Article

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Efficient access to imidazo[1,2-*a*]pyridines/pyrazines/pyrimidines via catalyst free annulation reaction under microwave irradiation in green solvent

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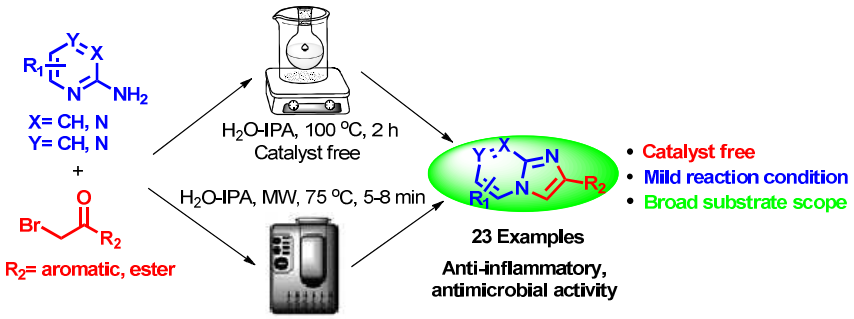
This article is dedicated to Prof Chung Ming Sun for his enormous contribution in combinatorial chemistry

Abstract:

An expeditious catalyst free heteroannulation reaction for imidazo[1,2-*a*]pyridines/pyrimidines /pyrazines was developed in green solvent under microwave irradiation. Using H_2O-IPA as the reaction medium, various substituted 2-aminopyridines/pyrazines/pyrimidines underwent annulation reaction with α-bromoketones under microwave irradiation to provide the corresponding imidazo[1,2-*a*]pyridines/pyrimidines/pyrazines in excellent yields. The synthetic methodology appears to be very simple and superior to the already reported procedures with the high abundance of commercial reagents and great ability in expanding the molecular diversity. The present synthetic sequence is visualized as an environmentally benign process which allows the introduction of three points of structural diversity to expand chemical space with excellent purity and yields. The anti-inflammatory and antimicrobial activities of the derivatives were evaluated. Screening results uncovered three derivatives with strong inhibition of albumin

denaturation and two derivatives were active on *Proteus* and *Klebsiella* bacteria. These positive bioassay results implied that the library of potential anti-inflammatory agents could be rapidly prepared in an eco-friendly manner, and provided new insights into drug discovery for medicinal chemists.

Graphical abstract



Introduction

Synthesis of highly functionalized, fused-heterocyclic compounds is important as these are the key structural elements frequently encountered in many natural products and biomolecules.[1] Among nitrogen fused azoles, imidazo[1,2-*a*]pyridines/pyrimidines/pyrazines are prevalent heterocycles in the medicinal chemistry, organometallics and material science research.[2] Molecules with imidazo[1,2-*a*]pyridine/pyrimidine/pyrazine moieties have a wide range of biological properties such as antifungal, antibacterial, antiviral, anticancer, analgesic antiepileptic, cardiac stimulating agent, and uterine relaxant.[3] However, in addition to these biological activities, these privileged scaffolds also exhibit numerous photophysical properties.[4] The core structure of imidazo[1,2-*a*]pyridines/pyrimidines has also been found in many drugs such as zolpidem (A), alpidem (B), zolimidine (C), olprinone (D), divaplon (E) and fasiplon (F) where as the imidazo[1,2-*a*]pyrazine moiety are the structural analogs of purine (G)[5] in figure 1.

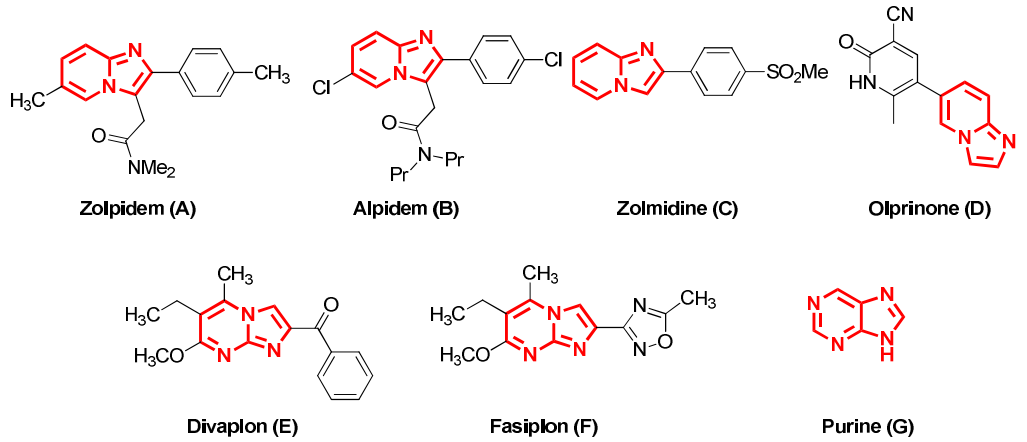


Figure 1. Biologically active imidazo[1,2-*a*]pyridines/pyrimidines/pyrazines moieties

In view of their wide ranging bioactivities, several synthetic methods have been developed for imidazo[1,2-*a*]pyridine/pyrimidine/pyrazine moieties. Several of them are classified as cyclocondensation, oxidative coupling, tandem reaction, aminooxygenation, and hydroamination reactions.[6] However, the most traditional approach for the synthesis of imidazo[1,2-

a]pyridine/pyrimidine/pyrazine derivatives involves the condensation reaction of α-haloketones with 2-aminopyridines/pyrimidines/pyrazines with or without catalysis. Since then a plethora of catalysts have been reported for the synthesis of imidazo[1,2-*a*]pyridine/pyrimidine/pyrazine derivatives, such as neutral Al_2O_3, $NaHCO_3$, solvent free conditions, microware irradiation, I_2/ketone, NaI, $TiCl_4$, and K_2CO_3.[7] To find an alternative, some researchers also used α-diazoketones and α-tosyloxy ketone instead of α-haloketones catalyzed by Lewis acids or ionic liquids to obtain the imidazo[1,2-*a*]pyridines/pyrimidines/pyrazines.[8] Recently Lin *et. al*. developed the microwave assisted, solvent and catalyst-free synthesis of imidazo[1,2-*a*]pyridines with limited substrate scope.[9] Nonetheless, most of the synthetic methodologies have some drawbacks such as the cost of synthesis, longer reaction time, harsh reaction conditions with the use of bases, use of toxic high boiling organic solvents, decomposition of substrates during overheating, limited substrate scope, and lower yields of the products. In comparison to the conventional heating, the application of microwave irradiation accelerates the synthetic process for a rapid transformation, with high yields, and mild reaction profile. Microwave assisted organic synthesis in water has attracted considerable attention owing to the non-toxic and non-flammable nature of water.[10] However the low solubility of organic compounds in water has been overcome by the use of an organic co-solvent, the exploitation of hydrophobic effects and the use of water at high temperatures under microwave irradiation. Using the application of microwave irradiation in H_2O-IPA as the reaction medium we therefore, wished to develop a convenient, microwave assisted catalyst free synthesis of imidazo[1,2-*a*]pyridines/pyrazines/pyrimidines. In comparison to already reported synthetic protocols described above, the present methodology for the synthesis of imidazo[1,2-*a*]pyridines/pyrazines/pyrimidines offered several advantages such as the use of microwave

