Original Article: Glycine as an efficient catalyst for the synthesis of tetra-substituted imidazole derivatives in aqueous medium

Jitendra Bhausaheb Gujar[a,*] | Balaji Shahaji Londhe[b] | Raghunath Narayan Zambare[c] | Rajesh Janardan Kavade[c] | Murlidhar Shridhar Shingare[d]

[a]*Department of Chemistry, K. B. P. Mahavidyalaya, Pandharpur*
[b]*Karmaveer Bhaurao Patil Mahavidyalaya, Pandharpur*
[c]*Department of Chemistry, Karmaveer Bhaurao Patil Mahavidyalaya, Pandharpur,*
[d]*Department of Chemistry, Dr. B. A. M.U., Aurangabad.*

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ABSTRACT

Using a single-pot, tandem reaction, cyclization through condensation of 1,2-diphenylethane-1,2-dione, benzaldehyde, aniline, and ammonium acetate was accomplished by orthodox condition. The reaction was conducted in aqueous medium with help of glycine. This compact purveyed corresponding tetra-substituted imidazole derivatives in high yields, shorter duration of reaction, and simple work-up procedures with the green facets by eschewing harmful reagents.

Introduction

In the modern discovery of drugs, the key facet is to develop organic transformations which afford extreme structural manifolds and variance with the least number of synthetic steps to accumulate compounds with specific properties. [1]

Multicomponent reactions [2-4] (MCRs) have arisen as a highly valuable tool for the rapid creation of molecular complexity and diversity. Various functionalities are associated in drug discovery such as its forthright designing, and atom efficacy, and convergent

***Corresponding Author:** *Jitendra Bhausaheb Gujar(gujarjitendra20@gmail.com)*

uniqueness provides significant minimization of waste, labor, time, and cost [5-7]. As an account, multicomponent reactions, as well as tandem or related reactions, receive more and more attention [8]. Imidazole ring-bearing motifs can show numerous pharmaceuticals, biological and new restorative activities [9-10].

In many naturally occurring and synthesized compounds, imidazole manifests an important class of scaffold. Due to their useful pharmacological and biological aspects, imidazole framework has been a more attentive part for organic chemists. Imidazole scaffolds acted as inhibitors of p38 MAP kinase, B-Raf kinase, [11] kinase (ALK5), [12] cyclooxygenase-2 [13], and biosynthesis of (IL-1) [14]. Aptly substituted imidazole derivatives are widely used as glucagon receptors [15] and CB1 cannabinoid receptor antagonists [16], modulators of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR) [17], antitumor [18], antibacterial [19] and anti-inflammatory agents [20].

Literature review discloses that a number of methods exist for the preparation of tetrasubstituted imidazole by means of the following synthetic route. Numerous catalysts have been reported for this reaction. This protocol is also carried out in the presence of Copper acetate, [21] Wang's resin with AcOH, [22] HY Zeolite, [23] Silica gel/NaHSO4, [24] Molecular iodine, [25] K5CoW12O40.3H2O, [26] HClO4-SiO2, [27] InCl3.3H2O, [28] BF3-SiO2, [29] Mercaptopropyl silica (MPS) [30] and 12-Phosphotungstic acid supported on silica (PWA-SiO2). [31]

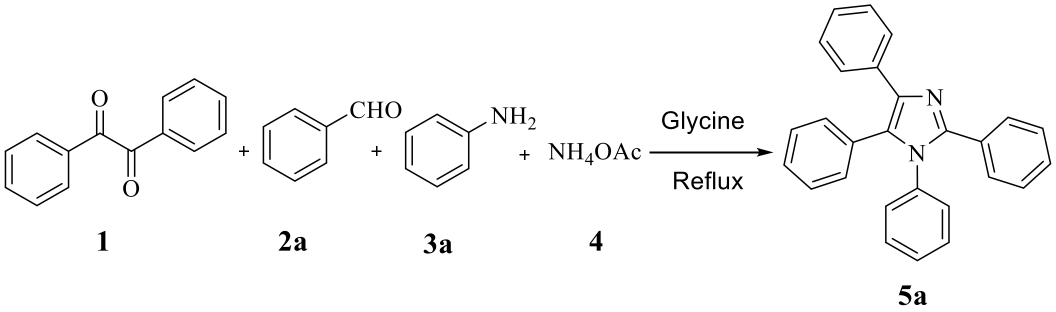
Though many of the reported transformations suffer from several drawbacks, such as inefficient yields, use of perilous and often costly acid catalysts, drastic reaction conditions, large reaction time, etc. In this regard, the development of a simple, effectual, atom efficient, and eco-benign protocol for the preparation of these compounds is essential.

