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Glucose Coated Nano Fe_3O_4 (Glu@Fe_3O_4): A Potential Organocatalyst for Synthesis of 4,7-Dihydro-2*H*-pyrazolo[3,4-*b*]pyridines in Ethanol

AMULYA SINHA, ARZOO SIDDIQUI, VAIBHAV TRIPATHI, GIRISH SINGH, AMIT YADAV, RUDRAKSH SRIVASTAVA, NIKHAT FATIMA, GAUTAM KUMAR and VIVEK BHADAURIA*

Green Laboratory, Department of Chemistry, Ewing Christian College, University of Allahabad, Prayagraj-211003, India

*Corresponding author: E-mail: bvivek17@gmail.com

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Two novel homologous series of target moieties, pyrazolo[3,4-*b*]pyridine-5-carboxylate substitutes (**4a-e**) as well as pyrazolo[3,4-*b*]pyridine-5-carbonitrile substitutes (**5a-g**) involving heterocyclic scaffold have been synthesized and characterized using FT-IR, NMR and MS spectrometry to ascertain the molecular structure. The synthetic procedure has been carried out by a one-pot three-constituent mechanistic pathway of pyrazol-3-amine, several aromatic aldehydes as well as selected CH-active compounds under green conditions *via* one-pot process in the presence of glucose coated nano Fe_3O_4 (Glu@Fe_3O_4) as an organocatalyst and ethanol as an efficient solvent. This conversion is congenial with a wide heterogeneity of functional group endurance. The optimized reaction conditions, good output, incorporation of organocatalyst, no necessity for column chromatographic procedure, economical and eco-friendly solvent are the merits of this reaction protocol. An ecofriendly, harmless, diversified, excellent paramagnetic behaviour possessing catalyst (Glu@Fe_3O_4) was prepared and characterization was performed incorporating Fourier transform infrared spectroscopy, as well as X-ray diffraction technique. The surface of magnetic nanoparticles enveloped with glucose imparted magnificent catalytic property. The catalyst could be reprocessed and reutilized until six rounds unaccompanied by major downfall in the catalytic efficiency.

Keywords: Pyrazolo[3,4-*b*]pyridine, Multicomponent reactions, Green catalyst, Magnetic nanoparticles.

INTRODUCTION

Currently, the organic synthesis has witnessed the development of effective innovations and environmentally acceptable solvents for organic transformations to synthesize valuable target heterocyclic compounds in a single step. This has become a universal goal for both researchers as well as the drug companies [1-4]. The emergence of multicomponent reactions (MCRs) like a prominent instrument in synthetic organic, combinative chemical science and also drug invention procedures is noteworthy [5-9]. MCRs have a number of outstanding advantages, including excellent yields, atom economy, high peculiarity, quick reaction times and resistance to potentially dangerous reagents and purifying procedures [10-17]. The invention of new compounds and techniques underwent a standard shift with the start of combinatorial processes in MCRs. Variability, atom efficiency, affordability and sustainability in the environment are now the main issues. The use of environmental friendly solvents stands as an essential aspect of sustainable chemical practices. Investigations are underway to find alternative eco-friendly solvents as harmful solvents pose risks to the environment. Designing alternative reaction conditions is an ongoing effort in sustainable chemistry to replace the existing toxic, flammable, and dangerous organic solvents [18-23]. The use of several eco-friendly alternative reaction media such as ionized fluids [24-26], hypercritical fluids [27-29] and polyethylene glycol [30], has been extensively investigated during the past few years. MCRs utilizing safe and environmentally friendly solvents are suitable for chemical transformations while ensuring no harm to the environment.

Heterocyclic compounds comprising nitrogen and sulphur are the essential building blocks of a broad spectrum of efficient natural goods and drugs [31-33]. The hybrid pyrazolopyridine derivatives are among the N-heterocycles that have captured the interest of chemists due to their varied biological properties; therefore, they serve as a versatile synthesized fundamental

component in pharmaceutical manufacturing processes [34]. Pyrazolopyridines are an intriguing class of chemical scaffolds that inhibit phosphatidylinositol 3-kinase (PI3-K), cyclin-dependent protein kinase-5 (cdk-5) as well as cyclin-dependent protein kinase-2 (cdk-2) [35,36]. Hence, the unique potential possessed by these compounds for curing various ailments incorporating bipolar disorder, diabetes mellitus, dementia, Alzheimer's disease, schizophrenia, depression and also cancer. Anxiolytic drugs such as cartazolate (A) [37], tracazolate (B) [38], etazolate (C) [39] and others are examples of pyrazolopyridine derivatives and are shown in Fig. 1. Moreover, it is known that the pyrazolopyridine derivatives have economic value as luminophores and fluorescent materials in organic light-releasing devices [40]. Such instances accentuate the significance of target moiety, as vital pharmacological agents in biologically active miniature molecular structures.

Since glucose is a vital carbohydrate for every living being and is referred to as the body's pivotal energy source, it can be regarded a natural and biocompatible agent [41,42]. Due to its polyhydroxyl structure, it has been utilized as an eco-friendly catalyst and has shown remarkable catalytic activity in several processes such as enantioselective Michael addition, epoxidation, *etc*. [43-46]. It has also demonstrated the function of an environmental friendly, green medium for conducting reactions [47,48]. In recent times, glucose coated superparamagnetic iron oxide nanoparticles have been prepared and involved in numerous biological processes [49]. Thus, glucose encapsulated superparamagnetic iron oxide nanoparticles might be considered a reusable and recyclable, green, diverse organocatalyst. Due to their unique surface-to-volume ratio, which affects intriguing aspects that are distinct from their bulk form, nanostructures play a significant role in the current scenario [50]. Thus, magnetic nanoparticles reveal versatility as well as highperformance capabilities in several areas [51], incorporating medical diagnostics and therapies [52,53], chemical science [54-56], sanitation, *etc.*

