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FeF_3-catalyzed MCR in PEG-400: ultrasound assisted synthesis of *N*-substituted 2-aminopyridines†

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FeF_3 catalyzed four component reaction under ultrasound irradiation was explored for the first time to prepare *N*-substituted 2-aminopyridines in good yields. The methodology involved the use of readily available starting materials and PEG-400 under mild reaction conditions in the presence of air. The one-pot methodology afforded a range of compounds of pharmacological interest indicating its potential in generating a diversity based library of small molecules useful for medicinal chemistry and drug discovery.

Being a well known N-heterocycle in many bioactive compounds and natural products[1] the pyridine ring is considered as one of the privileged structures in medicinal chemistry and drug discovery. For example, the pyridine framework has been explored for the discovery and development of several marketed drugs *e.g.* etoricoxib[2] (a cyclooxygenase-2 inhibitor, Fig. 1), piclamilast and roflumilast [inhibitors of phosphodiesterase 4 (PDE4)] (Fig. 1). The PDE4 inhibitors are known to be beneficial for the potential treatment of asthma and chronic obstructive pulmonary disease (COPD).[3a] To date roflumilast (Daxas® by Nycomed and Daliresp by Forest Lab)[3b] and apremilast (Otezla by Celgene) have been launched in Europe and US. However, adverse side effects such as nausea, emesis and cardiovascular issues have halted the progress of several other PDE4 inhibitors. Thus the search for a new chemical class possessing PDE4 inhibitory properties with improved therapeutic indexes is desirable. Accordingly, we have explored the 4-aryl substituted cyano pyridines (**A**, Fig. 1) for this purpose.[4] In further continuation of this research we became interested in evaluating PDE4 inhibitory properties of some *N*-substituted 2-amino analogs of **A** (*e.g.* **B**, Fig. 1) possessing an alkyl/aryl/heteroaryl moiety at the C-4 position of the pyridine ring. Our major focus was on the C-4 substituent as this group was found to be crucial for activity in the case of piclamilast and roflumilast (Fig. 1). We therefore required a robust and efficient method to generate a library of compounds based on the template **B** having a range of groups at the C-4 position for the detailed Structure Activity Relationship (SAR) studies.

In view of their usefulness in organic synthesis[5] several syntheses of 2-aminopyridine derivatives[6–9] have been reported that generally involves the reaction of 2-halo or 2-alkoxypyridines with ammonia or amines. The use of multi-component reactions (MCR) has also been explored for the synthesis of this class of compounds.[8,9] Indeed, a three component reaction involving the reaction of α,β-unsaturated ketones, cyano derivatives and amines afforded the desired pyridine derivatives.[8] Later a modified synthesis of 2-aminopyridines was reported *via* the reaction of α,β-unsaturated ketones with malononitrile and amines or ammonium acetate under mild conditions.[9] However, due to the several drawbacks associated with these

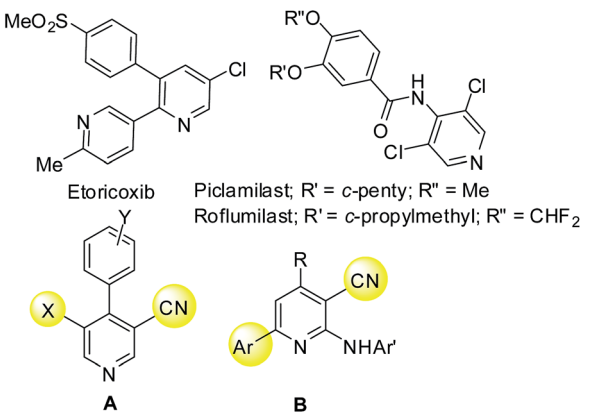

Fig. 1 Pyridine based known PDE4 inhibitors and design of new inhibitors (**B**).