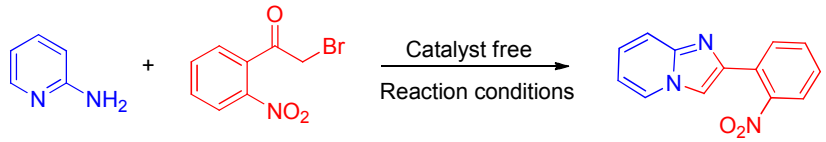
irradiation which reduces the reaction time to minutes for the fast delivery of target compounds, H_2O-IPA as a green and eco-friendly solvent, excellent yields with high purity and a broad substrate scope.

In continuation of our research to develop newer synthetic methodologies for the construction of bioactive heterocycles,[11] we aim to utilize microwave-assisted reaction in green solvents for the synthesis of imidazo[1,2-*a*]pyridines/pyrazines/pyrimidines from readily available chemicals in excellent yields.

Results and Discussion

In a model reaction, 2-aminopyridine **1**{*1*}, and 2-bromo-1-(2-nitrophenyl)ethanone **2**{*1*}, were chosen as substrates to optimize the reaction conditions. We initiated our studies by examining the conversion to imidazo[1,2-*a*]pyridines **3**{*1,1*} at room temperature under neat conditions. Disappointingly, only unreacted starting materials **1**{*1*} and **2**{*1*} were recovered from the reaction mixture (Table 1, entry 1). Increasing the temperature to 100 °C, a new spot was observed (Table 1, entry 2). The desired product was formed in only 30% yield using standard heating. Unfortunately, the reaction did not afford any cyclized product using polar aprotic solvents such as CH_3CN, and DMSO (Table 1, entries 3, 4). However, by changing the solvent system to H_2O-IPA at 100 ^oC, the reaction was completed in 2 hours with an 80% yield (Table 1, entry 5). The same reaction was performed under microwave irradiation to further enhance its efficiency. Initially the same set of reaction that was performed in EtOH under microwave irradiation took 25 minutes for completion with 85% yield (Table 1, entry 6). However, the desired product **3**{*1,1*} was obtained in better yield when the reaction was performed under microwave irradiation for 5 min using H_2O-IPA as solvent (95% yield, Table 1, entry 7).

Table 1. Optimization of catalyst free heteroannulation reaction of 2-aminopyridine **1**{*1*}, and 2-bromo-1-(2-nitrophenyl)ethanone **2**{*1*}.

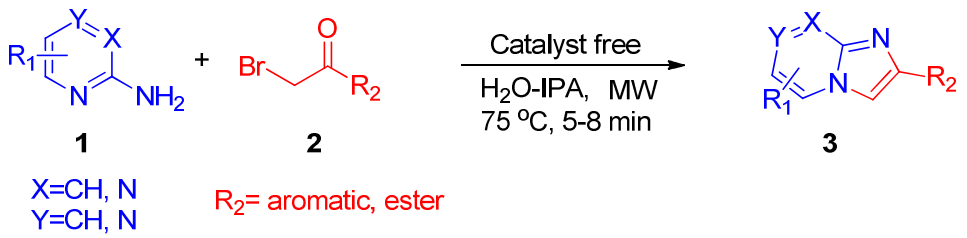


1{*1*} **2**{*1*} **3**{*1.1*}

entry	solvent	temperature	time	**3**{*1.1*} yield%[c]
1	Neat	rt	8 h	0%
2	Neat	100 °C	4 h	30%
3	CH_3CN	reflux	6 h	0%
4	DMSO	130 °C	6 h	0%
5	H_2O-IPA	100°C	2 h	80%
6	EtOH	MW[b], 75 °C	25 min	85%
7	H_2O-IPA	MW[b], 75 °C	5 min	95%

[a] reaction was performed using **1**{*1*} (1 mmol), **2**{*1*} (1 mmol), H_2O-IPA (4 mL, 1:1), [b] Microwave reactions were carried out in Microwave Model No. CATA R (Catalyst systems, Pune) using power 240 watt, [c] Yield of the isolated product.

We next evaluated the scope of the reaction by employing 2-aminopyridine **1**{*1-5*} and phenacyl bromide **2**{*1-7*}. Interestingly, the reaction efficiency was not affected by the substituent groups on both 2-aminopyridines **1**{*1-5*} and phenacyl bromides **2**{*1-7*}. Both the electron-withdrawing and electron-donating substituents were well tolerated under the microwave reaction conditions and proceeded smoothly to give the corresponding imidazo[1,2-*a*]pyridines derivatives **3** in excellent yields. All these reactions were performed under an open atmosphere. The overall reaction time is typically 5-8 mins as shown in Scheme 1.