A literature survey exhibits limited reports for the synthesis of target molecule involving the MCRs process. Fu *et al.* [57], for instance have demonstrated the Lewis acid $FeCl_3$-catalyzed synthetic procedure of pyrazolo[3,4-*b*]pyridines in a one-pot strategic approach from aldehydes, acetoacetanilides and 3-aminopyrazole in ethanolic medium. In a similar procedure, pyrazolo[3,4-*b*]quinoline analogues were synthesized in a PEG medium at 110 ºC by reacting 1,3-cyclohexanedione over acetoacetanilide. Utilizing toxic DMF as the reaction medium, Karnakar *et al.* [58] have synthesized pyrazolo[3,4-*b*]-pyridines using ultrasonic irradiation. These established methods do, however, have constraints like employment of expensive and hazardous chemicals and unfavourable reaction conditions. The intended product could not be isolated during the pyrazolo-[3,4-*b*]pyridine synthesis facilitated by PEG-400 at 60 ºC [15].

Taking into consideration the above facts on pyrazolo[3,4-*b*]pyridine synthesis, a simple process for synthesizing dihydropyrazolo[3,4-*b*]pyridine substitutes in a one-pot three components process of 3-aminopyrazole, aromatic aldehydes as well as selected active methylene molecules utilizing inexpensive ethanol as green solvent and glucose coated nano Fe_3O_4 (Glu@Fe_3O_4) as an organocatalyst in high yield.

EXPERIMENTAL

Analytical grade chemicals and reagents were procured from various reputed commercial sources and used as such. The uncorrected open glass capillary technique was utilized to obtain the melting points. The structural identification was analyzed by 400 FT spectrophotometer, BRUKER AVANCE II (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz). The chemical shift values are expressed in δ (ppm):, using $CDCl_3$ as a solvent and TMS as the internal standard. The silica gel G/UV-254 pre-coated TLC sheets with a 0.25 mm thickness were used to monitor the pro-gress of the reactions. At 70 eV, JEOL SX-102 (FAB) was used to analyze the mass spectra. A powder X-ray diffraction (XRD) spectra at room temperature was obtain to ascertain the crystal-line structure of the catalyst organonanoparticles emploing the instrument Philips X-Pert 1710 diffractometer incorporating Co*K*α radiation (λ = 1.78897 Å) at a voltage of 40 kV and current of 40 mA. The characteristic angle values ranging from 10º to 90º (2θ) was selected as the standard to report the data having a scan pace of 0.02º s^{-1}.

Preparation of catalyst [Glu@Fe_3O_4]: A conventional coprecipitation mechanistic process was employed to prepare superparamagnetic Fe_3O_4 nanoparticles. In brief, in a 150 mL round bottom flask, dissolved $FeCl_3{\cdot}6H_2O$ (10 mmol) alongwith $FeCl_2{\cdot}4H_2O$ (5 mmol) in 45 mL of distilled water. At room temperature, the reaction mixture was vigorously agitated for 2 min at 950 rpm. After that, few drops of NH_3 solution (25% w/w) were added to make a basic medium (pH ~ 11) and then stirred for 1 h to obtain black suspension, which was subsequently refluxed for 6 h. An external magnet was applied to

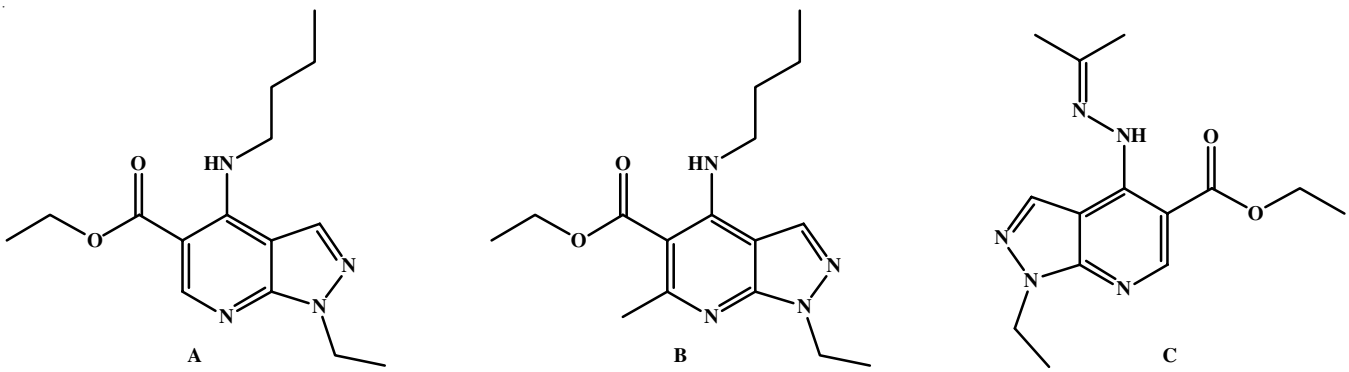
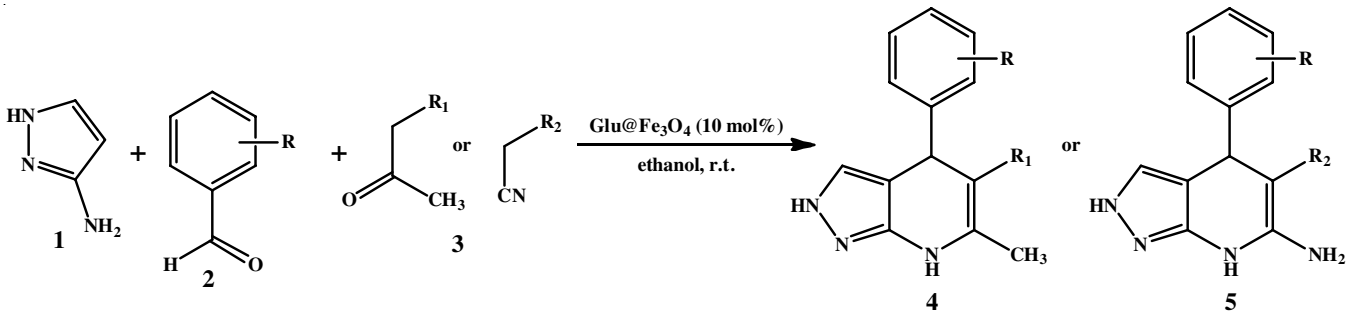