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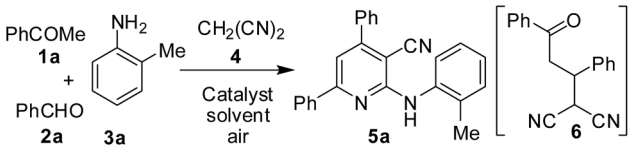
previously reported methods including poor to moderate yields, longer reaction time and limited substrate scope a faster method has been developed recently. In this strategy the MCR of α,β-unsaturated ketones (chalcones), malononitrile and amines was accelerated by microwave irradiation to achieve a chemoselective synthesis of *N*-substituted 2-aminopyridines.[10] Indeed, this method appeared to be an effective, faster (3–9 min) and good yielding (76–90%) process though it involved the use of DMF as a solvent and chalcone as one of the reactants. In another approach, following our earlier synthesis of pyridine derivatives *via* a 4-component reaction of β-ketoester, arylaldehyde, malononitrile and an alcohol[4] a $FeCl_3$-catalyzed similar 4-component reaction using arylamine in place of alcohol was developed for the synthesis of *N*-substituted 2-aminopyridines in 38–86% yield.[11a] Subsequently, a "Sn" mediated MCR in water leading to the same class of pyridines was reported by us.[11b] Once again all these methods involved relatively longer reaction time. The ultrasound assisted organic reactions[12] have attracted enormous attention due to the efficiency (*e.g.* shorter reaction time, milder conditions, higher yields *etc.*) and greenness (in terms of energy conservation and waste minimization) of these processes over the conventional heating methods. On the other hand, because of its non-hazardous nature polyethyleneglycol 400 (PEG-400) is considered as an environmental friendly solvent in various organic reactions.[13] Thus, in search of a more convenient and straightforward method for the synthesis of *N*-substituted 2-aminopyridines we decided to explore the use of ultrasound and PEG-400 for our purpose. Indeed, we were successful in our effort. Herein, we report a FeF_3 mediated four component reaction (4-CR) under ultrasound irradiation leading to the target pyridine derivatives from readily available starting materials (Scheme 1). Though as a catalyst FeF_3 has received some attention in organic synthesis[14,15] its use in the synthesis of pyridines has not been explored. To the best of our knowledge this is the first use of ultrasound assisted FeF_3-catalyzed MCR for the synthesis of this class of compounds.

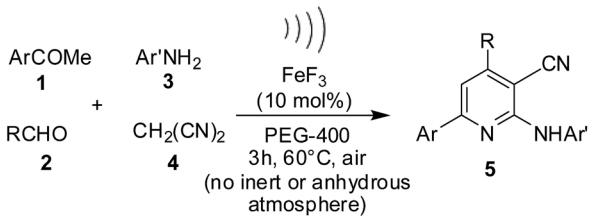
In the beginning of our study, it was necessary to test the feasibility of our anticipated ultrasound based 4-component reaction leading to the formation of the desired pyridine ring. Accordingly, the commercially available acetophenone (**1a**), benzaldehyde (**2a**), *o*-toluidine (**3a**) and malononitrile (**4**) were chosen as reactants for the MCR that was performed under various conditions in open air (Table 1). Initially, we performed the reaction in water in the presence of a range of catalysts under thermal heating (at 80 °C) for 10–11 h (entries 1–10, Table 1). However, except $SnCl_2 \cdot 2H_2O$ and FeF_3 none of other catalyst was found to be effective under the condition employed. We then opted for another green solvent *i.e.* PEG-400 (entries 11–16, Table 1). Once again $SnCl_2 \cdot 2H_2O$ and FeF_3 were found to be best among all the catalysts tested when the desired product **5a** was isolated in good yields. In order to decrease the reaction time and temperature we performed the reaction catalyzed by $SnCl_2 \cdot 2H_2O$ or FeF_3 under ultrasound irradiation in both water and PEG-400, respectively (entries 17–20, Table 1). To our delight the reaction was completed within 3 h in these cases when performed at 60 °C affording the product **5a** in 80–92% yield. Since the best yield of **5a** was obtained under the condition of entry 20 of Table 1 in the presence of FeF_3 hence this was identified as optimal reaction condition. The role of solvent PEG-400 and catalyst FeF_3 as well as effect of temperature at lower and higher than 60 °C was also examined (entries 21–25, Table 1). While the reaction proceeded under the solvent free

Table 1 Effect of reaction conditions on MCR of **1a**, **2a**, **3a** and **4**[a]