Glycine is appealing much more attention from organic chemists due to its inexpensive and eco-benign nature, thermal stability, and workup standard. Besides, Glycine is nonflammable and is available in high quantities with less prices. The application of glycine in transformation is highly beneficial as its presence makes the system neutral, which helps in maintaining acid or base susceptible functional groups unchanged [32].

Results and Discussion

As part of our enduring effort for accessing heterocyclic moieties, we proceeded with the development of efficient green methodologies and the implementation of using classical and non-classical approaches in various organic transformations [33,34]. We have thought out a protocol to classified cyclic motifs having various biological importance.

Searching for the best conditions to carry out reaction, 1,2-diphenylethane-1,2-dione 1, benzaldehyde 2a, aniline 3a, and ammonium acetate 4 were considered as a standard reaction.



Scheme 1. Standard model reaction.

Literature review shows lots of acidic and basic catalysts have been conveyed to carry out this transformation. Primarily, we started the reaction of 1,2-diphenylethane-1,2-dione (1 mmol), benzaldehyde (1 mmol), aniline (1 mmol), and ammonium acetate (1.2 mmol) for 20 h without any interference of catalyst at room temperature in water, which provided a very low yield of 1,2,4,5-tetrasubstituted imidazole.

Next, to study the effect of temperature in the enhancement of the yield, the stated reaction was heated at reflux condition but it was observed that very poor yield was obtained. Then, the reaction was further carried out in the presence of a promoter. Therefore, in the continuation study, we optimized various promoters. In the beginning, various Lewis acids such as $ZnCl_2$, $FeCl_3$, and $AlCl_3$ were demonstrated to run this reaction. It was observed that conversion of reactant to the product was slow and moderate. Further, few amino acids were used; unexpectedly, the transformation ensued efficiently and offered the product in good yields (Table 1). In the study, we found that glycine was effective among the used promoters. It was observed that when we incorporated glycine as promoter, the reaction progressed nicely with product yield 87% (Table 1, Entry 6). Additionally, it seems that the amount of glycine loaded affected the yield of the products. When different amounts such as 5, 10, 15, and 20 mol % of glycine were used, the yields were observed as 56%, 71%, 87%, and 87%, respectively (Table 2, Entries 1-4). Therefore, 15 mol % of glycine was decided to use and carry out the organic transformation. Excess utilization in the amount of promoter does not enhance the yield. Glycine is present in zwitterion form, as it has both poles i.e. positive and negative ends, the positive end enhances the electrophilic character of the carbonyl group present in aldehyde and benzil. The negative part of zwitterion plays an important role in the formation of imine, after that cyclocondensation reaction occurs that leads to the formation of 1,2,4,5-tetrasubstituted imidazole.

Table 1. Optimization for appropriate catalysts and solvents

Sr. No.	Catalyst	Solvent	Yield[b] (%)
1	$ZnCl_2$	Water	34
2	$FeCl_3$	Water	32
3	$AlCl_3$	Water	29
4	Alanine	Water	69
5	Valine	Water	62
6	**Glycine**	**Water**	**87**
7	Glycine	Toluene	70
8	Glycine	Ethanol	65
9	Glycine	Methanol	59
10	Glycine	DMF	62
11	Glycine	Acetonitrile	40
12	Glycine	Neat[c]	55
13	No Catalyst	Water	20

[a]*Reaction conditions*: Benzil (1 mmol), Benzaldehyde (1 mmol), Aniline (1 mmol), Ammonium Acetate (1.2 mmol), Promoter (15 mol%), in 10 mL solvent at reflux temp. [b]Isolated yields; [c] Reaction temp. was 100 °C

Table 2. Optimization for the appropriate amount of glycine with temperature

Sr. No.	Temperature(°C)	Amount of Catalyst (mol %)	Yield[b] (%)
1	Reflux	5	56
2	Reflux	10	71
3	**Reflux**	**15**	**87**
4	Reflux	20	87