Fig. 1. Anxiolytic drugs containing pyrazolo[3,4-*b* pyridine] moiety

isolate the prepared magnetic Fe_3O_4 nanoparticles and washed multiple times using distilled water followed by ethanol. The synthesized Fe_3O_4 nanoparticles were transferred to a flask containing mixture of glucose (20 mmol) dissolved in distilled water (40 mL). The ultrasonic radiations were passed through the mixture for 20 min. After being separated from the basic medium, the resultant superparamagnetic nanoparticles (Glu@Fe_3O_4) were thoroughly cleaned with distilled water, ethanol and then left to dry overnight at 60 ºC.

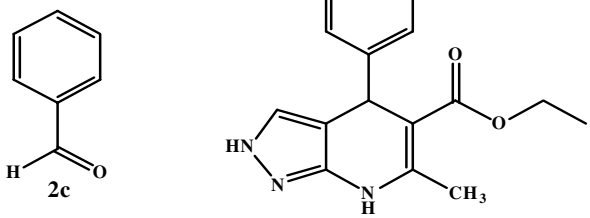
General synthetic procedure of pyrazolo[3,4-*b*]pyridines: 3-Aminopyrazole (**1**, 1 mmol), active methylene derivatives (**3a-c**, 1 mmol) and substituted benzaldehydes (**2a-e**, 1 mmol) were added to 5 mL of ethanol in a 100 mL round-bottom flask. The reaction mixture was constantly stirred at room temperature for 48 h. Throughout the reaction, TLC was used to analyze the progress of the reaction. In order to recover the catalyst, hot ethanol was added to the mixture once the reaction was completed as indicated by TLC and the reaction mixture allowed to cool (**Scheme-I**). After repeatedly washing with excess water and dichloromethane, the solid product was filtered and finall recrystallized with ethanol.

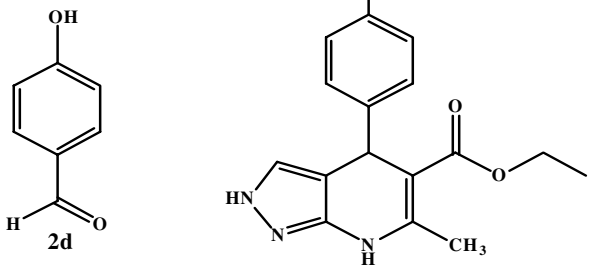
Ethyl-4-(4-methoxyphenyl)-6-methyl-4,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4a): White solid; time: 2 days; yield: 75%; m.p.: 230 ºC; IR (KBr, ν_{max}, cm^{-1}): 3142.72, 2931.36, 2837.77, 1883.23, 1705.00, 1609.00, 1586.00, 1516.00, 1321.82, 1292.56, 1248.09, 1080.51; ^1H NMR (400 MHz, $CDCl_3$) (δ, ppm): 1.01 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 2.84 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.15 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 7.01 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.25 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.49 (s, 1H, $CH_{pyrazole}$), 7.99 (s, 1H, NH), 13.75 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 169.1, 160.6, 156.3, 151.8, 143.1, 134.1, 129.7, 128.6, 122.6, 114.4, 113.1, 61.6, 55.6, 23.4, 13.9; HRMS (ESI) *m/z* for $[C_{17}H_{18}N_3O_3]$: 312.1332.

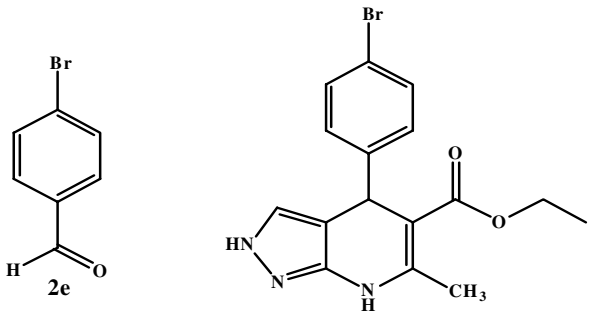


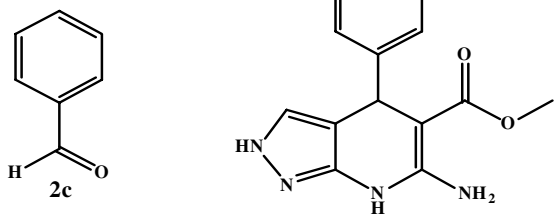
1 2 3 4 5

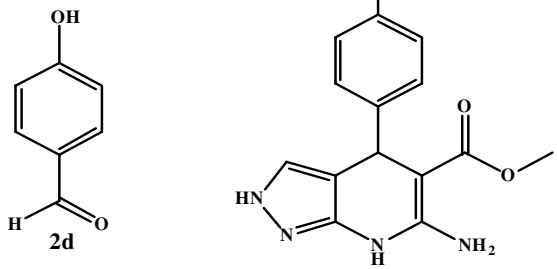
Compuond 4a-e		Compuond 5a-g	
Substituted benzaldehyde	Product	Substituted benzaldehyde	Product
2a	4a	2a	5a
2b	4b	2b	5b