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	PMA–SiO_2	H_2O	80	10	Traces
2	SiO_2	H_2O	80	10	Traces
3	Clay	H_2O	80	10	17
4	$CeCl_3 \cdot 7H_2O$	H_2O	80	10	30
5	Citric acid	H_2O	80	10	25
6	PTSA	H_2O	80	10	30
7	L-Proline	H_2O	80	10	Traces
8	$BiCl_3$	H_2O	80	11	40
9	$SnCl_2 \cdot 2H_2O$	H_2O	80	10	75
10	FeF_3	H_2O	80	10	80
11	PMA–SiO_2	PEG-400	80	10	20
12	Amberlite	PEG-400	80	10	Traces
13	Indion resin	PEG-400	80	10	Traces
14	PTSA	PEG-400	80	10	20
15	$SnCl_2 \cdot 2H_2O$	PEG-400	80	10	70
16	FeF_3	PEG-400	80	10	85
17	$SnCl_2 \cdot 2H_2O$	H_2O	60	3	80[c]
18	FeF_3	H_2O	60	3	80[c]
19	$SnCl_2 \cdot 2H_2O$	PEG-400	60	3	81[c]
20	**FeF_3**	**PEG-400**	**60**	**3**	**92**[c]
21	FeF_3	No solvent	60	3	60[c]
22	No catalyst	PEG-400	60	3	Traces[c]
23	FeF_3	PEG-400	70	3	91[c]
24	FeF_3	PEG-400	50	3	60[c]
25	FeF_3	PEG-400	RT	3	40[c]
26	FeF_3	PEG-400	60	0.5	30[d]
27	$FeCl_3$	PEG-400	60	6	80

[a] All the reactions were performed using **1a** (1.25 mmol), **2a** (1.25 mmol), **3a** (1.25 mmol), **4** (1.25 mmol), and a catalyst (10 mol%) in a solvent (0.3 mL) under open air. [b] Isolated yield. [c] The reaction was performed under ultrasound irradiation. [d] The compound 2-(3-oxo-1,3-diphenylpropyl) malononitrile (**6**) was isolated as a major product (60% yield) in this case.



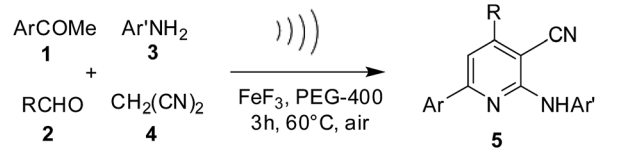
Scheme 1 Ultrasound assisted 4-component reaction leading to *N*-substituted 2-aminopyridines (**5**).

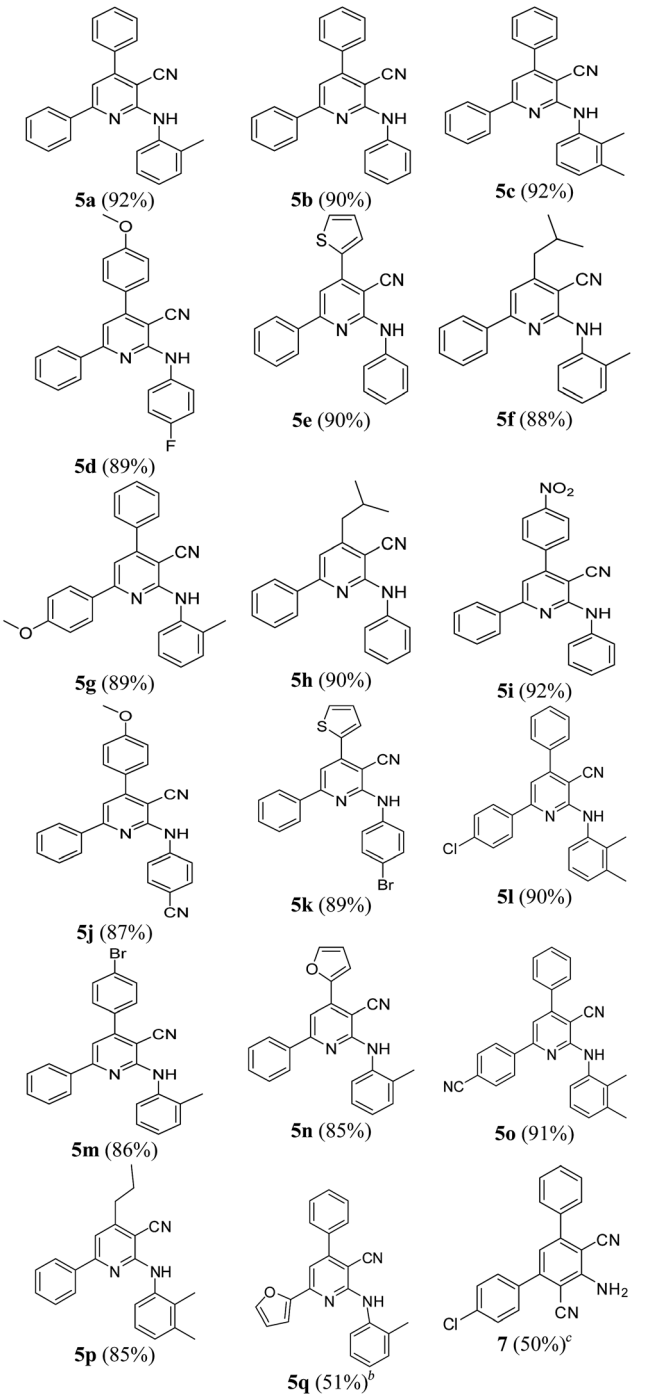
condition (entry 21, Table 1) almost no product was formed in the absence of catalyst (entry 22, Table 1). The use of higher reaction temperature did not improve the product yield further (entry 23, Table 1) whereas a decrease in temperature lowered the yield (entry 24 and 25, Table 1). To optimize the catalyst loading the reaction was performed in the presence of 5, 10, 15 and 20 mol% of FeF_3 when **5a** was obtained in 70, 92, 93 and 90% yield respectively indicating 10 mol% of catalyst as optimal amount. Notably, the reaction afforded **5a** in 30% yield along with 2-(3-oxo-1,3-diphenylpropyl)malononitrile (**6**) as a major product (60% yield) when stopped after 30 min (entry 26, Table 1). This observation suggested that the compound **6** is an intermediate in the present reaction. Finally, we examined the use of $FeCl_3$ as a catalyst in place of FeF_3 (entry 27, Table 1). While the reaction proceeded well in this case affording **5a** in good yield the duration of the reaction was 6 h.