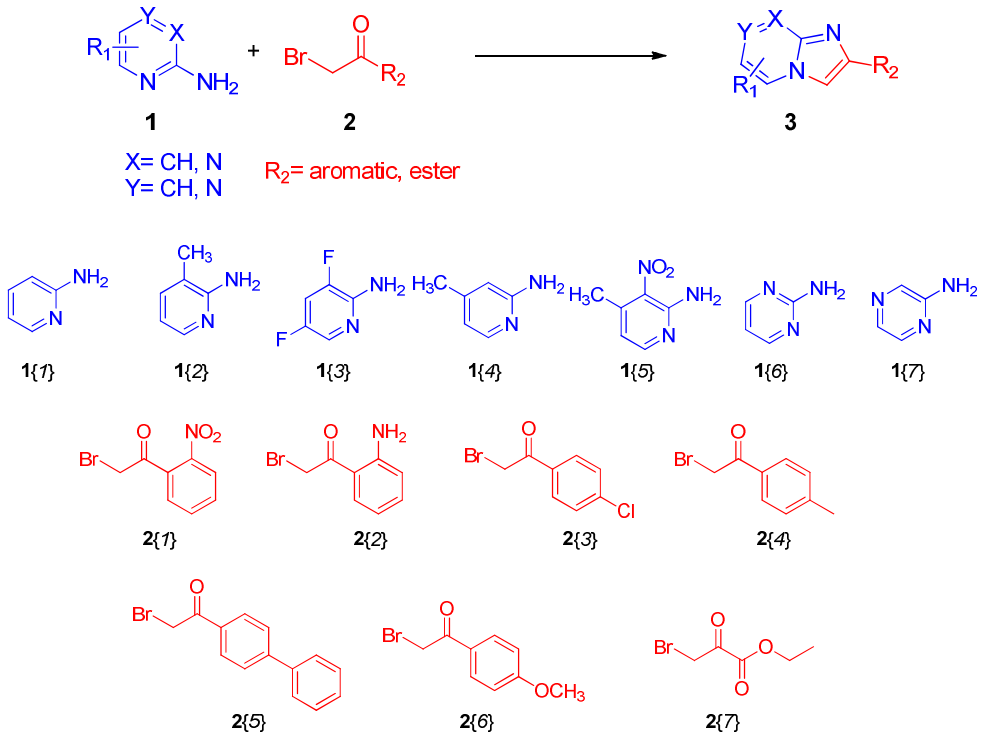


Scheme 1. Synthesis of imidazo[1,2-*a*]pyridines/pyrimidines/pyrazines **3.**

To further examine the efficiency of this heteroannulation reaction and to swiftly expand our unique compound library, we extended the substrate scope to 2-aminopyrimidine and 2-amino pyrazine as suitable substrates. As depicted in Table 2, entries 16-23, we were pleased to find that 2-aminopyrimidines **1**{*6*} and 2-aminopyrazines **1**{*7*} could be smoothly transformed to imidazo[1,2-*a*]pyrimidines/pyrazines **3**. After completion of the reaction, the corresponding imidazo[1,2-*a*]pyridines/pyrimidines/pyrazine derivatives were obtained with excellent yields followed by a simple work-up involving removal of solvents under reduced pressure, extraction, and solvent evaporation. Finally the crude products were purified by column chromatography followed by spectroscopic characterization using ^{1}HNMR, ^{13}C NMR, and mass spectroscopy (MS). More recently, it has been realized that in designing efficient, economic and ecofriendly strategies for chemical synthesis the concept of sustainable development plays an important role. In view of this, Sheldon *et al* introduced the E-factor, or environmental impact factor which helps to compute the amount of waste generated per kilogram of product to assess the "environmental acceptability" of a manufacturing process.[12] Furthermore, our green synthetic reaction conditions display lower E-factors (Table 2) for synthesizing the imidazo[1,2-*a*]pyridines/pyrimidines/pyrazines **3** which is consistent with the principles of atom economy in supporting information. Next, to measure the orally available drug properties, we calculated the physicochemical properties of the synthesized library using Lipinski's rule of five[13] by

calculating the molecular weight, c log P, the number of hydrogen bond donors and acceptors and the number of rotatable bonds of each member of the library. According to this rule, a potential molecule can have drug-like physical properties if the molecular weight is less than 500, the c log P value, which addresses bioavailability and delivery issues, is not more than 5, the hydrogen bond acceptors are not more than 10, the hydrogen bond donors are not more than 5 and there is not more than 10 rotatable bonds. However, for the design of a potential molecule, one Lipinski violation is allowed. Interestingly the predicted values of drug-like properties for these library members are within the accepted limits of Lipinski's rule of five for the entire portion of the library as shown in Table 2.

Table 2. Substrate Scope of the Reaction and Physical Properties of Compound **3**

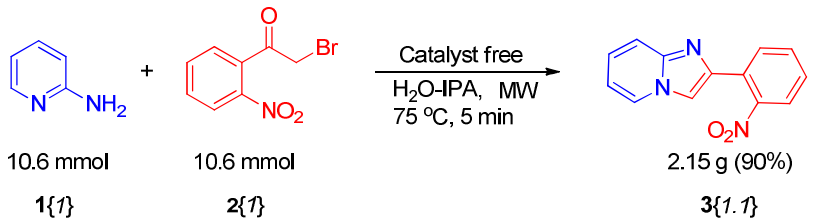


entry	product	yield (%)[a]	LRMS[b]	H-bond donor	H-bond acceptor	c log P[c]	E-factor
1	3{*1,1*}	95	239	1	5	3.25	0.48
2	3{*1,2*}	93	209	1	3	2.46	0.57
3	3{*1,3*}	95	228	0	2	4.21	0.49
4	3{*1,4*}	92	208	0	2	4.00	0.40
5	3{*1,5*}	96	270	0	2	5.39	0.41
6	3{*1,6*}	95	224	0	3	3.51	0.50
7	3{*2,3*}	92	242	0	2	4.72	0.52
8	3{*2,5*}	95	284	0	2	5.89	0.24
9	3{*2,4*}	93	235	0	2	4.50	0.45
10	3{*3,4*}	94	244	0	2	4.30	0.48
11	3{*3,5*}	95	306	0	2	5.69	0.39
12	3{*1,7*}	90	190	0	4	1.60	0.69
13	3{*4,4*}	95	222	0	2	4.50	0.51
14	3{*5,4*}	93	267	1	5	4.24	0.46
15	3{*4,6*}	96	238	0	3	4.04	0.46
16	3{*6,5*}	94	258	0	3	3.59	0.52
17	3{*6,3*}	95	229	0	3	3.10	0.50
18	3{*6,4*}	94	209	0	3	2.89	0.55
19	3{*6,6*}	95	225	0	4	2.40	0.51
20	3{*6,7*}	90	191	0	5	0.43	0.68
21	3{*7,3*}	92	229	0	3	3.10	0.55
22	3{*7,5*}	93	271	0	3	4.28	0.46
23	3{7,4}	92	209	0	4	2.89	0.57

[a]Isolated yields. [b]LRMS was recorded by GC-MS method. [c]Estimated c log P by ChemBioOffice 2010.

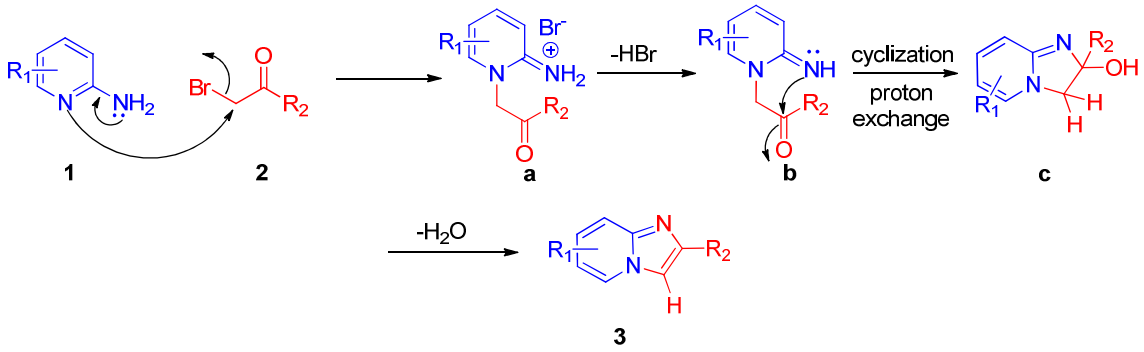
Additionally, we have investigated the potential synthetic applicability of this method on the gram scale using the model reaction. As depicted in Scheme 2, the reaction could afford 2.15 g

of **3**{*1,1*} in 90% yield without any significant loss of its efficiency, demonstrating the potential applications of the present method for a large scale synthesis of imidazo[1,2-*a*]pyridine scaffolds.



