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Multicomponent Diversity-Oriented Synthesis of Symmetrical and Unsymmetrical 1,4-dihydropyridines in Recyclable Glycine Nitrate ($GlyNO_3$) Ionic Liquid: A Mechanistic Insight Using Q-TOF, ESI-MS/MS**

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Abstract

Multicomponent reactions are eye-catching strategies to generate chemically diverse set of multifunctionalized heterocyclic motifs with high atom economy manner which render the transformations green. These strategies can further become more prolific if catalyst recyclability, compatibility and exploration of exact mechanistic pathway are taken into account. To this end, an inexpensive and recyclable glycine nitrate ($GlyNO_3$) ionic liquid has been efficiently employed to access diversely substituted symmetrical and unsymmetrical 1,4-dihydropyridines up to 93% yields via three and four components respectively. The catalyst recyclability and compatibility to access both symmetrical and unsymmetrical 1,4 DHPs under identical reaction conditions, are added benefits to its practical utility. Furthermore, progress of the reaction was monitored by Q-TOF, direct infusion electrospray ionization mass spectrometry (ESI-MS) and key cationic intermediate involved in reaction have been further identified by tandem MS experiment (Q-TOF, ESI-MS/MS) which served as proof-of-concept to the mechanistic model. This is the first report which revealed that the Hantzsch reaction predominately follow diketone path way among four competing reaction pathways.

Keywords

1,4-dihydropyridines; ionic liquid; mass spectrometry; multicomponent reaction; reaction mechanism

Introduction

The creation of multiple carbon-carbon or carbon-hetero bonds in one pot helps in minimization of waste, time and energy. These benefits broadly encompassed under the periphery of green chemistry and generally accomplished by multicomponent reaction (MCRs).[1] In the recent year MCRs have been utilized for the preparation of structurally diverse drug-like compounds;[2] as a consequence, they have emerged as significant tool in organic synthesis.[3]

One prominent MCR that produces an interesting class of nitrogen based heterocycles is the venerable Hantzsch reaction providing 1,4-dihydropyridines (1,4-DHPs) as privileged pharmacophores.[4] DHPs derivatives exhibit a wide ranging pharmacological properties.[5] Initially these molecules recognized as calcium channel modulator but latter on developed as cardiovascular and antihypertensive drugs, which includes, amlodipine, felodipine, nicardipine and nifedipine.[6] (Figure 1) Beside this, these structural motifs are also credited with versatile biological properties like anticonvulsant,[7] radioprotective,[8] selective antagonism of adenosine-A3 receptor,[9] anticancer,[10] HIV protease inhibition,[11] and treatment of Alzheimer disease.[12]

Conventionally, 1,4-DHPs accessed through Hantzsch reaction, reduction of pyridines, addition to pyridines, or cycloaddition etc.[13] which suffer from the drawbacks like low to moderate yields besides harsh conditions and longer reaction times. Consequently, several modifications have been developed for the classical Hantzsch approach.[14] However, in spite of their potential utility many of these methods still involve expensive and /or toxic catalysts, cumbersome product isolation procedures and incompatibility with certain functional groups, thus are not closer to principles of green chemistry. Hence,

the challenge for a sustainable environment calls for more general and viable routes which would be of great relevance to both synthetic and medicinal chemists.

In this context, ionic liquids (ILs) hailed as green solvent of the future which increases the portfolio of environmentally benign organic synthesis due to their particular properties such as undetectable vapour pressure, ease of recovery and reuse.[15] So far, ILs with cations derived from imidazolium and guanidinium based ILs have been used as catalysts for Hantzsch reaction.[16] Though these ILs help to reduce the risk of air pollution, concerns are being raised over their potential toxicity to aquatic environments and inaccessible biodegradability.[17]

Therefore, the development of bio-degradable ILs based on amino acids and their derivatives to replace the above cations is another promising approach because amino acids and their derivatives are the most abundant natural source of quaternary nitrogen precursors.[18] Moreover, low cost, easy preparation, and their properties to act as both anions and cations are added advantage of these amino acid ionic liquids[18b, e, 19] (AAILs).

In continuation of our ongoing endeavours in developing novel and practical multicomponent reactions to synthesized useful heterocyclic compounds,[20] we herein present the catalytic efficiency of glycine nitrate ($GlyNO_3$) ionic liquid under microwave irradiation (MW) for multicomponent synthesis of aromatic/heterocyclic symmetrical and unsymmetrical 1,4-DHPs under identical reaction condition (Scheme 1). Furthermore, detailed Q-TOF, ESI-MS and ESI-MS/MS based mechanistic study revealed that reaction predominately follow diketone path way among four competing pathways.

Results and Discussion

After an initial survey of reaction conditions, a mixture of 4-chlorobenzaldehyde (**1a**, 0.5 mmol), methylacetoacetate (**2a**, 2 equiv), ammonium acetate (**3a**, 2 equiv) and $GlyNO_3$ (0.4 equiv) as a catalyst was irradiated under focused monomode microwave (CEM, P = 100 W, 90 °C) for 20 min. in EtOH (0.5 mL) affording 1,4-dihydropyrimidinone **4a** in 45% yield (Table 1, entry 1). To further increase the yield of **4a,** different source of ammonium salt were screened (Table 1 entries 2-5) wherein satisfactory yield of **4a** up to 73% was obtained with ammonium carbonate (Table 1 entry 5). Thereafter the effect of amount of catalyst (Table 1, entries 6-7) was taken into account and yield of 82 % was obtained with 0.5 equiv. $GlyNO_3$ (Table 1, entry 6).

Further increase in amount of catalyst could not exert any positive influence on the yields of **4a** (Table 1, entry 7). Gratifyingly, the yield was improved to 87% with the increased in volume of EtOH up to 1mL (Table 1, entry 8). Further increase in volume of EtOH fails to enhance the yields of **4a**. Thereafter effects of different solvents and co-solvent (Table 1, entries 9-13), catalysts (Table 1, entries 14-17) were studied, but inferior yields were obtained compared to table 1, entry 8.

The control experiments in the absence of solvent and catalyst (Table 1, entries 18-19) afforded **4a** in low yield demonstrated the crucial role of solvent and catalyst. The reaction under conventional condition by refluxing the reaction mixture for 5h fails to improved the yield of **4a** (Table 1, entry 20). Surprisingly, a experiment with glycine (Table 1, entry 21) and HNO_3 (Table 1, entry 22) resulted drastic decrease in yield of **4a**, which emphasized the importance of $GlyNO_3$ IL in catalysis.

