy harvesting, energy storage [35], 
medical diagnosis, targeting of drugs [7,36–38], 
DNA adsorption [39], drug delivery applications 
[18], bio sensing [40] and CO$_2$ mitigation [41]. 

In this study, we reported the use of KCC-1-npr-NH$_2$-DPA (d-pencil amine) nanocatalyst as an 
efficient material for the synthesis of tetrahydrodi-
pyrazolopyridine (5a–l) compounds by MCR of 
aromatic aldehydes, hydrazinehydrate, ethyl acetoa-
cetate and ammonium acetate under reflux condi-
tions in ethanol as a solvent (Scheme 1). We found 
that KCC-1-npr-NH$_2$-DPA nanocatalyst produce 
our desired compounds in high yields (89–98%) 
with excellent recovery and simple work-up procedure. 
In addition, KCC-1-npr-NH$_2$-DPA has a good 
recycling properties and this advantage is important 
from economic point of view.

2. Experimental

2.1. Materials and methods

All chemical materials and solvents were purchased 
from Merck, Sigma Aldrich and Fluka in high purity 
and used without further purification. Melting 
points were measured in open capillaries using an 
Electrothermal MEL-TEMP apparatus (model 9200) 
and are uncorrected. X-ray diffraction (XRD) pat-
terns of KCC-1-based materials were recorded on a 
Siemens D 5000 X-Ray diffractometer (TX, USA) 
with a Cu K$_\alpha$ anode ($\lambda = 1.54$ Å$^{-1}$) operating at 40 kV 
and 100 mA. Scanning electron microscopy (SEM) 
images and Energy-dispersive X-ray spectroscopy 
(EDX) were recorded with FEG-SEM MIRA3 
TESCAN, Czech Republic) at 1000 kV. Transmission 
electron microscopy (TEM) analysis was conducted 
on a Carl Zeiss LEO 906 electron microscope 
operated at 100 kV (Oberkochen, Germany). 
Brunauer–Emmett–Teller (BET) was recorded on a 
Micromeritics NOVA 2000 apparatus at 77 K using nitrogen as the adsorption gas (FL, USA). The 
particle size distribution and zeta potential values were 
determined using Malvern particle size analyzer 
(Malvern, UK). The purity determination of the 
products and reaction monitoring were accom-
plished by TLC on silica gel poly gram SILG/UV 
254 plates.

2.2. Preparation of KCC-1

KCC-1 was synthesized according to the procedure 
described by Bayal et al. [42]. Briefly, 1 g cetyl tri-
methylammonium bromide (CTAB) was added to 
10 mL deionized water and after addition of 0.6 g 
urea, the mixture was stirred for about 3 h at room 
temperature. Then, 2 gr of tetraethyl orthosilicate 
(TEOS), 30 mL cyclohexane and 1.5 mL hexanol was 
added to the flask and sonicated for 30 min. To con-
tinue, the mixture was refluxed at 80°C for 24 h. 
Afterwards, the mixture was cooled to the room 
temperature and centrifuged to collect the KCC-1 as 
white sediment. The collected KCC-1 was washed 
several times with deionized water and ethanol and 
was dried at 60°C for 24 h. Finally, KCC-1 was cal-
cinated at 550°C for 6 h to remove the CTAB as 
templating agent.

Scheme 1. Synthesis of tetrahydrodipyrazolopyridines (5a–l) in the presence of KCC-1-npr-NH$_2$-DPA.
2.3. Preparation of KCC-1-npr-NH₂

In order to functionalize the KCC-1 surface with NH₂ moieties, 0.02 g KCC-1 was dispersed in the 1.2 mL dried toluene and sonicated for 30 min. Then 50 μL 3-aminopropyl triethoxysilane (APTES) was added to the mixture and refluxed for 20 h at 80 °C. The mixture was separated and washed with toluene several times and dried at 80 °C for 24 h.