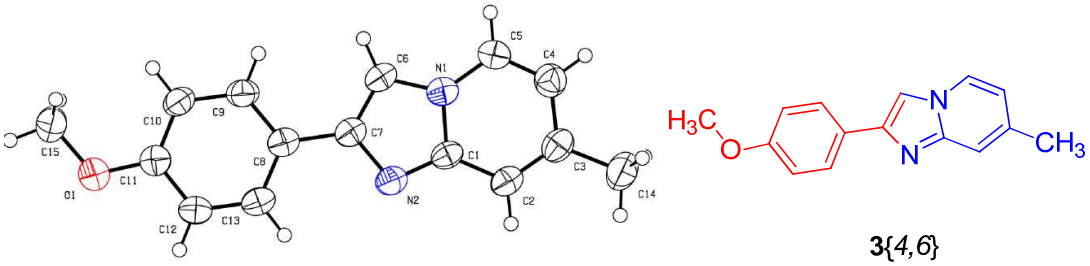
Scheme 2. Gram-scale synthesis of imidazo[1,2-*a*]pyridines **3**{*1,1*}.

A plausible mechanistic pathway for this heteroannulation reaction is outlined in Scheme 3. Probably the reaction occurs via a sequence of nucleophilic bromo-substitution followed by an intramolecular cyclization and subsequent elimination of water. Initially the bromo-group of phenacyl bromides **2** underwent nucleophilic substitution by pyridine N-atom through the electronic resonance of the 2-amino group of **1** leading to the N-alkylated adduct **a** which on liberation of HBr obtained the intermediate **b**. The next step of the reaction involves the intramolecular cyclization through the condensation of amine with carbonyl functionality of ketone followed by proton exchange to obtain the cyclic intermediate **c**. The final step of the reaction involves the elimination of a water molecule from intermediate **c** to afford imidazo[1,2-*a*]pyridines **3** derivatives.



Scheme 3. Possible mechanism for heteroannulation reaction to imidazo[1,2-*a*]pyridines **3** derivatives.

To further confirm the structure, we undertook the X-ray crystallographic study of compound **3**{*4,6*}.[14] The Figure 2 depicts the ORTEP diagram of compound **3**{*4,6*} (X-ray crystallographic data were specified in Supporting Information). The X-ray crystal structure of compound **3**{*4,6*} indicates that the 4-methoxy phenyl group was present at C7 carbon and the C6 carbon bears hydrogen atom which unequivocally confirms its structure.



3{*4,6*}

Figure 2. ORTEP diagram of compound **3**{*4,6*}**.**

To determine the anti-inflammatory activities of imidazo[1,2-*a*]pyridines/pyrimidines/pyrazines **3**, inhibition of the albumin denaturation power was evaluated.[15] It is well known that inflammation is a complex process, that can be associated with increased vascular permeability, protein denaturation, membrane alteration etc. There are many in vitro assays, available for the preliminary screening of compounds exhibiting anti-inflammatory activity. Albumin denaturation assay is one among those. Moreover, it has been reported that many compounds that are known to inhibit protein denaturation are good anti-inflammatory agents.[16] Because of *in vivo* denaturation of proteins, auto-antigens are produced in certain rheumatic diseases. The evaluations were carried out *in-vitro* at different concentrations and compared to well-known anti-inflammatory drug diclofenac sodium (Table 3). The inhibitory activity was carried out at

different concentrations and the percentage inhibition at 100 μM concentration of each compound in 2 % DMSO has been reported.

Table 3. % Inhibition of albumin denaturation.

entry	product	% Inhibition of albumin denaturation
1	3{*1,1*}	99.43
2	3{*1,2*}	43.90
3	3{*1,3*}	42.71
4	3{*1,4*}	43.61
5	3{*1,5*}	41.24
6	3{*1,6*}	19.05
7	3{*2,3*}	30.56
8	3{*2,5*}	68.29
9	3{*2,4*}	99.43
10	3{*3,4*}	92.88
11	3{*3,5*}	51.59
12	3{*1,7*}	23.81
13	3{4,4}	72.41
14	3{5,4}	84.31
15	3{4,6}	94.90
16	3{*6,5*}	95.36
17	3{*6,3*}	41.67
18	3{*6,4*}	82.94
19	3{*6,6*}	40.91
20	3{*6,7*}	54.17
21	3{*7,3*}	50.00
22	3{*7,5*}	41.93
23	3{7,4}	96.60
24	Diclofenac Sodium	84.73

The estimated inhibitory activity of imidazo[1,2-*a*]pyridines/pyrimidines/pyrazines **3** were measured and results were shown in Table 3. Most of the compounds exhibited moderate to strong activity with the exception of compounds **3**{*1,1*}, **3**{*2,4*}, and **3**{*7,4*} with 2-nitro and *p*-tolyl substitution on the imidazo[1,2-*a*]pyridine ring.

Likewise, imidazo[1,2-*a*]pyridines/pyrimidines/pyrazines **3** were screened for *in-vitro* antimicrobial activity against Gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus*, and *Klebsiella*) and Gram-positive (*Staphylococcus aureus*) bacteria by the conventional serial dilution method as shown in Table 4.