With the optimized reaction conditions in hand for synthesis of symmetrica1 1,4-DHPs (Table 1, entry 8), the generality and scope of this one pot three component Hantzsch reaction was then explored. For this, a wide range of substituted benzaldehyde including heterocyclic moieties (**1a-i**), methylacetoacetate (**2a**), and ammonium acetate (**3a**) was irradiated under focused MW (P = 100W, 90°C) for 20 min. which produced the corresponding 1,4-DHPs **4a** in good to excellent yields (Table 1, entries **4a-i**). During the substrate scope study, it has been observed that the catalyst exhibited remarkable activity for heterocyclic substituted benzaldehydes particularly for thiophene containing moiety (Table 1, entries **4d-i**). Therefore, we further extended our substrate scope by utilizing different dicarbonyl compound in congestion with thiophene-2-carboxaldehyde and ammonium carbonate, which afforded the desired compound in good yield (Table 1, entries **4j-l**).

After the successful synthesis of three components symmetrical 1,4-DHPs, our goal was to synthesize four component unsymmetrical 1,4-DHPs (also known as polyhydroquinoline) which enjoy the status of being privileged motifs in terms of their diverse biological profiles compared to symmetrical 1,4-DHPs.[21]

Recently, these motifs have been recognized as lead molecules in antidiabetic drug discovery.[22] There are plethora of reagents and catalyst reported in the literature for the synthesis of unsymmetrical 1,4-DHPs[23] however some of these suffer from limitations like usage of precious class of metal catalyst, longer reaction time (6-11h), two step synthesis, cumbersome product isolation, selectivity and recyclability issues

Recently Rajesh at el.[23x] have also reported hydromagnesite as a heterogeneous solid based catalyst for the synthesis of 1,4-DHPs. Despite promising results, this methodology has limited substrate scope due to non involvement of any heterocyclic benzaldehydes.

To the best of our knowledge, there are only few reports available in literature where synthesis of unsymmetrical and symmetrical 1,4-DHPs carried out under identical reaction condition which suffer from drawbacks like longer reaction time, poor substrate scope and tedious synthesis of catalyst.[24] Keeping in mind the sheer importance of unsymmetrical 1,4-DHPs, we were also intrigued to investigate whether our developed catalytic system could efficiently result in the synthesis of unsymmetrical 1,4-DHPs by overcoming the existing lacunae of reported protocols.[23]

Pleasingly, the mixture of 5-bromothiophene-2- carboxaldehyde (**1a**), methyl acetoacetate (**2a**), 5, 5-dimethyl-1, 3-cyclohexanedione (**2b**) and ammonium acetate (**3a**) successfully condensed in one pot under similar reaction condition[25] providing **5a** in 83 % yield. Thereafter, different substituted aromatic or heterocyclic benzaldehydes (**1a-i**) were condensed with **2a**, **2b** and **3a** to afford unsymmetrical 1,4-DHPs (Table 3, **5b–i**) in excellent yields.

From an economical point of view, the recyclability of $GlyNO_3$ was also taken into account. The IL retained high reactivity up to six cycles (Scheme 2).

Mechanistic Study

Mechanistically, it was presumed that there are four plausible pathways[26] for the synthesis of symmetrical 1,4-DHPs (Figure 2) These are i) enamine ii) diketone, iii) dienamine and iv) imine pathways (Figure 2 and see the supporting information).

In order to proven the feasibility of exact pathway among four competing mechanism involved in the synthesis of 1,4- dihydropyridines, preferably used Q-TOF electrospray ionization mass spectrometry (ESI-MS) technique for studying reaction intermediate because of its ability to "fish" ionic or ionized intermediates directly from reaction solutions into the gas phase, with high speed and sensitivity.[27] Moreover, its tandem version ESI-MS/MS is rapidly becoming the technique of choice for solution-phase mechanistic studies in chemistry.[28]

Therefore, we performed Q-TOF ESI (+ve) MS studies on aliquots of samples withdrawn after 10 min from $GlyNO_3$ catalyzed reaction of **1g**, **2a** and **3a** (Scheme 3)[29] at capillary voltage (3100 V), cone voltage (25 V), dissolution temp. (200°C) and source temp. (80°C).

The total ion chromatogram (TIC) revealed the presence of ions at m/z 308.26 (m_1), 325.29 (m_2), 344.31 (m_3), 327.31 (m_4), 224.15 (m_5),[30] 211.16(m_6), 179.09 (m_7), and 117.13 (m_8) corresponding to $[4g + H]^+$, $[4g + NH_3 + H]^+$, $[11a + H]^+$, $[10a + H]^+$, $[19a + H]^+$, $[7a + H]^+$, $[7a - OMe]^+$ and $[2a + H]^+$ respectively. The presence of characteristic peaks $m_3 = [11a + H]^+$, $m_4 = [10a + H]^+$ and $m_6 = [7a + H]^+$ in figure 3 revealed the possibility of diketone pathway (Figure 2) and absence of key intermediate **6a** (enamine) **13a (**dienamine) and **17a** (imine) (Scheme 4) in the TIC (Figure 3) ruled out the possibility of enamine, dienamine and imine pathways.

For further structure elucidation in context of diketone pathway and product formation, tandem MS/MS experiments were carried out for few selected ions observed in TIC (Figure 3) at *m/z* 308.17 = m_1, 325.29 = m_2, 344.31 = m_3 and 327.31 = m_4. The MS/MS or MS^2 spectra derived from the ion of *m/z* 308.17 = m_1 showed peak at *m/z*

276.14 and 224.15 assigned as $[4g - OCH_3]^+$ and $[4g - C_4H_3S + H]^+$ (Figure 4), confirmed the product formation.

In case of m_2, the MS^2 spectra (Figure 5) exhibited the parent ion $m_2 = [4g + NH_3 + H]^+$ and daughter ion with *m/z* 308.17, 224.28 corresponded to $[4g - NH_3 + H]^+$ and $[4g - C_4H_3S + H]^+$ respectively, confirmed the ammoniated adduct of desired product i.e. 4g (Scheme 3).