Having identified the best reaction conditions we focused on assessing the generality and scope of this methodology. Accordingly, a variety of compounds were prepared by using this FeF_3 catalyzed methodology (Table 2). A range of aldehydes (**2**) containing alkyl, aryl and heteroaryl moieties were employed. Indeed, alkyl moiety may include propyl (linear) or *s*-butyl (branched) group whereas the aryl ring may contain a strong electron donating (*e.g.* OMe) or electron withdrawing (*e.g.* NO_2) group. The heteroaryl moiety may include thienyl or furan group. The aryl ring of ketone (**1**) may bear substituent like OMe, Cl or CN whereas a range of substituents like Me, F, Br and CN may present on the benzene ring of aniline derivatives (**3**) employed. The reaction proceeded well in all these cases affording the corresponding pyridine derivatives in good to excellent yields. Notably, these reactions do not require the use of any inert or anhydrous atmosphere. The use of an aliphatic amine *i.e.* *n*-$BuNH_2$ was also explored. However the reaction afforded a 2,6-dicyanoaniline derivative[10] (**7**) instead of the desired 2-aminopyridine derivative. All the compounds synthesized were characterized by spectral and analytical data. For example, the IR absorption in the range 2220–2210 cm^{-1} indicated the presence of CN moiety. This was further supported by the appearance of a ^{13}C signal near 110 ppm (due to the CN moiety) and 90 ppm (due to the C-4 *i.e.* the CN bearing carbon of the pyridine ring) in the $^{13}CNMR$ spectra. Further a singlet appeared near δ 7.30 (though it was merged with other signals in some cases) in the $^{1}HNMR$ spectra were due to the C-5 proton of the pyridine ring.

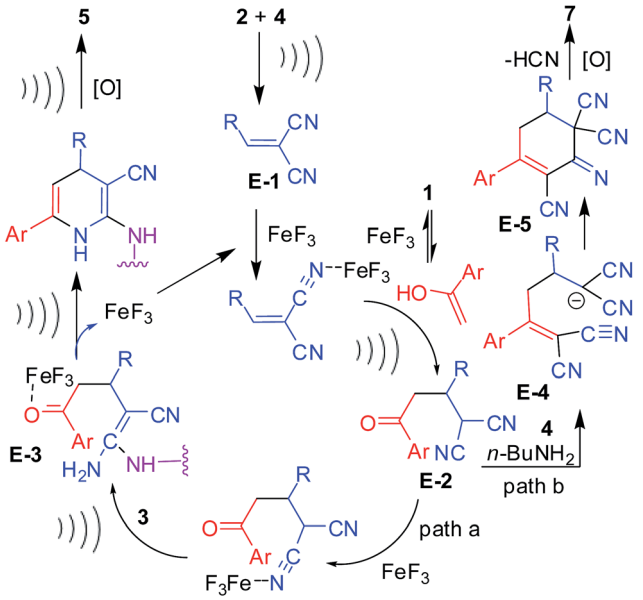
Based on the results presented in Table 1 especially the isolation of compound **6**, a plausible reaction mechanism is proposed in Scheme 2. Thus, the intermediate **E-1** is formed[16] *in situ via* the Knoevenagel condensation between **2** and **4** assisted by ultrasound. The catalyst FeF_3 appeared to play the role of a Lewis acid in the present reaction.[14a] Consequently, coordination of the nitrogen lone pair of **E-1** with the FeF_3 facilitates the Michael type of reaction[17] with the enol form of **1** affording the intermediate **E-2** (*cf.* compound **6**, entry 26 of Table 1). A further coordination of nitrogen lone pair of **E-2** with the FeF_3 (path a) facilitates a nucleophilic attack by the arylamine **3** followed by isomerization of the resulting species to give the intermediate **E-3**. An intramolecular cycloaddition of **E-3** (*via*