Table 4. Antimicrobial activities of imidazo[1,2-*a*]pyridines/pyrimidines/pyrazines **3.**

entry	product	MIC[a] (μM)				
		Proteus	*E.coli*	*P. aeruginosa*	*Staphylococcus*	*Klebsiella*
1	3{*1,1*}	78.4	76.2	>200	190.7	113.6
2	3{*1,2*}	142.1	129.2	173.9	154.5	>200
3	3{*1,3*}	110.9	100.2	39.1	80.8	101.6
4	3{*1,4*}	>200	>200	>200	>200	>200
5	3{*1,5*}	>200	>200	>200	>200	>200
6	3{*1,6*}	>200	>200	>200	>200	>200
7	3{*2,3*}	100.2	112.1	>200	129.6	87.2
8	3{*2,5*}	>200	>200	>200	>200	>200
9	3{*2,4*}	71.4	62.1	102.3	70.7	104.5
10	3{*3,4*}	100.9	93.5	88.7	87.2	131.1
11	3{*3,5*}	>200	>200	>200	>200	>200
12	3{*1,7*}	>200	>200	>200	>200	>200
13	3{*4,4*}	28.1	31.95	22.6	42.7	13.9
14	3{*5,4*}	159.1	>200	>200	>200	>200
15	3{*4,6*}	16.1	46.3	41.7	53.9	30.3
16	3{*6,5*}	81.5	118.1	149.8	112.4	34.8
17	3{*6,3*}	>200	>200	>200	>200	>200
18	3{*6,4*}	165.6	177.8	109.5	137.6	86.5
19	3{*6,6*}	>200	>200	>200	>200	>200
20	3{*6,7*}	>200	>200	>200	>200	>200
21	3{*7,3*}	>200	>200	>200	>200	>200
22	3{*7,5*}	>200	>200	>200	>200	>200
23	3{*7,4*}	65.7	138.3	>200	90.3	152.5
24	Ciprofloxacin	0.05	0.39	0.39	0.39	0.09

[a] MIC; Minimum inhibitory concentration (μM)

Minimum inhibitory concentration (MIC) values were evaluated and ciprofloxacin whose MIC values are reported in the literature was used as a standard reference drug only as a positive

control and is in no way related to the MIC values obtained for our test samples. Most of the compounds displayed antibacterial activities and is shown in Table 4. MIC values of compounds **3**{*1,1*}, **3**{*2,4*}, **3**{*4,4*}, and **3**{*4,6*} showed the ability to inhibit the growth of *E. coli* and *Proteus* whereas compounds **3**{*1,3*}, **3**{*2,4*}, **3**{*3,4*}, **3**{*4,4*}, and **3**{*4,6*} were effective towards Pseudomonas and Staphylococcus bacteria. Among all the compounds, only compounds **3**{*4,4*}, and **3**{*4,6*} were active towards inhibiting the growth of both gram negative and gram positive bacteria as shown in Table 4. The observed antibacterial activities of the synthesized compounds demonstrated the preliminary structure-activity relationships. Particularly, compounds **3**{*4,4*}, and **3**{*4,6*} bearing *p*-tolyl and *p*-OMe substitution as electron donating substituents were active towards inhibiting the growth of *Proteus* and *Klebsiella* bacteria. These results indicated that some of these compounds possessed selective antimicrobial activities and further development of such compounds might be of interest to medicinal chemists.

Conclusion

In conclusion, we have developed catalyst free heteroannulation for imidazo[1,2-*a*]pyridines/pyrimidines/pyrazines in green solvent under microwave irradiation. The salient features of this strategy include milder reaction conditions, inexpensive reagents, high-atom economy, and short reaction time in a single synthetic operation. All the synthetic compounds were studied for their anti-inflammatory activities *in vitro* and antimicrobial activities. Anti-inflammatory data indicated that compounds with 2-nitro or 4-methyl substituent on the imidazo[1,2-*a*]pyridine moiety showed significant albumin denaturation power and moreover some of tested compounds demonstrated the antimicrobial activity by inhibiting the growth of *Proteus* and *Klebsiella* bacteria. These results suggested that these heterocyclic molecules might

serve as interesting lead compounds for the development of new anti-inflammatory and/or antimicrobial agents. Further medicinal applications of the imidazo[1,2-*a*]pyridines/pyrimidines/pyrazines derivatives are currently under investigation in our laboratory.

Experimental section

Representative Procedure for the Synthesis of 2-(2-nitrophenyl)imidazo[1,2-*a*]pyridine 3{*1,1*}. In a round bottomed flask, a mixture of 2-aminopyridine **1**{*1*}(0.1 g, 1.06 mmol, 1.0 equiv), and 2-bromo-1-(2-nitrophenyl)ethanone **2**{*1*} (0.256 g, 1.06 mmol, 1.0 equiv) was added to 5 mL solution of H_2O-IPA (1:1). The reaction mixture was irradiated under microwave heating at 240 watt for 5 min at 75 ºC. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (10 mL, twice). The combined organic layer was dried over anhydrous $MgSO_4$. The combined filtrate was subjected to evaporation to obtain the crude compound, which was purified over silica gel column (60–120 mesh) using 5% ethyl acetate in hexane as eluent to obtain the corresponding 2-(2-nitrophenyl)imidazo[1,2-*a*]pyridine **3**{*1,1*}as the product.

*2-(2-nitrophenyl)imidazo[1,2-a]pyridine **3**{1,1}.*

Yield: 95%; Yellow solid; mp: 151-152 °C; R_f = 0.5 (20%EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 6.76 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.76 (s, 1H), 7.71(d, J = 8.04 Hz, 1H), 7.62 (t, J = 6.9 Hz, 2H), 7.45 (t, J =7.8 Hz, 1H), 7.19 (t, J=7.24 Hz, 1H), 6.80 (t, J = 6.76 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 140.0, 134.9, 126.5, 126.1, 123.2, 122.4, 120.5, 120.0, 118.2, 112.6, 107.6, 105.3; MS (GC-MS): 239; HRMS (EI, m/z) calcd for $C_{13}H_9N_3O_2$: m/z 239.0695; Found 239.0697; IR (cm^{-1}, KBr) 3149, 3020, 1519, 1354, 1276, 1193.

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Supporting Information Available.

The Supporting Information is available free of charge on the Publications website at. along with ^{1}H and ^{13}CNMR spectra of compounds **3**. Assays for the anti-inflammatory and antimicrobial assay for compounds **3,** calculation of E-factor, and X-ray data of compound **3**{*4,6*}.

References

1. Hu, F.; Szostak, M. Recent Developments in the Synthesis and Reactivity of Isoxazoles: Metal Catalysis and Beyond. *Adv. Synth. Catal.* **2015**, *357*, 2583-2614.