To further confirm the presence of intermediate (m_3) in context of diketone pathway, the MS^2 experiment was carried out of $m_3 = [11a + H]^+$ ion (Figure 6). The MS/MS spectra revealed the presence of ion with *m/z* 327.34, 309.31, 295.29 and 211.21 which are diagnose as $[11a - NH_2]^+$, $[11a - NH_2 - H_2O]^+$, $[11a - NH_2 - H_2O - CH_3]^+$ and $[11a - NH_2 - H_2O - CH_3 - C_4H_4O_2]^+$ respectively, confirmed the fragments of m_3 and their involvement in diketone pathway.

Most importantly, the key intermediate involved in diketone pathway $m_4 = [10a + H]^+$ was also ascertain by MS^2 experiment. The MS^2 spectra (Figure 7) exhibited the parent ion $m_4 = [10a + H]^+$ and daughter ions with *m/z* 295.18, 243.21 and 211.13 correspond to $[10a - OCH_3]^+$, $[10a - C_4H_3S]^+$ and $[10a - C_5H_7O_3]^+$ respectively, confirmed the fragments of ion m_4 and their involvement in diketone pathway.

On the basis of Q-TOF, ESI -MS/MS studies, it comes to know that $GlyNO_3$ IL catalyzed three component Hantzsch reaction follows diketone pathway among four competing mechanistic pathways (Figure 2).

On the other hand the possibility of enamines pathway cannot be ignored because of observation of peak $m_6 = [7a+H]^+$ (Figure 3) during the analysis of aliquots of samples withdrawn after 10 min, which is also one of the intermediate of enamine pathway

(Figure 2). Therefore two control experiments or experiments to validate our perception regarding diketone pathway were carried out in sequential one-pot two step ways (Scheme 5 and 6). The results revealed that 61% of product yield (Scheme 5) was obtained *via* diketone pathway compared to 22% yield *via* enamine pathway (Scheme 6).

At last on the basis of control experiments and Q-TOF, ESI-MS/MS study, we can say that the most predominant pathway for the synthesis of symmetrical 1,4-DHPs is diketone rather then enamine, dienamine and imine. This is the first report which proved the participation of diketone pathway in synthesis of symmetrical 1,4-DHPs using Q-TOF, ESI-MS/MS study.

Conclusion

In summary, an operationally simple and highly efficient one-pot multicomponent reaction for the synthesis of symmetrical and unsymmetrical 1,4 DHPs have been developed which have sheer importance in synthetic and medicinal chemistry. The methodology is practical, recyclable and economical besides being flexible since it also allows heterocyclic benzaldehydes to participate in synthesis of both symmetrical and unsymmetrical 1,4 DHPs under identical reaction condition. In addition the mechanistic study using Q-TOF, ESI-MS/MS revealed that the synthesis of symmetrical 1,4 DHPs predominate follow diketone pathway among four competing reaction pathways. At last, we anticipate that this catalytic system will find applications in academia and industry. The Q-TOF, ESI-MS/MS based study may also helpful to unveil the mechanistic study of many other reactions. The mechanistic study related to unsymmetrical 1,4 DHPs is currently under investigation.

Experimental Section

General procedure for the synthesis of symmetrical 1,4-dihydropyridins from substituted benzaldehydes (Table 2, 4a-l): Substituted benzaldehyde (0.5 mmol), dicarbonyl compound (2 equiv.), ammonium carbonate (2 equiv.) and glycine nitrate (0.5 equiv.) were taken in 1 mL ethanol in a round bottom flask and the reaction mixture was subjected to microwave irradiation using CEM monomode microwave at P = 100 W, 90°C for 20 min. After completion of reaction, the crude reaction mixture was filtered to obtain $GlyNO_3$. The filtrate was vacuum evaporated and then recrystallization from water–methanol which gave an isolated yield of 4a–l in the range of 52-93 % yields. Products were identified and confirmed by their ^1H, ^{13}C NMR spectra and HRMS values.

General procedure for the synthesis of unsymmetrical 1,4-dihydropyridins from substituted benzaldehydes (Table 3, 5a-i): Substituted benzaldehyde (0.5 mmol), methyl acetoacetate (1 equiv.), 5, 5-dimethyl-1, 3-cyclohexanedione (1 equiv.), ammonium carbonate (2 equiv.) and glycine nitrate (0.5 equiv.) were taken in 1 mL ethanol in a round bottom flask and the reaction mixture was subjected to microwave irradiation using CEM monomode microwave at P = 100 W, 90°C for 20 min. After completion of reaction, the crude reaction mixture was filtered to obtain $GlyNO_3$. The filtrate was vacuum evaporated and then recrystallization from water–methanol which gave an isolated yield of 5a–i in the range of 52-93 % yields. Products were identified and confirmed by their ^1H, ^{13}C NMR spectra and HRMS values.

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Electronic Supplementary Information (ESI) available:

^{1}H and ^{13}C NMR data and spectra of symmetrical and unsymmetrical 1,4-DHPs

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21 One of the main advantage of unsymmetrical 1,4-DHPs is utilization of two different dicarbonyl compounds which result increased in diversified derivative of 1,4 DHPs compared to symmetrical 1,4-DHPs where two similar

dicarbonyl are utilized. Overall the possibility of discovering new biological entities increased.

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25 The synthesis of four component unsymmetrical 1,4 DHPs carried out under similar reaction condition as adopted for three components synthesis of symmetrical 1,4 DHPs (Table 1, entry 8). The difference is only in the utilization of methylacetoacetate and dimedone (1:1 equiv) instead of 2 equiv of methylacetoacetate.

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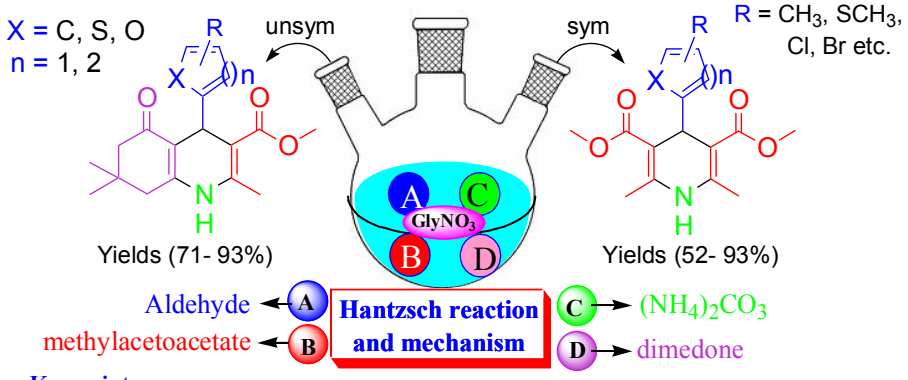
29 Thiophene-2-carboxaldehyde was taken as model substrate for mechanistic study because of following region i) gave maximum yield of product, ii) their better solubility in EtOH and iii) ease in Q-TOF, ESI-MS analysis.