Table 2 Ultrasound assisted synthesis of *N*-substituted 2-amino-pyridines (**5**) *via* FeF_3 catalyzed MCR[a]





[a] All the reactions were performed using **1** (1.25 mmol), **2** (1.25 mmol), **3** (1.25 mmol), **4** (1.25 mmol), and FeF_3 (10 mol%) in PEG-400 (0.3 mL) at 60 °C for 3 h under open air. [b] Reaction time 4 h. [c] *n*-$BuNH_2$ was used in place of an aromatic amine. Figure in the brackets indicates isolated yield.

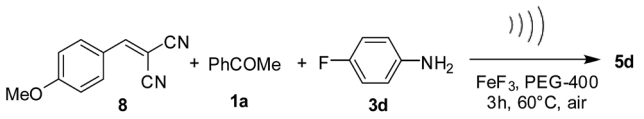


Scheme 2 Proposed reaction mechanism.

the loss of a water molecule) followed by oxidative aromatization in the presence of air afforded the desired product **5**. The **E-2** seems to follow a different pathway (path b) when an aliphatic amine *i.e.* *n*-BuNH$_2$ was used. Being a stronger base than aromatic amines, *n*-BuNH$_2$ facilitated Knoevenagel condensation of **E-2** with **4** leading to **E-4** which on subsequent intramolecular cyclization, HCN elimination and aromatization afforded **7**.[10]

The results of Table 1 (entry 16 *vs.* 20) clearly suggest that the synthesis of compound **5** was accelerated in the presence of ultrasound. It is known that cavitation caused by ultrasound is involved with the growth, oscillation, and collapse of bubbles under the action of an acoustic field.[18] The cavitational collapse on the other hand creates drastic conditions (*e.g.* the temperature of 2000–5000 K and pressure up to 1800 atmosphere) inside the medium within an extremely short period of time. Also, strong physical effects including shear forces, jets, and shock waves are caused by this collapse outside the bubble. Thus, these cavitation-induced overall effects perhaps explains the rate acceleration of the present reaction under ultrasound in the absence of which the reaction took relatively longer time and higher temperature (entry 16, Table 1).[19] Nevertheless, to gain further evidence, 2-(4-methoxybenzylidene)malononitrile (**8**) was prepared[16a] from 4-methoxybenzaldehyde (**2b**) and malononitrile (**4**) separately and treated with acetophenone (**1a**) and 4-fluoroaniline (**3d**) under the conditions of entry 20 of Table 1. The isolation of pyridine derivative **5d** in 90% yield (Scheme 3) suggested intermediacy of **E-1** (Scheme 2) in the present reaction.

To assess the PDE4 inhibitory potential of this class of compounds some of the pyridines synthesized were tested *in vitro* at 10 μM using PDE4B enzyme assay[20a] along with rolipram[20b] as a reference compound. Accordingly, compound **5d** and **5j** showed 69.0 ± 1.21 and 65.0 ± 2.04% inhibition



Scheme 3 The reaction of intermediate **8** with **1a** and **3d**.

compared to rolipram's 90 ± 4.30% inhibition whereas **5i** did not show any inhibition. Rest of the compounds showed 40–60% inhibition. It is evident that the nature of substituent(s) present on the C-4 aryl moiety seemed to have significant influence on PDE4 activities and the strong electron donating group OMe at the *para* position of the C-4 benzene ring was found to be favorable. This was further supported by the *in silico* docking studies performed by compound **5d** (Fig. 2) and **5j** (see ESI†) where the OMe group participated in favorable hydrophobic interactions with PDE4B.[21] Further *in vitro* studies are ongoing using these compounds.