2.4. Preparation of KCC-1-npr-NH₂-DPA

To a magnetically stirred, 10 mg of dipencilamine (DPA), 5 mg of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide and 3 mg of N-hydroxysuccinimide were added to the 50 mL of N,N-dimethyl sulfoxide (DMSO) and stirred for 2 h at room temperature and named as flask 1. In another flask, to a mixture of DMSO: toluene (1:7) (35 mL), 1 g of KCC-1 and 10 μL of APTES were added and stirred for 2 h at room temperature. Subsequently, ‘flask 1’ was added to the ‘flask 2’ and stirred for 24 h at room temperature. Finally, the KCC-1-npr-NH₂-DPA was collected by centrifugation and washed several times with anhydrous toluene and was dried at 50 °C and stored in a refrigerator as a white powder (Scheme 2).

2.5. General procedures for preparation of tetrahydrodipyrazolopyridine (5a–l)

A mixture of ethyl acetoacetate (2 mmol) (1) and hydrazine hydrate (2.0 mmol) (2) and KCC-1-NH₂-DPA (0.1 g) in EtOH (4 mL) was magnetically stirred for 10 min at 25 °C followed by addition of aromatic aldehyde (1.0 mmol) (3) and ammonium acetate (4.0 mmol) (4). The reaction mixture was heated under reflux conditions for 30 min and then cooled to 25 °C. Then the mixture monitored by TLC and after completion of the reaction, the nanocatalyst (KCC-1-NH₂-DPA) were separated by filtration. The formed precipitate was washed with warm EtOH and recrystallized in EtOH to afford the pure product. The catalyst was washed with acetone/water and used for next runs without a considerable loss of efficiency (Scheme 1).

2.6. Characterization of KCC-1, KCC-1-NH₂ and KCC-1-NH₂-Cys

The synthesis of KCC-1-npr-NH₂-DPA nanocatalyst involved several stages (Scheme 2). To investigate the morphology of KCC-1-npr-NH₂-DPA, FE-SEM images were recorded (Figure 1(a)). Moreover, the structure and size of the KCC-1-npr-NH₂-DPA NPs were evaluated utilizing (TEM) (Figure 1(b)). The uniform fibers of the KCC-1 with high surface area have several Si-OH groups that could grows from the inner to outside as shown in the TEM images. Also, the TEM images revealed the porous, fibrous and spherical form of the nanomaterials where the fibrous system is as a result of using the CTAB for the NPs design, with the fibrous-sphere revealing the formation of KCC-1-based NPs. The size of the KCC-1-npr-NH₂-DPA is about 25 nm. As shown in Figure S1, the KCC-1-npr-NH₂-DPA have a constant particle size range of 20–35 nm. EDX results indicates the atomic structure of the produced compound and that the KCC-1 is composed only with Si and O. Though, the carbon is arising from the SEM grid and CTAB as a pattern agent. Moreover, after functionalization with APTES, the weight
percent of N, O, S and C are increased which proofs the efficacious surface modification of KCC-1 with APTES and DPA (Figure S2).

The powder XRD patterns of KCC-1-npr-NH₂-DPA are shown in Figure 2. The XRD pattern of KCC-1-NH₂-DPA was performed from 3.0° (2θ) to 70.0° (2θ) to investigate the crystallinity of the produced nanomaterial in order to obtain additional information about their molecular structures. As can be observed, the result indicated that crystallinity was increased from KCC-1 to KCC-1-npr-NH₂-DPA, because of two significant peaks. The wide peak between 20 and 30 is related to the amorphous silica. Thus, the XRD templates of the KCC-1-npr-NH₂-DPA is similar to the fibrous mesoporous silica with DPA.

The N₂ adsorption–desorption isotherms of KCC-1-npr-NH₂-DPA NPs are shown in Figure S3. The BET and BJH analyses of the KCC-1-npr-NH₂-DPA were used to determine the porous structure of the nanoparticles (Figure S3c). The specific surface area and porosity of the materials were determined using the adsorption isotherm and calculated by BET. Also, BJH technique was used to evaluate the pore volume of the KCC-1, KCC-1-npr-NH₂ and KCC-1-npr-NH₂-DPA. The BET surface area of KCC-1, KCC-1-npr-NH₂ and KCC-1-npr-NH₂-DPA was obtained as 617, 367 and 78 m² g⁻¹. Also, the average pore size is 6.7 nm. The pore volumes, pore size, and surface area of KCC-1, KCC-1-npr-NH₂ and KCC-1-npr-NH₂-DPA are clearly proven by the reported results.