30 The peak $[19a + H]^+ = m_5$ corresponds to fragmented part of peak 4**g** i.e. $[4g-C_4H_3S]^+$ which is further stabilized to 3,5-dimethyl 2,6-dimethylpyridine-3,5-dicarboxylate $[19a + H]^+$ (see supporting information).

Graphical Abstract



Key points:-

i) First report proved the involvement of diketone pathway in 1,4 DHPs synthesis.
ii) Characterization of intermediates using Q-TOF, ESI-MS/MS.
iii) Catalyst compatibility to both symmetrical and unsymmetrical 1,4 DHPs under indetical reaction condition.

Glycine nitrate ionic liquid ($GlyNO_3$) has been explored for the synthesis of symmetrical and unsymmetrical 1,4-DHPs in good to excellent yield under identical reaction condition. Moreover, Q-TOF, ESI-MS/MS based mechanistic study revealed the diketone as predominate pathway for the synthesis of symmetrical1,4-DHPs.

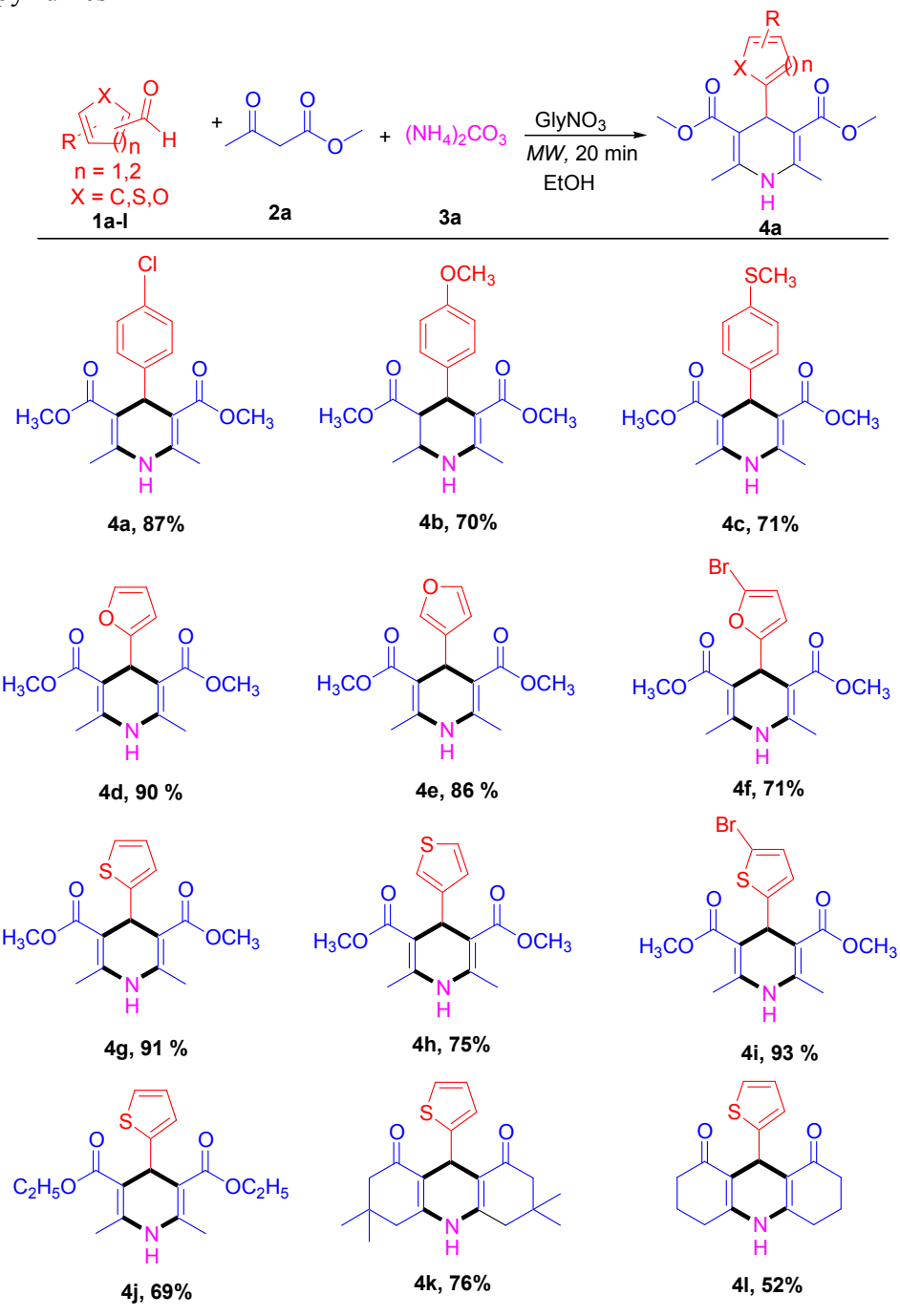
Table 1. Optimization study for the synthesis of 1,4-dihydropyridins [a]

1a 2a 3a 4a

S. No.	Ammonium salt	Solvent	Ionic Liquid	Yield[b] (%)
1	NH_4OAc	EtOH	$GlyNO_3$	45
2	NH_4BF_4	EtOH	$GlyNO_3$	30
3	NH_4Cl	EtOH	$GlyNO_3$	20
4	NH_4HCO_3	EtOH	$GlyNO_3$	70
5	$(NH_4)_2CO_3$	EtOH	$GlyNO_3$	73
6[c]	$(NH_4)_2CO_3$	EtOH	$GlyNO_3$	82
7[d]	$(NH_4)_2CO_3$	EtOH	$GlyNO_3$	80
8[e]	**$(NH_4)_2CO_3$**	**EtOH**	**$GlyNO_3$**	**87**
9	$(NH_4)_2CO_3$	H_2O	$GlyNO_3$	19
10	$(NH_4)_2CO_3$	DCM	$GlyNO_3$	34
11	$(NH_4)_2CO_3$	DMSO	$GlyNO_3$	20
12	$(NH_4)_2CO_3$	PEG 400	$GlyNO_3$	30
13	$(NH_4)_2CO_3$	EtOH:H_2O	$GlyNO_3$	40
14	$(NH_4)_2CO_3$	EtOH	$GlySO_4$	66
15	$(NH_4)_2CO_3$	EtOH	GlyTFA	40
16	$(NH_4)_2CO_3$	EtOH	GlyOAc	59
17	$(NH_4)_2CO_3$	EtOH	GlyCl	57
18	$(NH_4)_2CO_3$	-	$GlyNO_3$	29
19	$(NH_4)_2CO_3$	EtOH	-	26
20[f]	$(NH_4)_2CO_3$	EtOH	$GlyNO_3$	55
21	$(NH_4)_2CO_3$	EtOH	Glycine	65
22	$(NH_4)_2CO_3$	EtOH	HNO_3	20