2. (a) Bagdi, A. K.; Santra, S.; Monir, K.; Hajra, A. Synthesis of imidazo[1,2-*a*]pyridines: a decade update. *Chem. Commun*. **2015**, *51*, 1555–1575. (b) Song, G.; Zhang, Y.; Li, X. Rhodium and Iridium Complexes of Abnormal N-Heterocyclic Carbenes Derived from Imidazo[1,2-*a*]pyridine. *Organometallics* **2008**, *27*, 1936-1943. (c) Wan, J.; Zheng, C.-J.; Fung, M.-K.; Liu, X.-K.; Lee, C.-S.; Zhang, X.-H. Multifunctional electron-transporting indolizine derivatives for highly efficient blue fluorescence, orange phosphorescence host and two-color based white OLEDs. *J. Mater. Chem*. **2012**, *22*, 4502-4510. (d) Atack, J. R. The benzodiazepine binding site

of GABAA receptors as a target for the development of novel anxiolytics. *Expert Opin. Invest. Drugs*, **2005**, *14*, 601–618. (e) McNamara, C. W.; Lee, M. C. S.; Lim, C. S.; Lim, S. H.; Roland, J.; Nagle, A.; Simon, O.; Yeung, B. K. S.; Chatterjee, A. K.; McCormack, S. L.; Manary, M. J.; Zeeman, A.-M.; Dechering, K. J.; Santhakumar, T. R.; Henrich, P. P.; Gagaring, K.; Ibanez, M.; Kato, N.; Kuhen, K. L.; Fischli, C.; Rottmann, M.; Plouffe, D. M.; Bursulaya, B.; Meister, S.; Rameh, L.; Trappe, J.; Haasen, D.; Timmerman, M.; Sauerwein, R.W.; Suwanarusk, R.; Russell, B.; Renia, L.; Nosten, F.; Tully, D. C.; Kocken, C. H. M.; Glynne, R. J.; Bodenreider, C.; Fidock, D. A.; Diagana T. T.; Winzeler, E. A. Targeting *Plasmodium* phosphatidylinositol 4-kinase to eliminate malaria. *Nature* **2013**, *504*, 248-253. (f) Teranishi, K. Luminescence of imidazo[1,2-*a*]pyrazin-3(7*H*)-one compounds. *Bioorg. Chem*. **2007**, *35*, 82-111. (g) Goel, R.; Luxami, V.; Paul, K. Recent advances in development of imidazo[1,2-*a*]pyrazines: synthesis, reactivity and their biological applications. *Org. Biomol. Chem.* **2015**, *13*, 3525–3555.

3. (a) Fisher, M. H.; Lusi, A. Imidazo[1,2-*a*]pyridine anthelmintic and antifungal agents. *J. Med. Chem*. **1972**, *15*, 982-985. (b) Rival, Y.; Grassy, G.; Taudou, A.; Ecalle, R. Antifungal activity in vitro of some imidazo[1,2-*a*]pyrimidine derivatives. *Eur. J. Med. Chem*. **1991**, *26*, 13-18. (c) Gudmundsson, K. S.; Johns, B. A. Synthesis of Novel Imidazo[1,2-*a*]pyridines with Potent Activity against Herpesviruses. *Org. Lett*. **2003**, *5*, 1369-1372. (d) Rival, Y.; Grassy, G.; Michel, G. Synthesis and Antibacterial Activity of Some Imidazo [1, 2-*a*]pyrimidine Derivatives. *Chem. Pharm. Bull*. **1992**, *40*, 1170–1176. (e) Gudmundsson, K. S.; Williams, J. D.; Drach, J. C.; Townsend, L. B. Synthesis and Antiviral Activity of Novel Erythrofuranosyl Imidazo[1,2-*a*]pyridine C-Nucleosides Constructed via Palladium Coupling of Iodoimidazo[1,2-*a*]pyridines and Dihydrofuran. *J. Med. Chem*. **2003**, *46*, 1449-1455. (f) Ismail, M. A.; Brun, R.; Wenzler, T.; Tanious, F. A.; Wilson, W. D.; Boykin, D. W. Novel Dicationic Imidazo[1,2-*a*]pyridines and

5,6,7,8-Tetrahydro-imidazo[1,2-*a*]pyridines as Antiprotozoal Agents. *J. Med. Chem.* **2004**, *47*, 3658-3664 (g) Catena, R. J. L.; Farrerons, G. L.; Fernandez, S. A.; Serra, C. C.; Balsa, L. D.; Lagunas, A. C.; Salcedo, R. C.; Fernandez, G. A. WO 05014598A1, **2004** *Chem. Abstr*. **2005**, *142*, 240458z. (h) Kaminski, J. J.; Perkins, D. G.; Frantz, J. D.; Solomon, D. M.; Elliott, A. J.; Chiu, P. J. S.; Long, J. F. Antiulcer agents. 3. Structure-activity-toxicity relationships of substituted imidazo[1,2-*a*]pyridines and a related imidazo[1,2-*a*]pyrazine. *J. Med. Chem.* **1987**, *30*, 2047-2055. (i) Sablayrolles, C.; Cros, G. H.; Milhavet, J. C.; Rechenq, E.; Chapat, J.-P.; Boucard, M.; Serrano, J. J.; McNeill, J. H. Synthesis of imidazo[1,2-*a*]pyrazine derivatives with uterine-relaxing, antibronchospastic, and cardiac-stimulating properties. *J. Med. Chem.* **1984**, *27*, 206-212.

4. (a) Teranishi, K.; Nishiguchi, T.; Ueda, H. Enhanced chemiluminescence of 6-(4-methoxyphenyl)imidazo[1,2-*a*]pyrazin-3(7*H*)-one by attachment of a cyclomaltooligosaccharide (cyclodextrin). Attachment of cyclomaltononaose (delta-cyclodextrin). *Carbohydr. Res*. **2003**, *338*, 987-993. (b) Velazquez-Olvera, S.; Salgado-Zamora, H.; VelazquezPonce, M.; Campos-Aldrete, E.; Reyes-Arellano, A.; PerezGonzalez, C. Fluorescent property of 3-hydroxymethyl imidazo[1,2-*a*]pyridine and pyrimidine derivatives. *Chem. Cent. J.* **2012**, *6*, 83.

5. (a) Langer, S. Z.; Arbilla, S.; Benavides, J.; Scatton, B. Zolpidem and alpidem: two imidazopyridines with selectivity for omega 1- and omega 3-receptor subtypes. *Adv. Biochem. Psychopharmacol*. **1990**, *46*, 61-72. (b) Mizushige, K.; Ueda, T.; Yukiiri, K.; Suzuki, H. Olprinone: a phosphodiesterase III inhibitor with positive inotropic and vasodilator effects. *Cardiovasc. Drug Rev.* **2002**, *20*, 163-174. (c) Almirante, L.; Polo, L.; Mugnaini, A.; Provinciali, E.; Rugarli, P.; Biancotti, A.; Gamba, A.; Murmann, W. Derivatives of Imidazole. I. Synthesis and Reactions of Imidazo[1,2-*a*]pyridines with Analgesic, Antiinflammatory, Antipyretic, and

Anticonvulsant Activity. *J. Med. Chem*. **1965**, *8*, 305-312. (d) Feely, M.; Boyland, P.; Picardo, A.; Cox, A.; Gent, J. P. Lack of anticonvulsant tolerance with RU 32698 and Ro 17-1812. *Eur. J. Pharmacol*. **1989**, *164*, 377-380. (e) Tully, W. R.; Gardner, C. R.; Gillespie, R. J.; Westwood, R. 2-(Oxadiazolyl)- and 2-(thiazolyl)imidazo[1,2-*a*]pyrimidines as agonists and inverse agonists at benzodiazepine receptors. *J. Med. Chem*. **1991**, *34,* 2060-2067. (f) Glennon, R. A.; Rogers, M. E.; Smith, J. D.; El-Said, M. K.; Egle, J. L. Mesoionic xanthine analogs: phosphodiesterase inhibitory and hypotensive activity. *J. Med. Chem*. **1981**, *24*, 658-661.