FTIR was employed to confirm the proper functionalization of the KCC-1 fibrous structure with –NH₂ and DPA moieties. As shown in Figure S4, the typical peaks of the silica based nanomaterials could be seen in the range of 1049–1075 cm⁻¹ representing the Si-O-Si asymmetric stretching. Also, a Si-OH peak could be observed at 799 cm⁻¹ which showed the asymmetric bending and stretching vibration. In addition, the peak at around 1377 cm⁻¹ is assigned to the amide bonds between the carboxyl of DPA and amine group of the KCC-1-npr-NH₂.

3. Results and discussion
Having proven the complete, proper and correct synthesis of the nanocatalyst the catalytically performance was evaluated for the synthesis of tetrahydrodipyrazolopyridines. In order to optimize the MCR conditions and obtain well catalytic activity, synthesis of tetrahydrodipyrazolopyridine was used as a model and investigated under different reaction parameters including the amount of the catalyst, time, temperature, and solvent type. Initially, the effect of solvent on the synthesis of tetrahydrodipyrazolopyridine compounds using the KCC-1-npr-NH₂-DPA was studied. According to obtained results, the type of solvent has significant effect on the performance of the nanocatalyst. For example, cyclohexane, n-Hexane and CCl₄, which are non-polar solvents, gave tetrahydrodipyrazolopyridine at a lower yield than other solvents (Table 1, entries 5–7) and the aprotic polar solvents including THF, CH₂CN, CH₂Cl₂, CHCl₃, DMF, EtOAc, toluene and DMSO gave product in low yields (Table 1, entries 8–15). Moreover, the protic solvents improved reaction performance. Methanol and iPrOH gave tetrahydrodipyrazolo pyridine in average yields (Table 1,
entries 16 and 17). In contrast, the utilization of water caused in an increased yield of 70%, while the yield was considerably increased up to 97% when ethanol was used as an organic solvent in the presence of KCC-1-npr-NH$_2$-DPA NPs. In this research, it was found that conventional heating under reflux conditions in ethanol (as a solvent; Table 1) for 30 min in the presence of 0.0001 g of KCC-1-npr-NH$_2$-DPA gave more efficient conditions for desired tetrahydrodipyrazolopyridines. We also examined the essential role of temperature in the synthesis of tetrahydrodipyrazolopyridine in the presence of KCC-1-npr-NH$_2$-DPA NPs as the catalyst. In this case, the tetrahydrodipyrazolopyridines were obtained with excellent isolated yield at 76°C and results clearly indicated that reaction completion is related to reaction temperature. The optimum

![Figure 3. Optimization of the conditions for synthesis of tetrahydrodipyrazolopyridines: ethyl acetoacetate (2 mmol), hydrazine hydrate (2.0 mmol), aromatic aldehyde (1.0 mmol) and ammonium acetate (4.0 mmol), KCC-1-npr-NH$_2$-DPA (0.1 mg), EtOH (4 mL), under reflux conditions, 1 h.](image)

![Figure 4. Effect of time on yield of tetrahydrodipyrazolopyridines: ethyl acetoacetate (2 mmol), hydrazine hydrate (2.0 mmol), aromatic aldehyde (1.0 mmol) and ammonium acetate (4.0 mmol), KCC-1-npr-NH$_2$-DPA (0.1 mg), EtOH (4 mL), under reflux conditions for 30 min.](image)

| Entry | Solvent | Temp. (°C) | Yield (%) |
|-------|---------|------------|-----------|
| 1     | EtOH    | r.t.       | 69        |
| 2     | EtOH    | reflux     | 98        |
| 3     | H$_2$O  | r.t.       | 54        |
| 4     | H$_2$O  | reflux     | 70        |
| 5     | Cyclohexane | r.t. | 18 |
| 6     | n-Hexane | r.t.       | 19        |
| 7     | CCl$_4$ | r.t.       | 21        |
| 8     | THF     | r.t.       | 35        |
| 9     | CH$_3$CN | r.t. | 40 |
| 10    | CH$_2$Cl$_2$ | r.t. | 32 |
| 11    | CHCl$_3$ | r.t.       | 44        |
| 12    | DMF     | r.t.       | 22        |
| 13    | EtOAc   | r.t.       | 48        |
| 14    | Toluene | r.t.       | 35        |
| 15    | DMSO    | r.t.       | 39        |
| 16    | Methanol| r.t.       | 64        |
| 17    | i-PrOH  | r.t.       | 57        |