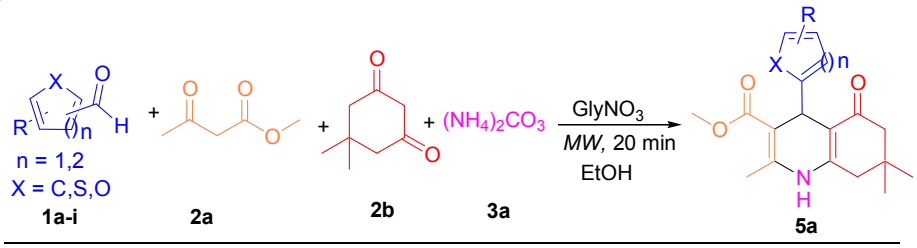
[a] Experimental conditions: 0.5 mmol of 4-chlorobenzaldehyde, methylacetoacetate (2 equiv), $(NH_4)_2CO_3$ (2 equiv), $GlyNO_3$ (0.5 equiv) in 1 mL of EtOH under MW at P = 100 W, 90°C for 20 min, [b] Isolated yield (after recrystallization in water and methanol). [c] $GlyNO_3$ (0.5 equiv), [d] $GlyNO_3$ (0.6 equiv) [e] EtOH (1mL), [f] reflux for 5h. For entries 1-7 EtOH = 0.5 mL, entries 8-22 solvent = 1 mL.

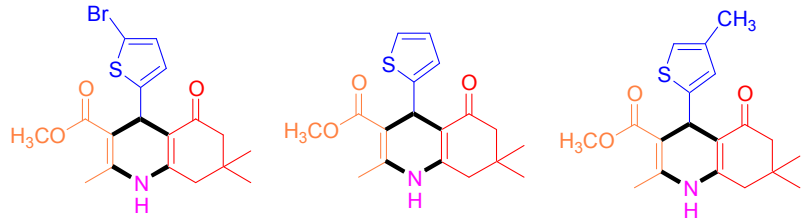
Table 2. Substrate scope of *GlyNO$_3$* catalyzed synthesis of symmetrical 1,4-dihydropyridines [a]

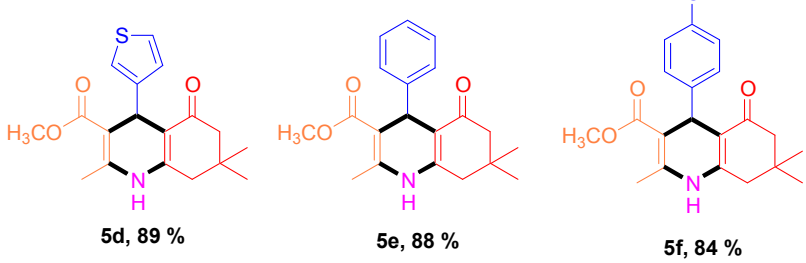


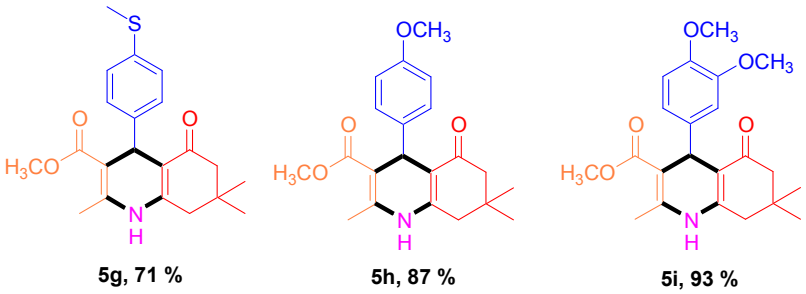
[a] Experimental conditions: 0.5 mmol of substituted benzaldehyde, methylacetoacetate (2 equiv), $(NH_4)_2CO_3$ (2 equiv), $GlyNO_3$ (0.5 equiv) in 1 mL of EtOH under MW at P = 100 W, 90°C for 20 min, [b] Isolated yield (after recrystallization in water & methanol).

Table 3. Substrate scope of *GlyNO$_3$* catalyzed synthesis of unsymmetrical 1,4-dihydropyridines [a]