6. (a) Fisher, M. H.; Lusi, A. Imidazo[1,2-*a*]pyridine anthelmintic and antifungal agents. *J. Med. Chem*. **1972**, 15, 982-985. (b) Nair, D. K.; Mobin, S. M.; Namboothiri, I. N. N. Synthesis of Imidazopyridines from the Morita Baylis Hillman Acetates of Nitroalkenes and Convenient Access to Alpidem and Zolpidem. *Org. Lett*. **2012**, *14*, 4580-4583. (c) Yan, H.; Wang, Y.; Pan, C.; Zhang, H.; Yang, S.; Ren, X.; Li, J.; Huang, G. Iron(III)-Catalyzed Denitration Reaction: One-Pot Three-Component Synthesis of Imidazo[1,2-*a*]pyridine Derivatives. *Eur. J. Org. Chem*. **2014**, 2754-2763. (d) Schwerkoske, J.; Masquelin, T.; Perun, T.; Hulme, C. New multi-component reaction accessing 3-aminoimidazo[1,2-*a*]pyridines. *Tetrahedron Lett.* **2005**, *46*, 8355-8357. (e) Wang, H.; Wang, Y.; Liang, D.; Liu, L.; Zhang, J.; Zhu, Q. Copper-catalyzed intramolecular dehydrogenative aminooxygenation: direct access to formyl-substituted aromatic N-heterocycles. *Angew. Chem., Int. Ed.* **2011**, *50*, 5678-5681. (f) Wang, H.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. A Direct Intramolecular C−H Amination Reaction Cocatalyzed by Copper(II) and Iron(III) as Part of an Efficient Route for the Synthesis of Pyrido[1,2-*a*]benzimidazoles from N-Aryl-2-aminopyridines. *J. Am. Chem. Soc*. **2010**, *132*, 13217-13219. (g) Donohoe, T. J.; Kabeshov, M. A.; Rathi, A. H.; Smith, I. E. D. Direct preparation of thiazoles, imidazoles, imidazopyridines and thiazolidines from alkenes. *Org. Biomol. Chem*. **2012**, *10*, 1093-1091. (h)

Ge, W.; Zhu, X.; Wei, Y. Aerobic Multicomponent Tandem Synthesis of 3-Sulfenylimidazo[1,2-*a*]pyridines from Ketones, 2-Aminopyridines, and Disulfides. *Eur. J. Org. Chem.* **2013**, 6015-6020. (i) Al-Tel, T. H.; Al-Qawasmeh, R. A. Post Groebke–Blackburn multicomponent protocol: Synthesis of new polyfunctional imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine derivatives as potential antimicrobial agents. *Eur. J. Med. Chem.* **2010,** *45,* 5848-5855. (j) Peshkov, V. A.; Peshkov, A. A.; Pereshivko, O. P.; Hecke, K. V.; Zamigaylo, L. L.; van der Eycken, E. V.; Gorobets, N. Y. Three-Component Reaction of a 2-Aminoazine, a 2-Oxoaldehyde, and a Cyclic 1,3-Dicarbonyl Compound for the Synthesis of Imidazo[1,2-*a*]azine Derivatives. *ACS. Comb. Sci*. **2014**, *16,* 535-542. (k) Ermolatev, D. S.; Gimemez, V. N.; Babaev, E. V.; van der Eycken, E. V. Efficient Pd(0)-Mediated Microwave-Assisted Arylation of 2-Substituted Imidazo[1,2-*a*]pyrimidines. *J. Comb. Chem.* **2006**, *8*, 659-663. (l) Guchhait, S. K.; Madaan, C. Towards molecular diversity: dealkylation of tert-butyl amine in Ugi-type multicomponent reaction product establishes tert-butyl isocyanide as a useful convertible isonitrile. *Org. Biomol. Chem*. **2010**, *8*, 3631-3634. (m) Guchhait, S. K.; Chaudhary, V.; Madaan, C. A chemoselective Ugi-type reaction in water using TMSCN as a functional isonitrile equivalent: generation of heteroaromatic molecular diversity. *Org. Biomol. Chem*. **2012**, *10*. 9271-9277.

7. (a) Ponnala, S.; Kumar, S. T. V. S. K.; Bhat, B. A.; Sahu, D. P. Synthesis of Bridgehead Nitrogen Heterocycles on a Solid Surface. *Synth.Commun*. **2005**, *35*, 901-906. (b) Zhu, D.-J.; Chen, J.-X.; Liu, M.-C.; Dinga, J.-C.; Wu, H.-Y. Catalyst: and solvent-free synthesis of imidazo[1,2-a]pyridines. *J. Braz. Chem. Soc*. **2009**, *20*, 482-487. (c) Stasyuk, A. J.; Banasiewicz, M.; Cyrański, M. K.; Gryko, D. T. Imidazo[1,2-*a*]pyridines Susceptible to Excited State Intramolecular Proton Transfer: One-Pot Synthesis via an Ortoleva–King Reaction. *J. Org.*

Chem. **2012**, *77*, 5552-5558. (d) Cai, L.; Brouwer, C.; Sinclair, K.; Cuevas, J.; Pike, V. W. Titanium(IV) Chloride Promoted Syntheses of New Imidazo[1,2-*a*]pyridine Derivatives under Microwave Conditions. *Synthesis* **2006**, 133-145. (e) Chunavala, K. C.; Joshi, G.; Suresh E.; Adimurthy, S. Thermal and Microwave-Assisted Rapid Syntheses of Substituted Imidazo[1,2-*a*]pyridines Under Solvent- and Catalyst-Free Conditions. *Synthesis* **2011**, 635-641. (f) González, S. M.; Hernández, A. I.; Varela, C; Rodríguez-Arístegui, S.; Alvarez, R. M.; García, A. B.; Lorenzo, M.; Rivero, V.; Oyarzabal, J.; Rabal, O.; Bischoff, J. R.; Albarrán, M.; Cebriá, A.; Alfonso, P.; Link, W.; Fominaya, J.; Pastor, J. Imidazo[1,2-*a*]pyrazines as novel PI3K inhibitors. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1874-1878. (g) González, S. M.; Hernández, A. I.; Varela, C.; Rodríguez-Arístegui, S.; Lorenzo, M.; Rodríguez, A.; Rivero, V.; Martín, J. I.; Saluste, C. G.; Ramos-Lima, F.; Cendón, E.; Cebrián, D.; Aguirre, E.; Gomez-Casero, E.; Albarrán, M.; Alfonso, P.; García-Serelde, B.; Oyarzabal, J.; Rabal, O.; Mulero, F.; Gonzalez-Granda, T.; Link, W.; Fominaya, J.; Barbacid, M.; Bischoff, J. R.; Pizcueta, P.; Pastor, J. Identification of ETP-46321, a potent and orally bioavailable PI3K α, δ inhibitor. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3460-3466.