**Reaction conditions:** ethyl acetoacetate (2 mmol), hydrazine hydrate (2.0 mmol), 4-nitrobenzaldehyde (1.0 mmol) and ammonium acetate (4.0 mmol), KCC-1-npr-NH$_2$-DPA (0.1 g), EtOH (4 mL), under reflux conditions for 30 min. Isolated yield (%).
temperature for this reaction was 76 °C. The higher temperatures lead to alterations in the efficiency of the reaction (Table 1, entries 1 and 2). Next, the amount of catalyst necessary to complete the reaction efficiently was investigated. It was detected that the variation in the KCC-1-npr-NH$_2$-DPA NPs amount had an efficient influence. The highest amount of KCC-1-npr-NH$_2$-DPA was 0.1 mg, which obtained a desired product at 98% yields (Figure 3). Also, excellent yields of tetrahydrodipyrazolo pyridine using this catalyst system for 30 min were obtained (Figure 4).

To further investigate the efficiency of the nanocatalyst, we compared the catalytic performance of our catalyst with different control experiments and the results are shown in Table 2. Originally, a standard reaction was accomplished using KCC-1, KCC-1-npr-NH$_2$, DPA and KCC-1-npr-NH$_2$-DPA; and the results confirmed that the desired product was not formed (Table 2, entries 1 and 4) after 1 h of reaction time in different amounts. When KCC-1-npr-NH$_2$-DPA was used as the catalyst, a reaction was performed and completed (Table 2, entry 4).

Ultimately, the reaction conditions were optimized, and to carry out this approach, we specially evaluated this methodology utilizing hydrazine hydrate, ethyl acetoacetate, ammonium acetate and a variety of different substituted aromatic aldehydes in the presence of KCC-1-npr-NH$_2$-DPA in ethanol under reflux conditions. As shown in Table 3, the type of substituents on the aromatic ring and electronic effects did not show extremely evident effects in terms of yields under the reaction conditions. Aromatic aldehydes containing electron-donating groups and electron-withdrawing were used and reacted well to afford the desired tetrahydrodipyrazolo pyridines in excellent yields with high purity.

It is undeniable that for a catalytic process, the recovery and reuse of catalyst materials is highly preferable. In this regard, the recyclability of the KCC-1-npr-NH$_2$-DPA was investigated using the model reaction of hydrazine hydrate, ethyl acetoacetate, aromatic aldehydes and ammonium acetate under identical reaction conditions. After the completion of reaction, the recovered catalyst from the reaction mixture was washed with acetone/water and dried at room temperature and reused for subsequent reactions. It is obvious that the heterogeneous property of the KCC-1-npr-NH$_2$-DPA facilitates the effective recovery of the nanocatalyst.

**Table 2. Influence of different nanocatalysts for the synthesis of tetrahydrodipyrazolo pyridine (5a).**

| Entry | Catalyst       | Yield (%) |
|-------|----------------|-----------|
| 1     | KCC-1          | 87        |
| 2     | KCC-1-npr-NH$_2$ | 92        |
| 3     | DPA            | 91        |
| 5     | KCC-1-npr-NH$_2$-DPA | 98 |

Reaction conditions: ethyl acetoacetate (2 mmol), hydrazine hydrate (2.0 mmol), 4-nitrobenzaldehyde (1.0 mmol) and ammonium acetate (4.0 mmol), KCC-1-npr-NH$_2$-DPA (0.1 g), EtOH (4 mL), under reflux conditions for 30 min. Isolated yield (%).