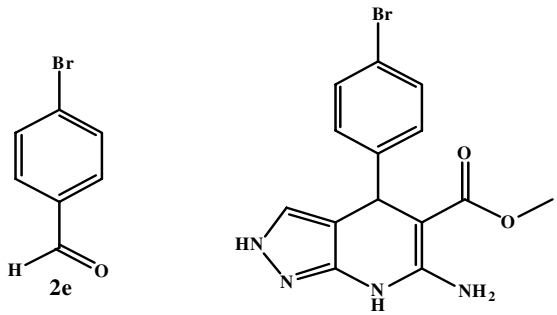


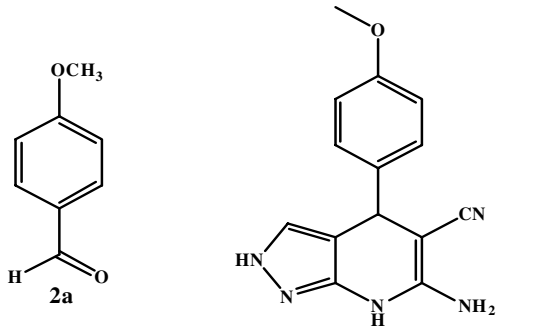


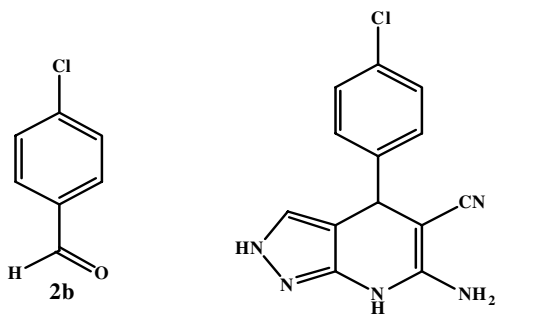












Scheme-I: Synthetic route of 4,7-Dihydro-2H-pyrazolo[3,4-*b*]pyridines using glucose coated nano Fe_3O_4 as catalyst

Ethyl-4-(4-chlorophenyl)-6-methyl-4,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4b): White solid; time: 2.5 days; yield: 70%; m.p.: 250 ºC; IR (KBr, ν_{max}, cm^{-1}): 3133.87, 2927.74, 1727.00, 1578.89, 1490.02, 1320.90 1240.32, 1190.29, 1089.02. ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 1.01 (t, *J* = 7.1 Hz, 3H, OCH_2-CH_3), 2.33 (s, 3H, CH_3), 3.86 (q, *J* = 8.0 Hz, 2H, OCH_2CH_3), 6.32 (s, 1H, CH), 7.16 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.41 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.94 (s, 1H, $CH_{pyrazole}$), 12.59 (s, 1H, NH), 10.45 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 168.2, 155.9, 150.1, 141.3, 132.7, 128.8, 122.1, 111.7, 97.1, 86.6, 60.8, 29.1, 22.3, 13.1; HRMS (ESI) *m/z* for [$C_{16}H_{15}N_3O_2Cl$]: 317.6100.

Ethyl-6-methyl-4-phenyl-4,7-dihydro-2*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylate (4c): White solid; time: 3 days; yield: 68%; m.p.: 235 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 1.53 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 2.81 (s, 3H, CH_3), 4.23 (q, *J* = 8.0, Hz, 2H, OCH_2CH_3), 4.84 (s, 1H, CH), 7.17 (d, 1H, Ar-H), 7.35 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.36 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.69 (s, 1H, $CH_{pyrazole}$), 10.97 (s, 1H, NH), 12.57 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 13.8, 19.2, 64.4, 123.6, 129.7, 130.4, 132.1, 141.4, 145.8, 156.9, 168.5; HRMS (ESI) *m/z* for [$C_{16}H_{17}N_3O_2$]: 283.1396.

Ethyl-4-(4-hydroxyphenyl)-6-methyl-4,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4d): White solid; time: 2 days; yield: 74%; m.p.: 240 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 12.56 (s, 1H, NH), 10.92 (s, 1H, NH), 7.69 (s, 1H, $CH_{pyrazole}$), 7.46 (d, *J* = 8.1 Hz, 2H, Ar- H), 6.97 (d, *J* = 8.1 Hz, 2H, Ar-H), 5.97 (s, 1H, OH), 4.86 (s, 1H, CH), 2.39 (s, 3HCH_3), 4.15 ((q, *J* = 8.0 Hz, 2H, OCH_2CH_3), 1.52 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 168.6, 158.2, 152.4, 150.3, 139.2, 131.2, 130.6, 110.3, 98.6, 62.4, 38.2, 18.9, 13.2; HRMS (ESI) *m/z* for [$C_{16}H_{17}N_3O_3$]: 299.1402.

Ethyl-4-(4-bromophenyl)-6-methyl-4,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4e): Yellowish white solid; time: 3 days; yield: 69%; m.p.: 246 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 1.11 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 2.50 (s, 3H, CH_3), 4.10 (q, *J* = 7.3 Hz, 2H, OCH_2CH_3), 4.88 (s, 1H, CH), 7.40 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.61 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.99 (s, 1H, $CH_{pyrazole}$), 9.36 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 169.2, 154.8, 149.8, 132.7, 131.6, 130.1, 123.6, 101.2, 62.6, 43.5, 18.6, 13.6; HRMS (ESI) *m/z* for [$C_{16}H_{15}N_3O_2Br$] (*m/z*): 361.0396.