In conclusion, we have developed an ultrasound assisted four component reaction for the synthesis of *N*-substituted 2-aminopyridines. The combination of catalyst FeF$_3$ and PEG-400 was found to be most effective for this MCR. The advantages and drawbacks of the methodology are presented. The methodology is free from the use of inert or anhydrous atmosphere and involved the use of commercially available starting materials *e.g.* acetophenones, arylaldehydes, anilines and malononitrile to give the desired pyridine derivatives under mild reaction conditions. A range of *N*-substituted 2-aminopyridines were prepared by using this one-pot methodology in good to excellent yields (85–92%) within 3 h. Two of these compounds showed encouraging PDE4 inhibition *in vitro* and interaction *in silico*. Though as a catalyst FeF$_3$ has received some attention in

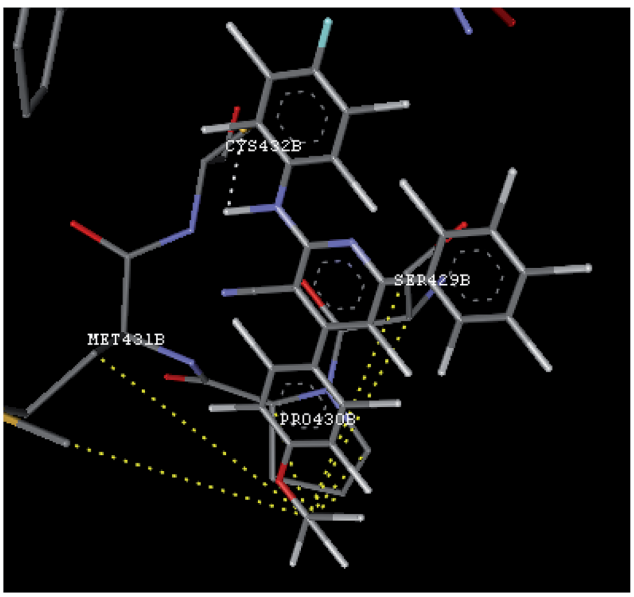


Fig. 2 Docking of compound **5d** into PDE4B: dotted white bond showing H-bond interactions and yellow bonds shows hydrophobic interactions with the binding site residues, protein is represented by sticks and is colored according to the atom types.

organic synthesis however its uses are not only uncommon in the synthesis of pyridines but also in MCR. Additionally, our study highlights the potential of the present FeF_3 catalyzed methodology in generating diversity based library of small molecules related to 2-aminopyridine useful for medicinal/pharmaceutical chemistry and drug discovery. Thus the present methodology may attract considerable attention both in organic synthesis and medicinal chemistry.

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19 To test the scalability of this MCR and recyclability of the catalyst the reaction was performed at a gm scale [*e.g.* acetophenone (**1a**, 4.0 g, 0.033 mmol), 4-nitrobenzaldehyde (**2e**, 5.03 g, 0.033 mmol), aniline (**3b**, 3.1 g, 0.033 mmol), malononitrile **4**, 2.2 g, 0.033 mmol and FeF_3 (0.375 g, 10 mol%) in PEG-400 (8 mL)] when the desired product **5i** was isolated in 90% yield (see ESI†). The filtered catalyst was collected, dried under vacuum below 50 °C and reused for next cycle of the same reaction when **5i** was isolated in 86% yield.

20 (*a*) P. Wang, J. G. Myers, P. Wu, B. Cheewatrakoolpong, R. W. Egan and M. M. Billah, *Biochem. Biophys. Res. Commun.*, 1997, **234**, 320; (*b*) J. Demnitz, L. LaVecchia, E. Bacher, T. H. Keller, T. Muller, F. Schurch, H. P. Weber and E. Pombo-Villar, *Molecules*, 1998, **3**, 107.

21 (*a*) The molecular docking simulations were carried out using GRIP method of docking in Biopredicta module of Vlife MDS (Molecular Design Suite) 4.6 (for detailed procedure, see ESI†); (*b*) G. L. Card, B. P. England, Y. Suzuki, D. Fong, B. Powell, B. Lee, C. Luu, M. Tabrizizad, S. Gillette, P. N. Ibrahim, D. R. Artis, G. Bollag, M. V. Milburn, S. H. Kim, J. Schlessinger and K. Y. Zhang, *Structure*, 2004, **12**, 2233; (*c*) A. Grosdidier, V. Zoete and O. Michielin, *Nucleic Acids Res.*, 2011, **39**, W270.