**Table 3. Synthesis of tetrahydrodipyrazolo pyridines in the presence of the KCC-1-npr-NH$_2$-DPA catalyst in ethanol.**

| Entry | Product no. | R$^1$ | Time (min) | Yield (%) | MP (°C) | Found | Reported |
|-------|-------------|-------|------------|-----------|--------|-------|----------|
| 1     | 5a          | p-NO$_2$ | 30         | 98        | >300   | >300  |
| 2     | 5b          | m-NO$_2$ | 30         | 95        | 285–286| 285–288|
| 3     | 5c          | o-NO$_2$ | 30         | 94        | 187–189| 187–189|
| 4     | 5d          | p-Me    | 30         | 90        | 244–247| 244–246|
| 5     | 5e          | o-Me    | 30         | 89        | 292–293| 290–292|
| 6     | 5f          | H       | 30         | 92        | 238–241| 240–242|
| 7     | 5g          | p-O$_2$H | 30         | 92        | 185–188| 185–187|
| 8     | 5h          | p-CI    | 30         | 94        | 255–257| 254–256|
| 9     | 5i          | p-Br    | 30         | 92        | 164–166| 165–167|
| 10    | 5j          | p-OH    | 30         | 95        | 268–269| 267–268|
| 11    | 5k          | p-NMe$_2$| 30         | 89        | 241–243| 240–242|
| 12    | 5l          | p-F     | 30         | 93        | 256–258| 258–260|

Reaction conditions: ethyl acetoacetate (2 mmol), hydrazine hydrate (2.0 mmol), aromatic aldehyde (1.0 mmol) and ammonium acetate (4.0 mmol), KCC-1-npr-NH$_2$-DPA (0.1 g), EtOH (4 mL), under reflux conditions for 30 min. Isolated yield (%).

![Figure 5. Reusability of KCC-1-npr-NH$_2$-DPA.](image-url)
from the reaction mixture during the work-up procedure so that the catalyst could be recycled and reused up to eight consecutive trials without remarkable loss of its catalytic activity (Figure 5) and the recyclability test of catalyst was stopped after eight runs. Thus, these results indicated that the nanocatalyst was stable and could tolerate the MCR conditions.

In order to show the special efficiency of the KCC-1-npr-NH₂-DPA in comparison with different catalysts which used for similar reactions, we summarize numerous results for the synthesis of 4-(3,5-dimethyl-1,4,7,8-tetrahydroydipyrazolo[3,4-b:4',3'-e]pyridin-4-yl)phenol (5j) in Table 4. Our study has some advantages in compare with other mention studies including high yield of synthetic compound, reasonable time reaction and easy catalyst recovery. In this regard, some of other reported have shorter reaction time.

4. Conclusions

In summary, we prepared a new fibrous oregano-silica (KCC-1-npr-NH₂-DPA) and used it as a nanocatalyst for the synthesis of tetrahydroydipyrazolo pyridine derivatives in ethanol as a solvent with excellent yield under reflux reaction conditions. This catalyst could be recovered and reused at least eight times with no significant decrease in its activity and selectivity. Our method has some advantages, containing short reaction times, mild reaction conditions, the reusability of the heterogeneous catalyst, high yields and convenient workup process.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This research was supported by Tabriz University and Tabriz University of Medical Sciences.

Notes on contributors

Sajjad Azizi received his M.Sc. in organic chemistry from Tabriz University. He has published mainly on organic synthesized using heterogenis nano-catalysts. Also, he is a researcher in the field of pharmaceutical science based on analytical methods. He is a researcher with over 145 publications and research interests in nano-catalyst and nanomaterial base electrochemistry.

Nasrin Shadjou received her Ph.D. in organic chemistry from K.N. Toosi University of Technology, Tehran, Iran. She currently is an associated professor of Nanochemistry at Department of Nanochemistry, Nano Technology Research Center, Urmia University. She is a researcher with over 156 publications and research interests in nanocatalyst and nanomaterial base electrochemistry. Her research interests include the preparation of metal silica mesoporous and graphene quantum dot materials in particular smart silica materials, and their applications in health science and environmental technology.