Ethyl-6-amino-4-(4-methoxyphenyl)-4,7-dihydro-2*H*-pyrazolo[3,4-*b*] pyridine-5-carboxylate (5a): White solid; time: 5 days; yield: 73%; m.p.: 249 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 10.92 (s, 1H, NH), 7.54 (s, 1H, NH), 7.25 (s, 1H, $CH_{pyrazole)}$, 7.07 (d, *J* = 8.4 Hz, 2H, ArH), 5.56 (s, 2H, NH_2), 4.89 (s, 1H, CH), 4.76 (q, *J* = 7.3 Hz, 2H, OCH_2CH_3), 3.82 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3), 1.24 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 166.7, 161.6, 156.8, 145.0, 136.4, 129.8, 128.2, 118.9, 104.0, 84.6, 70.7, 64.9, 29.9, 14.1; HRMS (ESI) *m/z* for [$C_{16}H_{18}N_4O_3$]: 314.1483.

Ethyl-6-amino-4-(4-chlorophenyl)-4,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (5b): White solid; time: 2 days; yield: 72%; m.p.: 245 ºC; IR (KBr, ν_{max}, cm^{-1}): 3036.04, 2987.00, 2225.00, 1723.60, 1612.80, 1588.74, 1491.91, 1365.52, 1265.97, 1081.14; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 1.24 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 2.17 (q, *J* = 7.3 Hz, 2H, OCH_2CH_3), 3.51 (s, 2H, NH_2), 3.79 (s, 1H, CH), 4.80 (d, *J* = 8.4 Hz, 2H, ArH), 5.69 (d, *J* = 8.4 Hz, 2H.ArH), 6.17 (s, 1H, $CH_{pyrazole}$), 7.10 (s, 1H, NH), 7.29 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 165.9, 143.5, 136.9, 135.7, 131.1, 128.3, 126.9, 120.6, 101.0, 66.0, 57.3, 29.6, 17.7; HRMS (ESI) *m/z* for [$C_{15}H_{15}N_4O_2Cl$]: 318.1100.

Ethyl-6-amino-4-phenyl-4,7-dihydro-2*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxylate (5c): White solid; time: 2 days; yield: 66%; m.p.: 250 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 12.58 (s, 1H, NH), 10.79 (s, 1H, NH), 7.59 (s, 1H, $CH_{pyrazole}$), 7.36 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.35 (d, *J* = 8.4 Hz, 2H, ArH), 7.16 (s, *J* = 8.4 Hz, 1H, ArH), 6.41 (s, 2H, NH_2), 4.62 (s, 1H, CH), 4.01 (q, *J* = 7.3 Hz, 2H, OCH_2CH_3), 1.09 (t, *J* = 7.3 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 168.3, 165.8, 154.9, 144.6, 130.8, 129.8, 128.2, 126.3, 105.6, 86.4, 64.8, 39.6, 13.8; HRMS (ESI) *m/z* for [$C_{15}H_{16}N_4O_2$]: 284.1365.

Ethyl-6-amino-4-(4-hydroxyphenyl)-4,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (5d): White solid; time: 2.5 days; yield: 69%; m.p.: 249 ºC; IR (KBr, ν_{max}, cm^{-1}): 3296.37, 2924.46, 2853.14, 2232.60, 1732.30, 1588.43, 1444.13, 1383.96, 1210.90, 1176.23, 1021.10; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 1.40 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 2.36 (q, *J* = 7.3 Hz, 2H, OCH_2-CH_3), 3.93 (s, 2H, NH_2), 4.32 (s, 1H, CH), 8.14 (s, 1H, NH), 6.04 (d, *J* = 8.4 Hz, 2H, ArH), 6.95 (d, *J* = 8.4 Hz, 2H.ArH), 7.23 (s, 1H, $CH_{pyrazole}$), 7.96 (s, 1H, NH), 7.23 (s, 1H, $CH_{pyrazole}$); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 162.8, 160.3, 133.9, 130.7, 124.7, 116.1, 92.9, 86.2, 62.4, 36.7, 29.6, 14.4; HRMS (ESI) *m/z* for [$C_{15}H_{16}N_4O_3$]: 300.1298.

Ethyl-6-amino-4-(4-bromophenyl)-4,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (5e): Cream white solid; time: 3.5 days; yield: 64%; m.p.: 247 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 12.46 (s, 1H, NH), 10.80 (s, 1H, NH), 7.80 (s, 1H, $CH_{pyrazole}$), 7.49 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.29 (d, *J* = 8.4 Hz, 2H, ArH), 6.36 (s, 2H, NH_2), 4.66 (s, 1H, CH), 4.01 (q, *J* = 7.3 Hz, 2H, OCH_2-CH_3), 1.09 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 168.1, 164.2, 152.8, 140.3, 131.0, 130.9, 130.1, 119.5, 101.6, 86.5, 63.5, 37.6, 14.8; HRMS (ESI) *m/z* for [$C_{15}H_{14}N_4O_2Br$]: 362.0475.

6-Amino-4-(4-methoxyphenyl)-4,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (5f): Yellowish white solid, time: 2.5 days; yield: 70%; m.p.: 233 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.62 (s, 1H, NH), 7.45 (s, 1H, NH), 7.25 (s, 1H, $CH_{pyrazole}$), 7.08 (d, *J* = 8.4 Hz, 2H, ArH), 6.95 (d, *J* = 8.4 Hz, 2H, Ar-H), 4.65 (s, 2H, NH_2), 3.82 (s, 3H, OCH_3), 1.27 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 177.8, 165.1, 152.4, 130.7, 129.8, 128.5, 114.2, 65.2, 55.4, 29.6, 23.0, 14.1; HRMS (ESI) *m/z* for [$C_{14}H_{13}N_5O$]: 267.1186.