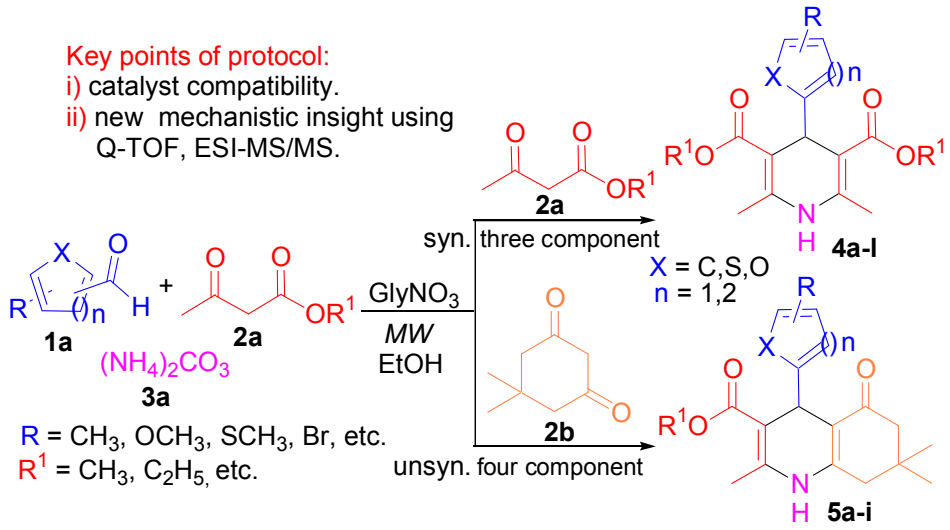




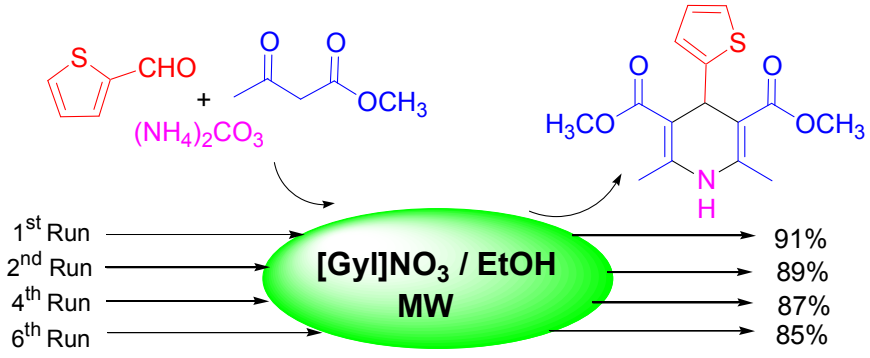




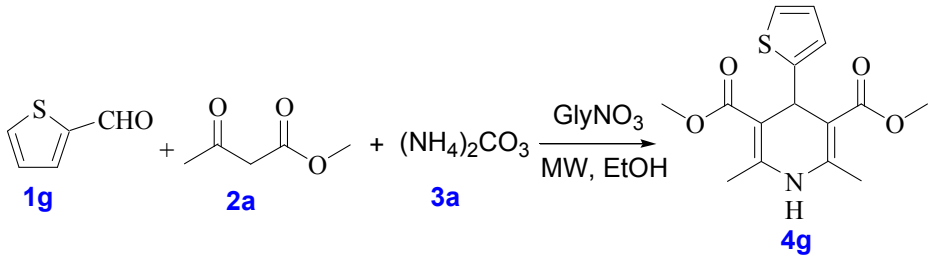
[a] Experimental conditions: 0.5 mmol of substituted benzaldehyde, **2a** (1 equiv), **3a** (1 equiv), $(NH_4)_2CO_3$ (2 equiv), $GlyNO_3$ (0.5 equiv) in 1mL of EtOH under MW at P = 100 W, 90°C, for 20 min. [b] Isolated yield (after recrystallization in water & methanol).



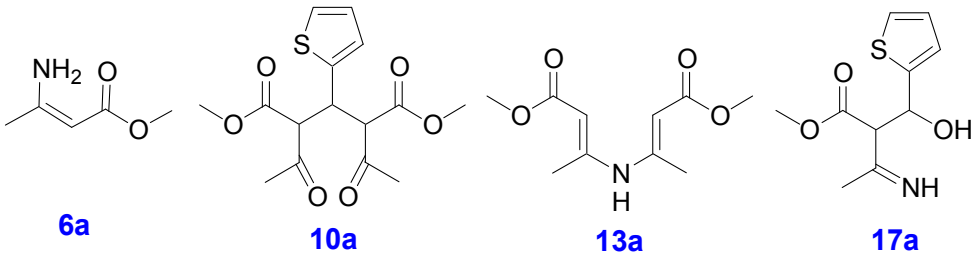
Scheme 1. Synthesis of symmetrical and unsymmetrical 1,4-dihydropyridines in $GlyNO_3$ ionic liquid via three and four component reaction.



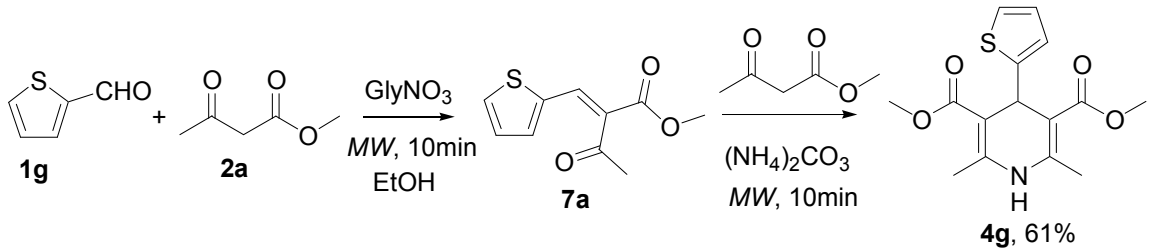
Scheme 2. Recyclability study of catalyst for the synthesis of 1,4-dihydropyridines



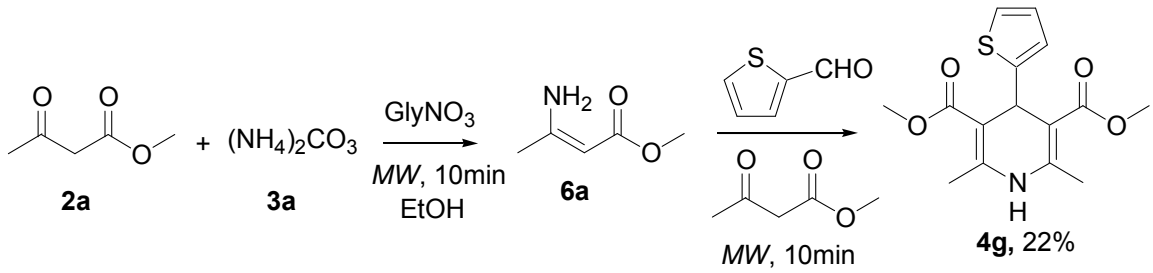
Scheme 3. The one-pot three component Hantzsch reaction



Scheme 4. Key intermediates of four plausible pathways



Scheme 5. Sequential one-pot two step synthesis of 1,4-DHP via diketone pathway.



Scheme 6. Sequential one-pot two step synthesis of 1,4-DHP via enamine pathway.