5	r.t.	5	Trace
6	40	10	36
7	50	15	46
8	60	15	51
9	80	15	68

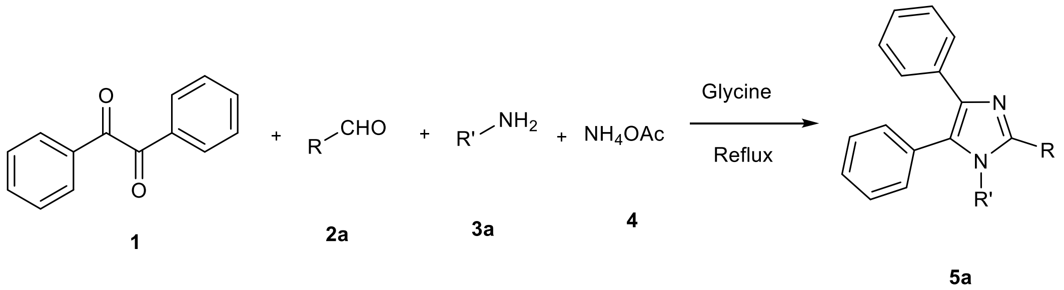
[a]Reaction conditions: Benzil (1 mmol), Benzaldehyde (1 mmol), Aniline (1 mmol), Ammonium Acetate (1.2 mmol), glycine 15 mol% in 10mL water isolated yields.

In a multicomponent reaction, the solvent shows an effective role. The influence of various solvents has been checked. Optimization for the appropriate solvents has been carried with a variety of solvents including EtOH, MeOH, DMF, CH_3CN, toluene and water. It was found that water was more effective than the above solvent for this reaction (Table 1).

To improve the yield of the product and minimize the reaction period, the reaction was optimized with room temperature and elevated temperature. In searching for appropriate temperature, the mentioned reaction was carried out at different temperatures. It was observed that enhancement in temperature led to improvement in the product yields.

For simplification of optimized reaction conditions, various aryl aldehydes and different anilines have been used to undergo this condensation. All the aromatic aldehydes with functionalities as well as various anilines were found to be equally acquiescent to these conditions. Representative results are shown in Table 3. Confirmation of the products was compared with the help of 1H NMR, 13C NMR, and mass spectroscopic data.

Table 3. Synthesis of highly substituted 1, 2, 4, 5-tetra imidazoles[a]



Product	R	R'	Time (h)	Yield[b] (%)	M. P. (°C)[c]
5a	Ph	Ph	2	85	216-218
5b	4-Cl-Ph	Ph	2	83	148-152
5c	4-OMe-Ph	Ph	2	83	180-184
5d	4-OH-Ph	Ph	2	85	287-289
5e	2-OH-Ph	Ph	2	82	258-260
5f	4-Me-Ph	Ph	2	80	183-185
5g	Piperonyl	Ph	2	79	194-196
5h	2-Furyl	Ph	2	80	193-195
5i	Ph	4-Me-Ph	2	78	173-176
5j	Ph	4-Cl-Ph	2	85	190-192
5k	4-Cl-Ph	4-Cl-Ph	2	83	188-191
5l	4-Me-Ph	4-Cl-Ph	2	78	165-167
5m	4-Me-Ph	4-Me-Ph	2	45	187-189

Conclusion

To summarize, we have established a simple route in the development of tetra-substituted imidazole scaffolds using benzil, aldehydes, anilines, and ammonium acetate promoted by glycine as a cheaply and easily available source. The proficient role of glycine as a catalyst was demonstrated. This protocol is facile, economic, and highly efficient. Furthermore, the present protocol serves marked enhancement with regard to operational simplicity, progression of reaction, and high isolated yields of the products.

Experimental

General experimental: (5a-m)