Mohammad Hasanzadeh is an assistant professor of pharmaceutical analysis at Tabriz University of Medical Sciences (TUOMS) at Drug Applied Research Center. He studied Electrochemistry at K.N. Toosi University of Technology (Tehran, Iran) and gained his M.Sc. in 2008. In 2010, he founded Drug Applied Research Center and worked at that center as the Ph.D. candidate for 4 years. Dr. Hasanzadeh has also received International Razi Award for excellence in research in basic sciences in 2010. He has published more than 200 articles in peer-reviewed journals. He has been the PI of more than 10 national research projects funded by the Ministry of Health of Iran. Recently, he has focused on the immunosensing methods based on advanced nanomaterials. Also, he has some of important approach on the science and engineering of nanomaterials and nano-devices used in health such as: a) IFIA (The International Federal of Inventors Associations) CUP for the best invention of the 3rd International Olympiad of inventors, Originators and innovators, 2012; b) Gold Medal Cup in 2th, 3rd, and 4th International Invention Festival in 2012, 2013, and 2014, respectively; c) Distinguished in Nanotechnology, Business Plan Group, 2011 (7th National Sheikh Bahaie Technology Festival).

ORCID

Mohammad Hasanzadeh http://orcid.org/0000-0003-4918-1239

References

1. Samar C, Ismail A, Helmi T, et al. Substituted pyrazolo[3,4-b]pyridin-3-ones and pyrazolo[3,4-b]pyridine-5-carbaldehyde, new one-pot synthesis strategy amelioration using vinamidinium salts, antibacterial and antifungal activities promising environmental protection. J Bacteriol Parasitol. 2017:8:1–8.
2. Maqbool T, Nazeer A, Khan MN, et al. Pyrazolopyridines II: synthesis and antibacterial screening of 6-aryl-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-4-carboxylic Acids. Asian J Chem. 2014;26:2870–2872.
3. Salem MS, Ali MAM. Novel pyrazolo[3,4-b]pyridine derivatives: synthesis, characterization, antimicrobial and antiproliferative profile. Biol Pharmac Bull. 2016;39:473–483.
4. Sindhu J, Singh H, Khurana J, et al. Synthesis and biological evaluation of some functionalized 1H-1,2,3-triazole tethered pyrazolo[3,4-b]pyridin-6(7H)-ones as antimicrobial and apoptosis inducing agents. Med Chem Res. 2016;25:1813–1830.

5. Quiroga J, Villarreal Y, Gálvez J, et al. Synthesis and antifungal in vitro evaluation of pyrazolo[3,4-b]pyridines derivatives obtained by azadiels-alder reaction and microwave irradiation. Chem Pharm Bull. 2017;65:143–150.

6. Mohamed NR, Khaireldin NY, Fahmyb A, et al. Facile synthesis of fused nitrogen containing heterocycles as anticancer agents. Der Pharm Chem. 2010; 2:400–417.

7. Gudmundsson KS, Johns BA, Allen SH. Pyrazolopyridines with potent activity against herpesviruses: effects of C5 substratetions on antiviral activity. Bioorg Med Chem Lett. 2008;18:1157–1161.

8. de Mello H, Echevarria A, Bernardino AM, et al. Antileishmanial pyrazolopyridine derivatives: synthesis and structure-activity relationship analysis. J Med Chem. 2004;47:5427–5432.

9. Warshakoon NC, Wu S, Boyer A, et al. Design and synthesis of a series of novel pyrazolopyridines as HIF-1alpha prolyl hydroxylase inhibitors. Bioorg Med Chem Lett. 2006;16:5687–5690.

10. Wenglowsky S, Moreno D, Rudolph J, et al. Pyrazolopyridine inhibitors of B-RafV600E. Part 3: an increase in aqueous solubility via the disruption of crystal packing. Bioorg Med Chem Lett. 2012;22: 912–915.

11. Chioua M, Samadi A, Soriano E, et al. Synthesis and biological evaluation of 3,6-diamino-1H-pyrazolo[3,4-b]pyridine derivatives as protein kinase inhibitors. Bioorg Med Chem Lett. 2009;19: 4566–4569.

12. Mitchell CJ, Ballantine SP, Coe DM, et al. Pyrazolopyridines as potent PDE4B inhibitors: 5-heterocycle SAR. Bioorg Med Chem Lett. 2010;20: 5803–5806.