6-Amino-4-(4-chlorophenyl)-4,7-dihydro-2*H*-pyrazolo-[3,4-*b*]pyridine-5-carbonitrile (5g): Creamy white solid; time: 3.5 days; yield: 68%; m.p.: 238 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 4.86 (s, 1H, CH), 6.69 (s, 2H, NH_2), 7.30 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.41 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.67 (s, 1H,

$CH_{pyrazole}$), 10.95 (s, 1H, NH), 12.56 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 178.6, 157.2, 133.9, 132.8, 131.6, 127.2, 119.6, 61.7, 32.7; HRMS (ESI) *m/z* for [$C_{13}H_{10}N_5Cl$]: 271.0624.

RESULTS AND DISCUSSION

Characterization of prepared organocatalyst: FT-IR spectrum of Glu@Fe_3O_4: The broad signal at 3416.2 cm^{-1} in the FT-IR spectra of Fe_3O_4 and Fe_3O_4 encapsulated with glucose (Glu@Fe_3O_4) is indicative of the –OH functional group, which are associated with the stretching vibrations of C(sp^3)-H, C(sp^2)-H and Fe-O bonds, respectively and the peak locations are 2924.3, 2857.4, 1100.1 and 581.2 cm^{-1} (Fig. 2).

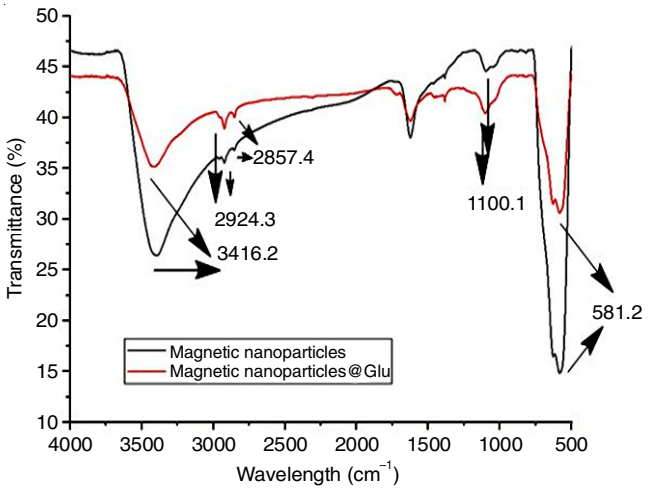


Fig. 2. FTIR spectra of Glu.@Fe_3O_4

XRD studies: The synthesized Glu@Fe_3O_4 was analyzed to assess its crystalline structure using X-ray diffraction patterns. The six peaks (2θ = 37º, 43º, 55º, 59º, 65º and 70º) are the representative of Fe_3O_4 crystalline structure. Therefore, it is clear that the glucose coating has no effect on the magnetic nanoparticles' structure (Fig. 3).

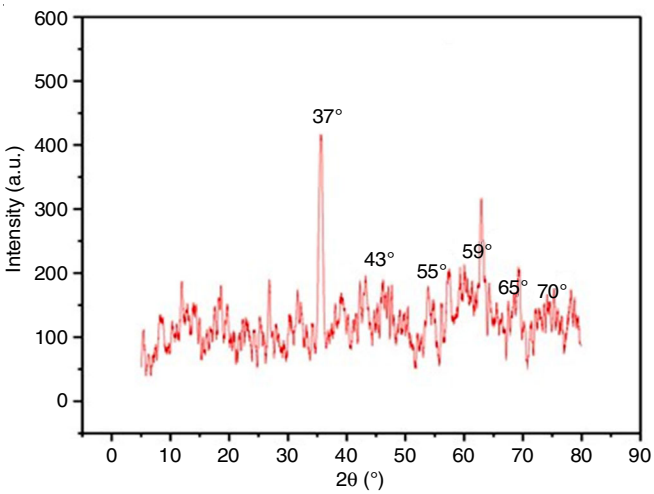


Fig. 3. XRD pattern of Glu@Fe_3O_4

Chemistry: A model reaction using 3-amino pyrazole (**1**), 4-methoxybenzaldehyde (**2a**) and ethyl acetoacetate (**3a**) was carried out in order to assess the viability of the proposed reaction hypothesis. The effects of various types of solvent and temperature shown in Table-1, described the yield percentage of the obtained product **4a**.

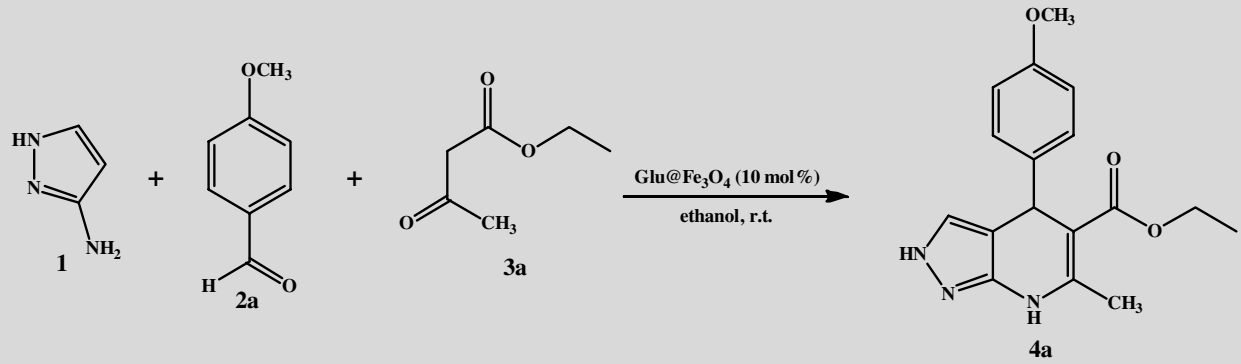
The rate of the reaction is also influenced by the solubility of the reactants. At different temperatures, a variety of solvent types, including polar-aprotic (CH_3CN) and polar-protic (H_2O, MeOH, EtOH, ethylene glycol and PEG-400) was assessed (Table-1). Although the reaction took place in a polar aprotic solvent, product **4a** was obtained in a poor yield (Table-1, entry 10). Ethylene glycol, MeOH, PEG-400 and H_2O were used as solvents and the corresponding yields were 65%, 60%, 40% and 30%, respectively **4a** (Table-1, entries 5-9 and 11). Using ethanol as a solvent and addition of prepared organocatalyst (Glu.@Fe_3O_4) at room temperature resulted in the highest yield of 75% (Table-1, entry 4). Ethanol outperformed all other studied solvents in terms of product yield and reaction rate for the model reaction. After 5 days, the reaction at 70 ºC yielded 38% of product, when it was tested at different reaction temperatures using ethanol as a solvent (Table-1, entry 2). At 60 ºC, a 40% increase in product yield and 4-day reaction time were observed (Table-1, entry 2). With an observed yield of 40%, the reaction was completed in three days at room temperature. The excellent yield (75%) of product **4a** was obtained in 2 days when the reaction was carried out at room temperature with an organocatalyst (Glu.@Fe_3O_4) present (Table-1, entry 4). Even after a considerable period, the neat reaction failed (Table-1, entry 12). Therefore, the optimal temperature for carrying out the model reaction was determined to be room temperature.