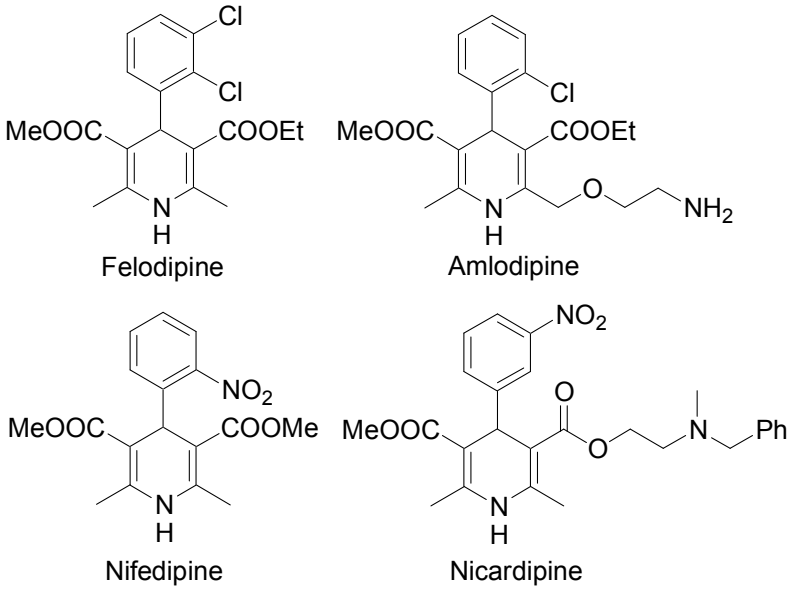


Figure 1. 1, 4 DHPs used as clinical drugs.

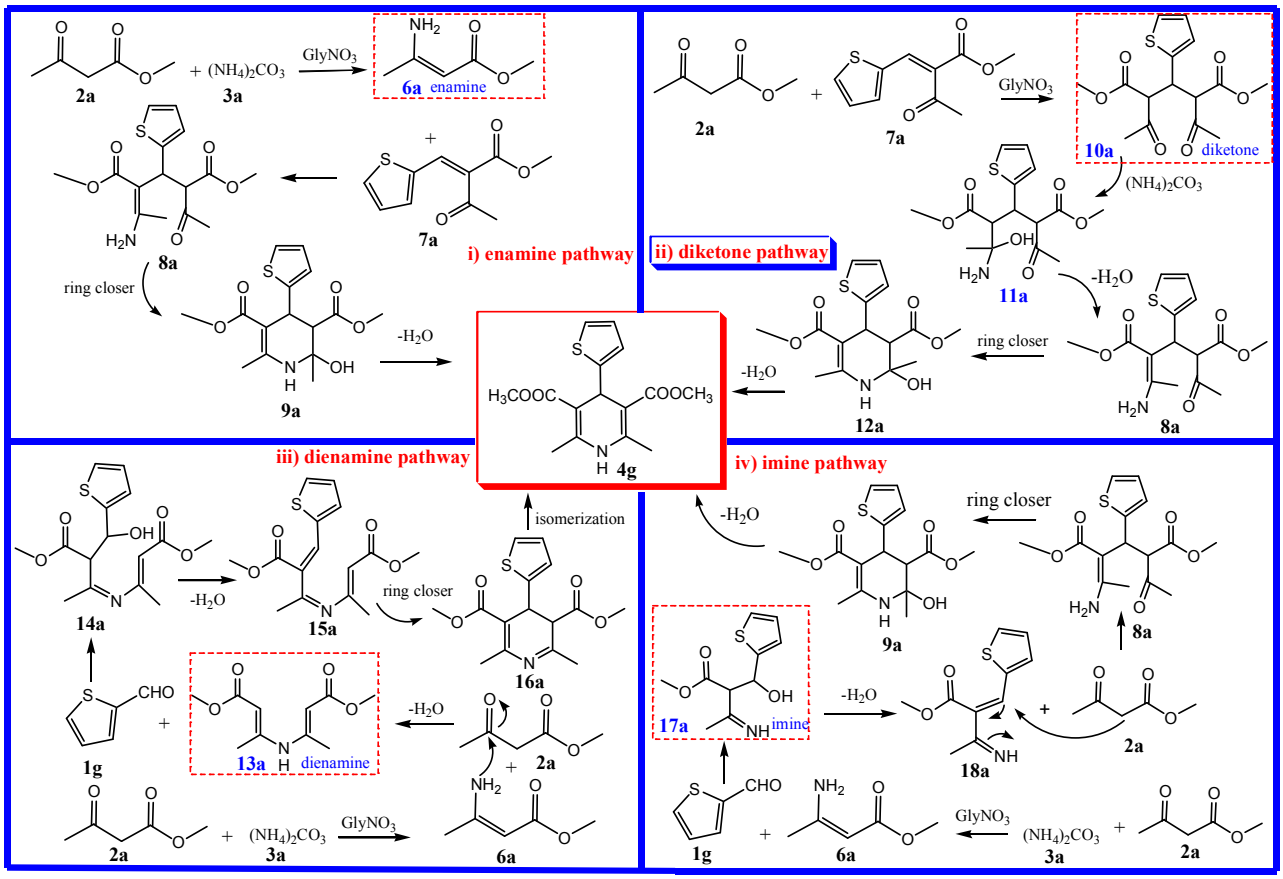


Figure 2. Different plausible pathways for the synthesis of 1, 4-dihydropyridines.