13. Tschammer N, Elsner J, Goetz A, et al. Highly potent 5-aminotetrahydroazopyrazolopyridines: enantioselective dopamine D3 receptor binding, functional selectivity, and analysis of binding: ligand interactions. J Med Chem. 2011;54:2477–2491.

14. Eissa IH, El-Naggar AM, El-Hashash MA. Design, synthesis, molecular modeling and biological evaluation of novel 1H-pyrazolo[3,4-b]pyridine derivatives as potential anticancer agents. Bioorg Chem. 2016;67: 43–67.

15. Esteve V, Villacampa M, Menendez JC. Multicomponent reactions for the synthesis of pyroroles. Chem Soc Rev. 2010;39:4402–4421.

16. Indumathi S, Menendez JC, Perumal S. L-proline catalysed domino reactions for the synthesis of heterocycles. Curr Org Chem. 2013;17:2038–2064.

17. Pagadala R, Maddila S, Jonnalagadda SB. Eco-efficient ultrasonic responsive synthesis of pyrimidines/pyridazines. Ultrasound Sonochem. 2014;21:472–477.

18. Safaei-Gholmi J, Sadeghzhadeh R, Shabbazi-Alavi H. A pseudo six-component process for the synthesis of tetrahydrodiarylpyrazolo pyridines using an ionic liquid immobilized on a FeNi 3 nanocatalyst. RSC Adv. 2016;6:33676–33685.

19. Dou J, Gan D, Huang Q, et al. Functionalization of carbon nanotubes with chitosan based on MALI multicomponent reaction for Cu2+ removal. Int J Biol Macromol. 2019;136:476–485.

20. Jiang R, Liu M, Huang H, et al. Facile fabrication of organic dyed polymer nanoparticles with aggregation-induced emission using an ultrasound-assisted multicomponent reaction and their biological imaging. J Colloid Interface Sci. 2018;519:137–144.

21. Jiang R, Huang L, Liu M, et al. Ultrafast microwave-assisted multicomponent tandem polymerization for rapid fabrication of AIE-active fluorescent polymeric nanoparticles and their potential utilization for biological imaging. Mater Sci Eng C. 2018;83:115–120.

22. Long Z, Liu M, Jiang R, et al. Preparation of water soluble and biocompatible AIE-active fluorescent organic nanoparticles via multicomponent reaction and their biological imaging capability. Chem Eng J. 2017;308:527–534.

23. Ghadzi A, Bardajee G, Mirshokrayi A, et al. Facile, novel and efficient synthesis of new pyrazolo[3,4-b]pyridine products from condensation of pyrazole-5-amine derivatives and activated carbonyl groups. RSC Adv. 2015;5:89652–89658.

24. Chen Z, Shi Y, Shen Q, et al. Facile and efficient synthesis of pyrazololoisoquinoline and pyrazolopyridine derivatives using recoverable carbonaceous material as solid acid catalyst. Tetrahedr Lett. 2015;56:4749–4752.

25. Sohal HS, Kaur M, Khare R, et al. p-TSA catalysed, one-pot synthesis and antimicrobial evaluation of some novel fused dipyrazolo-1, 4-dihydropyridine derivatives. Am J Org Chem. 2014;4:21–25.

26. Gunasekaran P, Prasanna P, Perumal S. l-Proline-catalyzed three-component domino reactions for the synthesis of highly functionalized pyrazolo[3,4-b]pyridines. Tetrahedr Lett. 2014;55:329–332.

27. Santra S, Rahman M, Roy A, et al. Nano-indium oxide: an efficient catalyst for one-pot synthesis of 2,3-dihydroquinazolin-4(1H)-ones with a greener prospect. Catal Commun. 2014;49:52–57.

28. Mobaraki A, Movassagh B, Karimi B. Hydrophobicity-enhanced magnetic solid sulfonic acid: a simple approach to improve the mass transfer of reaction partners on the surface of heterogeneous catalyst in water-generating reactions. Appl Catal A: Gen. 2014;472:123–133.

29. Koukabi N, Kolvari E, Khazaei A, et al. Hantzsch reaction on free nano-Fe2O3 catalyst: excellent reactivity combined with facile catalyst recovery and recyclability. Chem Commun. 2011;47:9230–9232.