Effect of dosage of organocatalyst: Table-2 depicts the amount of catalyst to be used during the reaction sequence. On performing the reaction with catalyst (5 mol%), the observed yield was 50% (Table-2, entry 2), whereas with catalyst (10 mol%), the observed yield was 70% (Table-2, entry 3). Thus, on enhancing the catalytic amount to 15 mol%, output reduced to 68% (Table-2, entry 4). As the maximum yield was obtained with catalyst (10 mol%), hence we performed further reactions taking 10 mol% as the suitable amount of catalyst.

The synthesis of two series of novel dihydro-2*H*-pyrazolo-[3,4-*b*]pyridines with excellent yields served as an evaluation of the reaction methodology's scope and application. Several experimental procedures were carried out with 3-aminopyrazole (**1**), benzaldehyde derivative (**2a-e**) and active methylene compounds (**3a-c**). It was found that specific aromatic aldehydes could be effectively reacted with in a single pot, yielding high-quality and unusual product yields. Aromatic aldehydes were found to have phenyl rings with diverse functional groups on them, including halogens and electron donors. The target dihydro-2*H*-pyrazolo-pyridine derivative (**4a**) was isolated in a higher yield of 75% by benzaldehydes with an electron-releasing methoxy **2a** group, while the product moiety (**4b**) was synthesized in a somewhat lower yield of 70% containing chloro group as substitutent.

Furthermore, when examining the reactions involving several active methylene compounds to broaden the scope. It was determined that two different methylene molecules, specifically ethyl cyanoacetate (**3b**) and malononitrile (**3c**), had

TABLE-1
EVALUATION OF CATALYST AND TEMPERATURE EFFECT AND OPTIMIZATION OF SOLVENTS ON THE REACTION TIME[a] AND % YIELD[b]



Entry	Catalyst	Solvent	Amount of catalyst (mol%)	Temperature (°C)	Time (days)	% Yield[b]
1	–	EtOH	–	60	4.0	40
2	–	EtOH	–	70	5.0	38
3	–	EtOH	–	r.t.	3.0	40
4	Glu@Fe_3O_4	EtOH	10	r.t.	2.0	75
5	Glu@Fe_3O_4	Ethylene Glycol	10	r.t.	2.0	65
6	Glu@Fe_3O_4	MeOH	10	r.t.	2.0	60
7	Glu@Fe_3O_4	PEG-400	10	r.t.	3.0	40
8	Glu@Fe_3O_4	Water:EtOH(1:1)	10	r.t.	3.0	44
9	Glu@Fe_3O_4	Water:EtOH(3:2)	10	r.t.	3.0	34
10	Glu@Fe_3O_4	CH_3CN	10	r.t.	2.5	36
11	Glu@Fe_3O_4	Water	10	r.t.	3.0	30
12	–	Neat	–	60	7.0	–

Reaction conditions[a]: **1** (1 mmol), **2a** (1 mmol) and **3a** (1 mmol) and solvent (5 mL). [b]Isolated yield of product.

TABLE-2
CATALYST LOADING[a]

Entry	[Glu@Fe_3O_4] (mol %)	Time (days)	Yield (%)[b]
1	–	7	40
2	5	3.5	50
3	10	2	75
4	15	2	68

[a]Reactions are performed on a 1mmol scale at room temperature. [b]Isolated yield of pure product.

substituted ethyl acetoacetate (**3a**). All the reactions yielded equivalent products in satisfactory amounts.

Without using column chromatographic separation process, the obtained results demonstrated that the one-pot synthesis of dihydro-2*H*-pyrazolo[3,4-*b*]pyridine is extremely viable under the ethanolic medium involving 3-aminopyrazole with aryl aldehydes and active methylene compounds. The suggested methodology includes a variety of alternation patterns and displays a wide range of substrate scope.

Mechanism: The suggested mechanistic reaction pathway for the synthesis of dihydro-2*H*-pyrazolo-pyridine derivatives is shown in **Scheme-II**. The formation of the condensed intermediate (**I**), which undergoes the immediate Michael type addition of 3-amino pyrazole (**1**) to the intermediate **I**, led to the formation of intermediate **II**. Then, the mild acidic nature of Glu@Fe_3O_4 initiates the Knoevenagel condensation between the active methylene compound ethyl acetoacetate (**3a**) and a carbonyl (C=O) group of benzaldehyde **2a**. Following an intramolecular cyclization and tautomerization, the intermediate **II** finally formed the target product moiety, 4,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridine (**4a**).