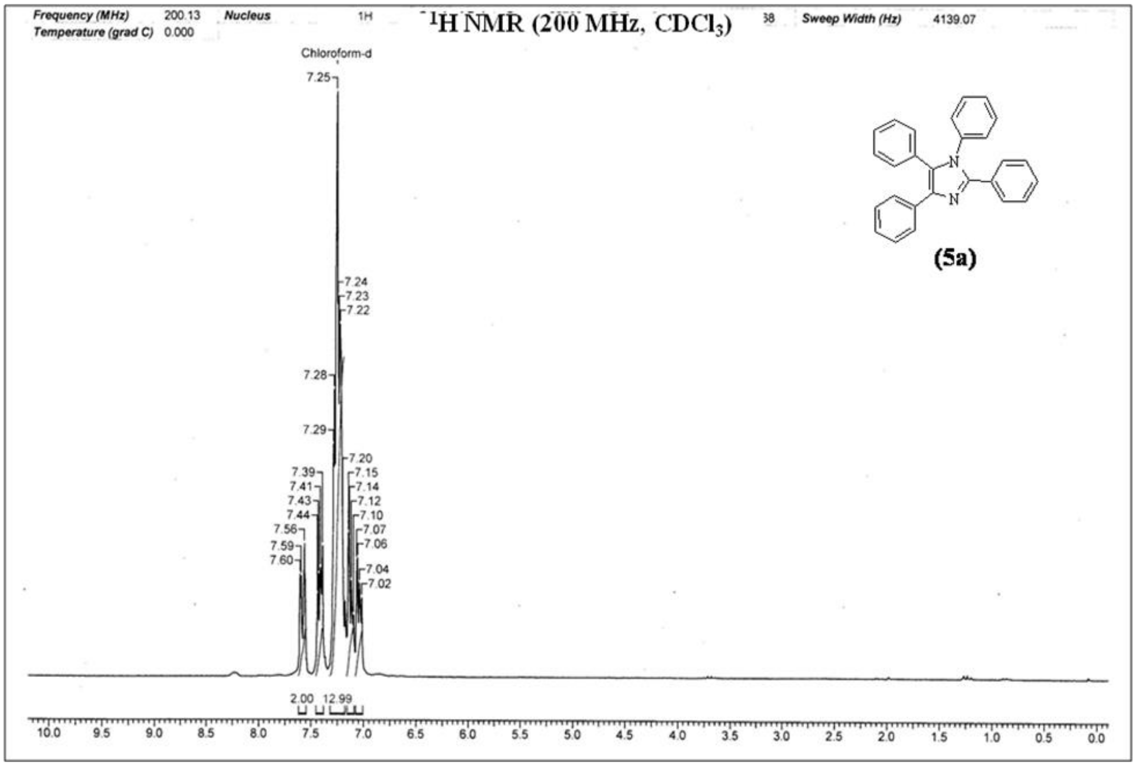
Conventional Technique: In RBF, Benzil (1mmol) aldehyde (1 mmol), aniline (1 mmol), and Ammonium acetate (1.2 mmol) in 10 mL water and glycine (15 mol %) was added, and the reaction mixture was heated to reflux for 2 h. Progression in the transformation was checked with help of TLC using ethyl acetate and n-hexane solvent in the ratio: 1:9. After completion of reaction, the solid material was allowed to cool with water. Thus, the solid product was obtained by simple filtration, and purified by crystallization in aqueous ethanol.

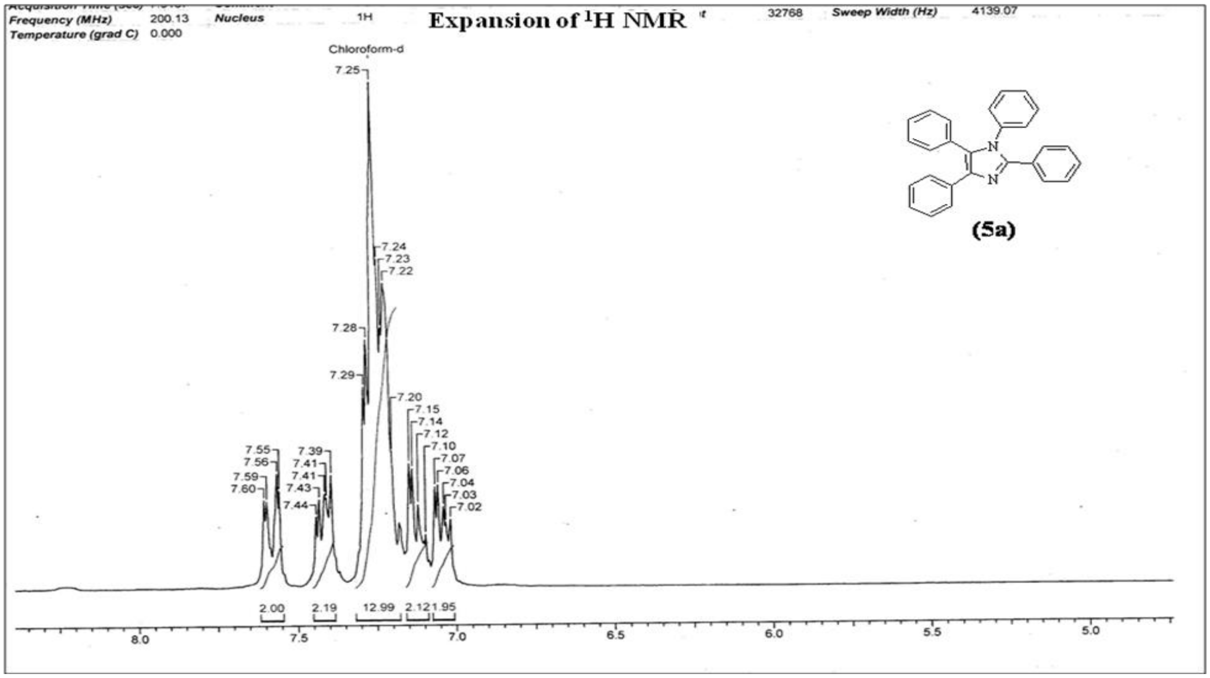
Spectral data of a representative compound Fig 1, (5a).