30. Zhang D, Zhou G, Sun Z, et al. Magnetically recyclable nanocatalysts (MRNCs): a versatile integration of high catalytic activity and facile recovery. Nanoscale. 2012;4:6244–6255.

31. Khater HM. Effect of nano-silica on microstructure formation of low-cost geopolymer binder. Nanocomposites. 2016;2:84–97.

32. Soundhar A, Rajesh M, Jayakrishna K, et al. Investigation on mechanical properties of polyurethane hybrid nanocomposite foams reinforced with roseelle fibers and silica nanoparticles. Nanocomposites. 2019;5:1–12.

33. Tameh FA, Safaei-Gholmi J, Mahmoudi-Hashemi M, et al. One-pot multicomponent reaction synthesis of spiropyrindoles promoted by guanidine-functionalized magnetic Fe3O4 nanoparticles. RSC Adv. 2016;6:74802–74811.
34. Shylesh S, Schünemann V, Thiel WR. Magnetically separable nanocatalysts: bridges between homogeneous and heterogeneous catalysis. Angew Chem Int Ed. 2010;49:3428–3459.
35. Huddleston JG, Visser AE, Reichert WM, et al. Characterization and comparison of hydrophilic and hydrophobic room temperature ionic liquids incorporating the imidazolium cation. Green Chem. 2001;3:156–164.
36. El-Borai MA, Rizk HF, Beltagy DM, et al. Microwave-assisted synthesis of some new pyrazolopyridines and their antioxidant, antitumor and antimicrobial activities. Eur J Med Chem. 2013;66:415–422.
37. Abu-Melha S. Synthesis and antimicrobial activity of some new heterocycles incorporating the pyrazolopyridine moiety. Archiv der Pharmazie. 2013;346:912–921.
38. Pfefferkorn JA, Tu M, Filipski KJ, et al. The design and synthesis of indazole and pyrazolopyridine based glucokinase activators for the treatment of Type 2 diabetes mellitus. Bioorg Med Chem Lett. 2012;22:7100–7105.
39. Safaei-Ghomi J, Shahbazi-Alavi H. A flexible one-pot synthesis of pyrazolopyridines catalyzed by Fe3O4@SiO2-SO3H nanocatalyst under microwave irradiation. Sci Iran. 2017;24:1209.
40. Soleymani J, Hasanzadeh M, Somi MH, et al. Highly sensitive and specific cytosensing of HT 29 colorectal cancer cells using folic acid functionalized-KCC-1 nanoparticles. Biosens Bioelectron. 2019;132:122–131.
41. Singh B, Polshettiwar V. Design of CO 2 sorbents using functionalized fibrous nanosilica (KCC-1): insights into the effect of the silica morphology (KCC-1 vs. MCM-41). J Mater Chem A. 2016;4:7005–7019.
42. Bayal N, Singh B, Singh R, et al. Size and fiber density controlled synthesis of fibrous nanosilica spheres (KCC-1). Sci Rep. 2016;6:24888.
43. Zhao K, Lei M, Ma L, et al. A facile protocol for the synthesis of 4-aryl-1,4,7,8-tetrahydro-3,5-dimethylpyrazolo[3,4-b:4′,3′-c]pyridine derivatives by a Hantzsch-type reaction. Monatsh Chem. 2011;142:1169.
44. Shabalala NG, Pagadala R, Jonnalagadda SB. Ultrasound-accelerated rapid protocol for the improved synthesis of pyrazoles. Ultrason Sonochem. 2015;27:423–429.
45. Safaei-Ghomi J, Shahbazi-Alavi H, Sadeghzadeh R, et al. Synthesis of pyrazolopyridines catalyzed by nano-CdZr4(PO4)6 as a reusable catalyst. Res Chem Intermed. 2016;42:8143–8157.
46. Sadeghzadeh SM. A heteropolyacid-based ionic liquid immobilized onto magnetic fibrous nano-silica as robust and recyclable heterogeneous catalysts for the synthesis of tetrahydrodipyrazolopyridines in water. RSC Adv. 2016;6:75973–75980.