Recyclability studies: Following the successful completion of the reaction, the prepared organocatalyst was isolated from the solution, as often accomplished by using an external magnet. It was then repeatedly cleaned with water and ethanol, dried and utilized for subsequent reaction sequences. It was found that the organocatalyst was reused in five reaction cycles without the loss of activity and selectivity (Fig. 4).

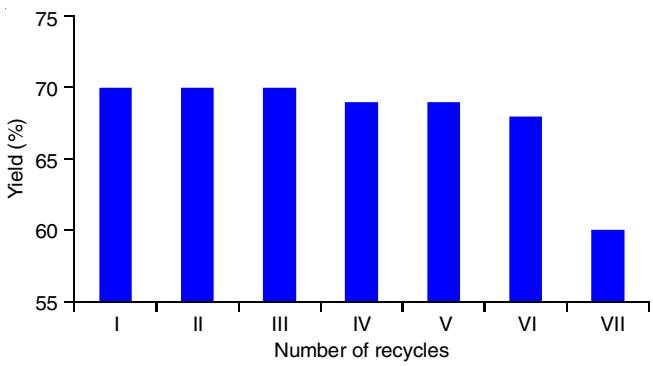
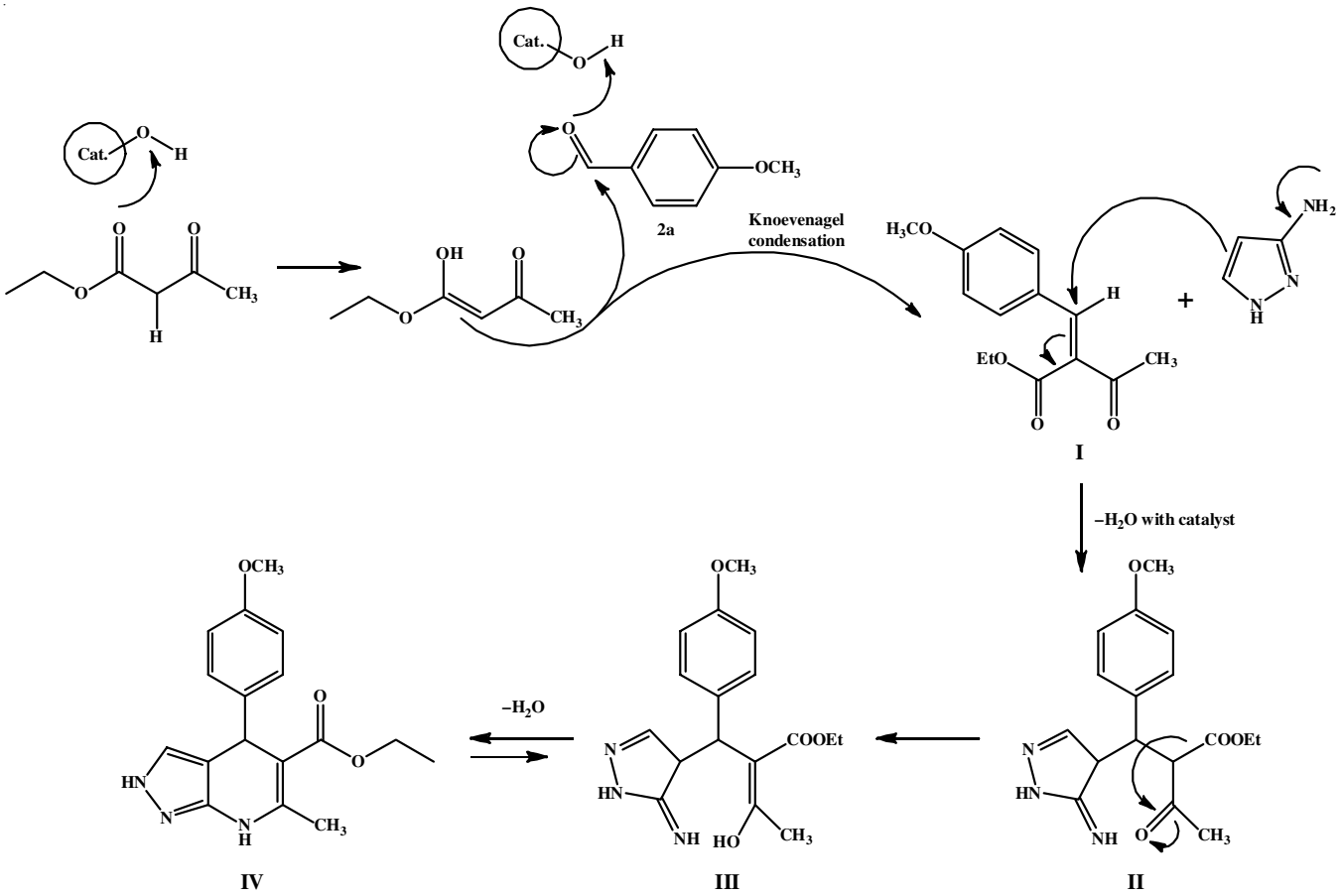


Fig. 4. Recyclability of the catalyst

Conclusion

Through the utilization of green solvent ethanol at room temperature and organocatalyst (Fe_3O_4@Glu) in a one-pot three components procedure, we were able to synthesize novel 6-methyl-4,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridine heterocyclic



Scheme-II: Feasible mechanism

moiety in excellent yields in a significantly eco-friendly manner. The greater applicability of the three-component approach was attained by incorporating active methylene compounds and achieving elevated yields of the target molecule. This approach has the advantages of being easy to use, producing high yields, using a safe solvent and without requiring column chromatographic separation. Compared to the present known methods, this described process is far superior and more environmental friendly.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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