^{1}H-NMR(200MHz,$CDCl_3$): δppm = 7.02 (d, 1H, *J* = 2.0 Hz), 7.06 (d, 1H, *J* = 2.0 Hz), 7.10 (d, 1H, *J* = 4.0 Hz), 7.14 (d, 1H, *J* = 2.0 Hz), 7.20-7.29 (m, 12H), 7. 39-7.44 (m, 2H), 7.55 (d, 1H, *J* = 2.0 Hz), 7.59 (d, 1H, *J* = 2.0 Hz)

^{13}C-NMR(50MHz, $CDCl_3$): δppm= 126.6, 127.4, 127.9, 128.0, 128.3, 128.4, 128.9, 130.9, 130.9, 131.1, 134.4, 137.2, 138.4, 146.8.

Mass (ES-MS): m/z 373.0532 (M^+).

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7.24
7.23
7.22
7.28
7.29
7.20
7.15
7.14
7.12
7.10
7.07
7.06
7.04
7.03
7.02
7.55
7.56
7.59
7.60
7.39
7.41
7.41
7.43
7.44
(5a)
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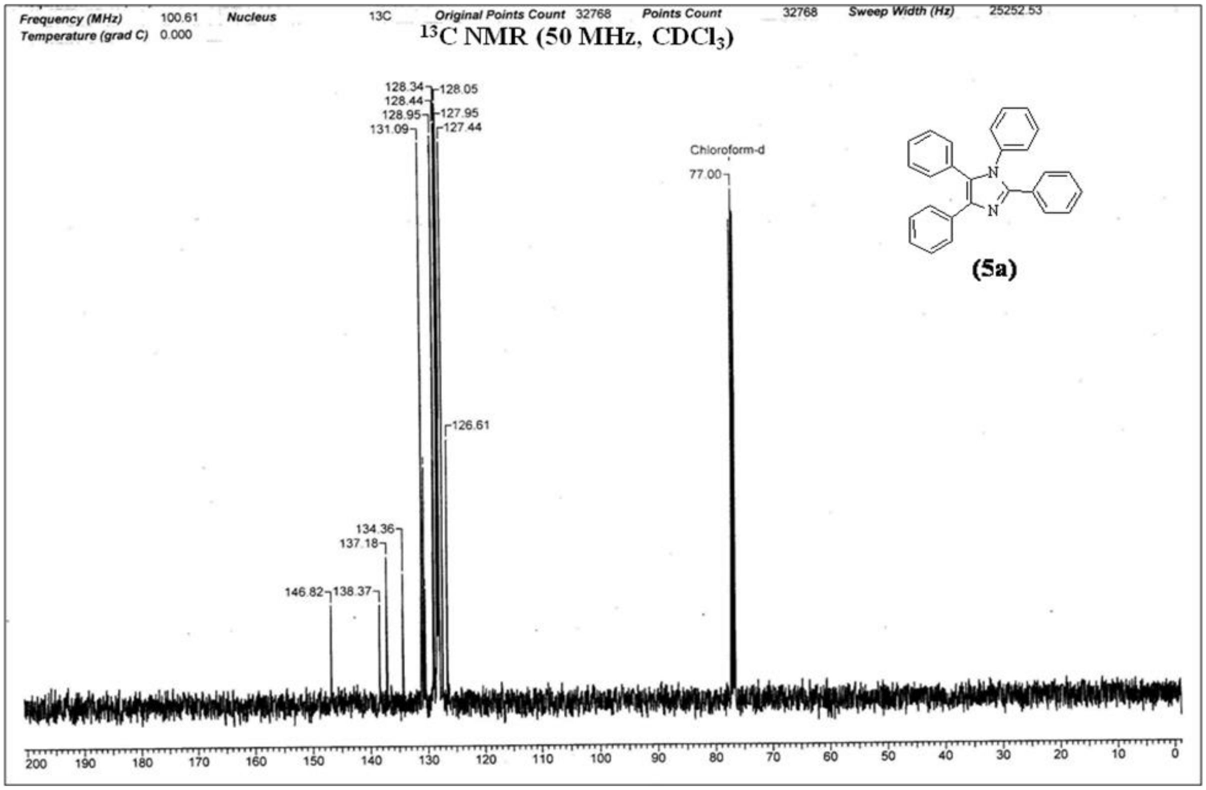
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128.34
128.44
128.95
131.09
128.05
127.95