8. (a) Xie, Y.-Y.; Chen, Z.-C.; Zheng, Q.-G. Organic Reactions in Ionic Liquids: Ionic Liquid-Accelerated Cyclocondensation of α-Tosyloxyketones with 2-Aminopyridine. *Synthesis* **2002**, 1505-1508. (b) Ueno, M.; Togo, H. Environmentally Benign Preparation of Heteroaromatics from Ketones or Alcohols, with Macroporous Polystyrenesulfonic Acid and (Diacetoxy-iodo)benzene, Followed by Thioamide, Amidine, and 2-Aminopyridine. *Synthesis* **2004**, 2673-2677. (c) Yadav, J. S.; Reddy, B. V. S.; Rao, Y. G.; Srinivas, M.; Narsaiah, A. V. $Cu(OTf)_2$-catalyzed synthesis of imidazo[1,2-*a*]pyridines from α-diazoketones and 2-aminopyridines. *Tetrahedron Lett*. **2007**, *48*, 7717-7720.

9. Kong, D.; Wang, X.; Shi, Z.; Wu, M.; Lin, Q.; Wang, X. Solvent- and catalyst-free synthesis of imidazo[1,2-*a*]pyridines under microwave irradiation. *J. Chem. Res.* **2016**, *40*, 529-531.

10. (a) Leadbeater, N. E.; Marco, M. Transition-Metal-Free Suzuki-Type Coupling Reactions . *Angew. Chem., Int. Ed*. **2003**, *42*, 1407-1409. (b) Leadbeater, N. E.; Smith, R. J. Real-Time Monitoring of Microwave-Promoted Suzuki Coupling Reactions Using in Situ Raman Spectroscopy. *Org. Lett*. **2006**, *8*, 4589-4591. (c) Santra, S.; Andreana, P. R. A Bioinspired Ugi/Michael/Aza-Michael Cascade Reaction in Aqueous Media: Natural-Product-like Molecular Diversity. *Angew. Chem., Int. Ed.* **2011**, *50*, 9418-9422. (d) Polshettiwar, V.; Varma, R. S. Microwave-Assisted Organic Synthesis and Transformations using Benign Reaction Media. *Acc. Chem. Res*. **2008**, *41*, 629–639. (e) Kappe, C. O.; Pieber, B.; Dallinger, D. Microwave Effects in Organic Synthesis: Myth or Reality?. *Angew. Chem. Int. Ed*. **2013**, *52*, 1088–1094. (f) Zhou, J.; Xu, W.; You, Z.; Wang, Z.; Luo, Y.; Gao, L.; Yin, C.; Peng, R.; Lan, L. A new type of power energy for accelerating chemical reactions: the nature of a microwave-driving force for accelerating chemical reactions. *Sci. Rep*. **2016**, *6*, 25149.

11. (a) Maiti, B.; Chanda, K.; Selvaraju, M.; Tseng, C. C.; Sun, C. M. Multicomponent Solvent-Free Synthesis Of Benzimidazolyl Imidazo[1,2-*a*]-pyridine Under Microwave Irradiation. *ACS Comb. Sci*. **2013**, *15*, 291-297. (b) Maiti, B.; Chanda, K. Diversity oriented synthesis of benzimidazole-based biheterocyclic molecules by combinatorial approach: a critical review. *RSC. Adv*. **2016**, *6*, 50384-50413. (c) Meena, DR.; Maiti, B.; Chanda, K. Cu(I) catalyzed microwave assisted telescopic synthesis of 3,5-disubstituted isoxazoles in green media. *Tetrahedron Lett*. **2016**, *57*, 5514-5517. (d) Rajasekhar, S.; Maiti, B.; Chanda, K. A Decade Update on Benzoxazoles, a Privileged Scaffold in Synthetic Organic Chemistry. *Synlett,* **2017**, *28*, 521-541. (e) Rao, R. N.; Maiti, B.; Chanda, K. Application of Pictet–Spengler Reaction to

Indole-Based Alkaloids Containing Tetrahydro-β-carboline Scaffold in Combinatorial Chemistry. *ACS Comb. Sci*. **2017**, *19*, 199-228.

12. (a) Sheldon, R. A. The E Factor: fifteen years on. *Green Chem*. **2007**, *9*, 1273-1283. (b) Sheldon R. A. Fundamentals of green chemistry: efficiency in reaction design. *Chem. Soc. Rev*. **2012**, *41*, 1437-1451.

13. (a) Lipinski, C. A.; Lombardo, F.; Dominay, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev*. **1997**, *23*, 3-25. (b) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev*. **2001**, *46*, 3-26. (c) Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J. Med. Chem*. **2002**, *45*, 2615-2623.

14. Final product **3**{*4,6*} was crystallized by slow evaporation of a solution of ethyl acetate−hexane (1:1, v/v) at room temperature. Crystal data: $C_{15}H_{14}N_2O$, M = 238.28, monoclinic, space group $P2_1/c$, a = 15.722Å, b = 5.794Å, c = 13.681Å, The crystal data has been deposited at Cambridge Crystallographic Data Centre [CCDC No. 1584234]. Copies of the data can be obtained free of charge via a www.ccdc.cam.ac.uk/data_request/cif.

15. Muzushima, Y.; Kobayashi, M. Interaction of anti-inflammatory drugs with serum proteins, especially with some biologically active proteins. *J. Pharm. Pharmacol*.,**1968**, *20*, 169-173.

16. (a) Maddili, S. K.; Yandrati, L. P.; Siddam, S.; Kannekantia, V; K.; Gandham, H. Green synthesis, biological and spectroscopic study on the interaction of multi-component Mannich bases of imidazo[2,1-*b*]benzothiazoles with human serum albumin. *J. Photochem. Photobiol., B*

2017, *176*, 9-16. (b) Shah, M.; Parveen, Z.; Khan, M. R. Evaluation of antioxidant, anti-inflammatory, analgesic and antipyretic activities of the stem bark of *Sapindus mukorossi*. *BMC Complement Altern. Med*. **2017**, *17*, 526.