127.44
Chloroform-d
77.00
126.61
134.36
137.18
146.82
138.37
(5a)
200
190
180
170
160
150
140
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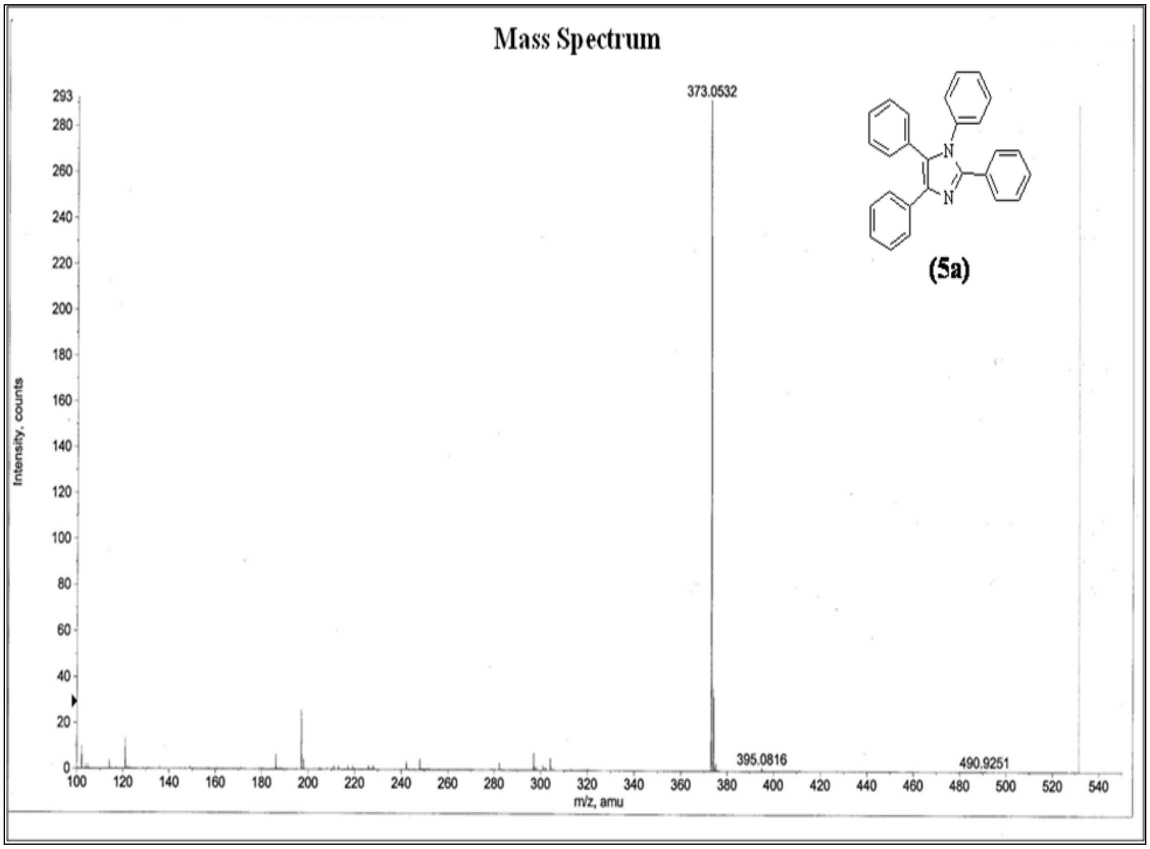

Fig 1. Spectral data of a representative compound

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Conflict of Interest

Regarding this research article, the authors do not have any conflict of interest.

Orcid:

Jitendra Bhausaheb Gujar: https://orcid.org/0000-0003-3334-4339
Balaji Shahaji Londhe: https://orcid.org/0000-0003-2690-6268
Raghunath Narayan Zambare: https://orcid.org/0000-0002-7213-3369
Rajesh Janardan Kavade: https://orcid.org/0000-0001-7666-627X
Murlidhar Shridhar Shingare: https://orcid.org/0000-0002-6847-0979

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