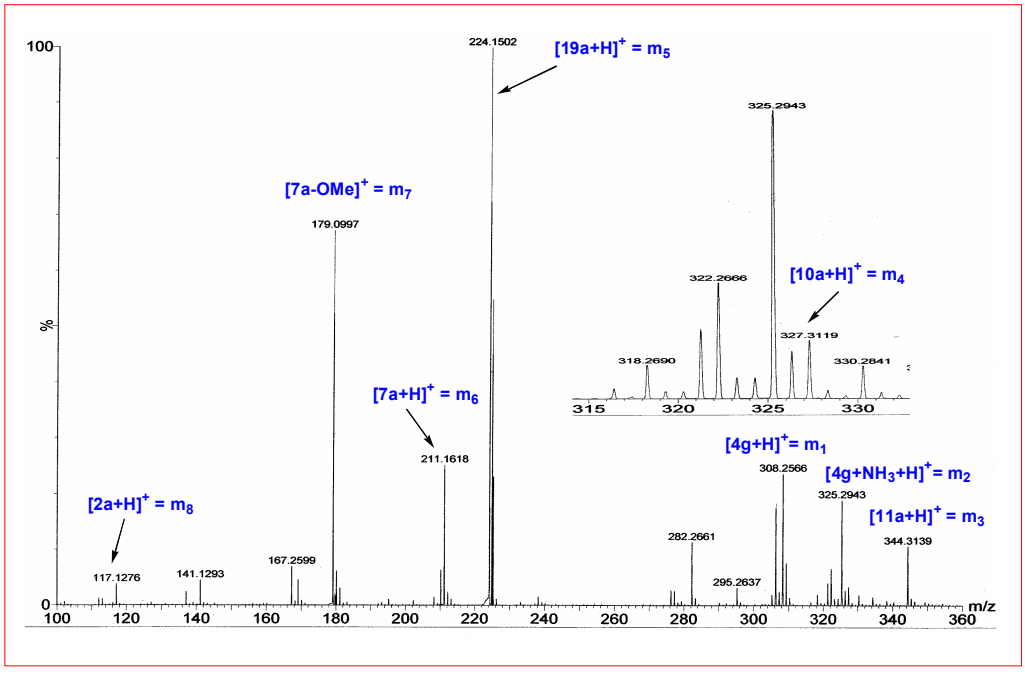


Figure 3. TIC of Q-TOF, ESI (+) MS of sample withdraw after 10 min for three-component Hantzsch reaction of **1g**, **2a** and **3a** catalyzed by $GlyNO_3$.

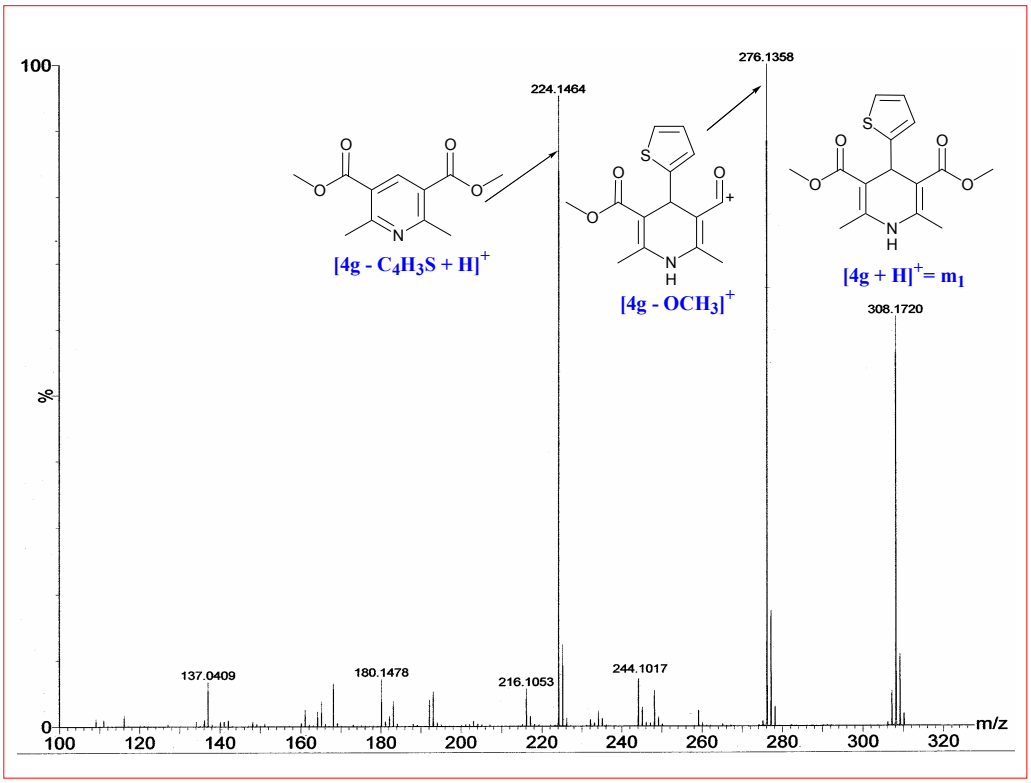


Figure 4. On line Q-TOF, ESI (+) MS/MS of peak m_1 =308.17 as shown in figure 2.

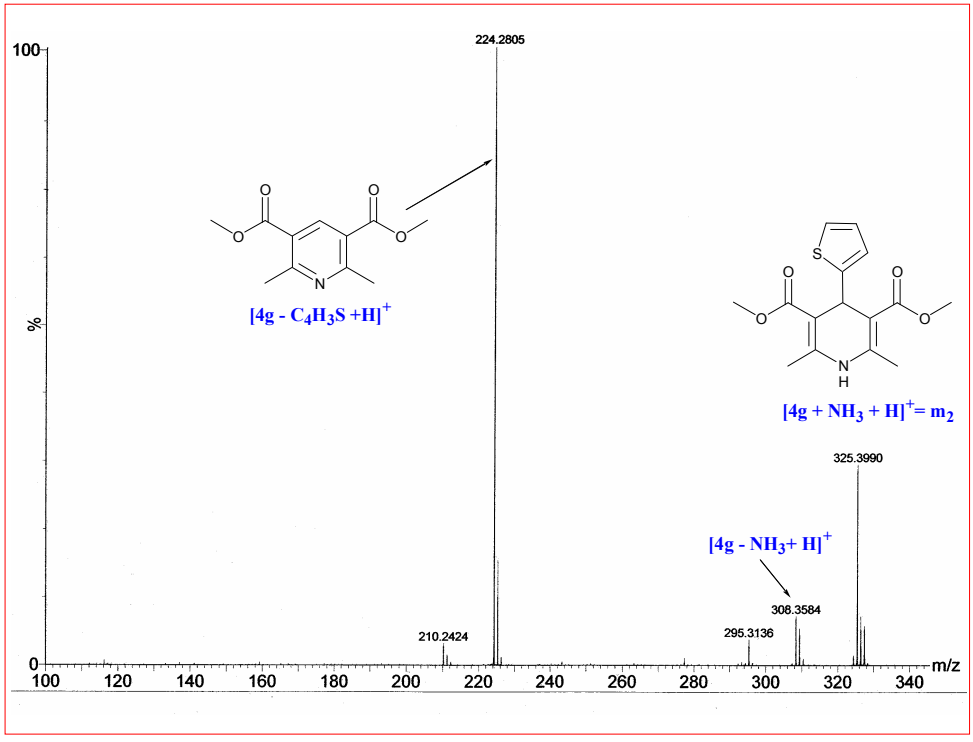


Figure 5. On line Q-TOF, ESI (+) MS/MS of peak m_2 =325.29 as shown in figure 2.

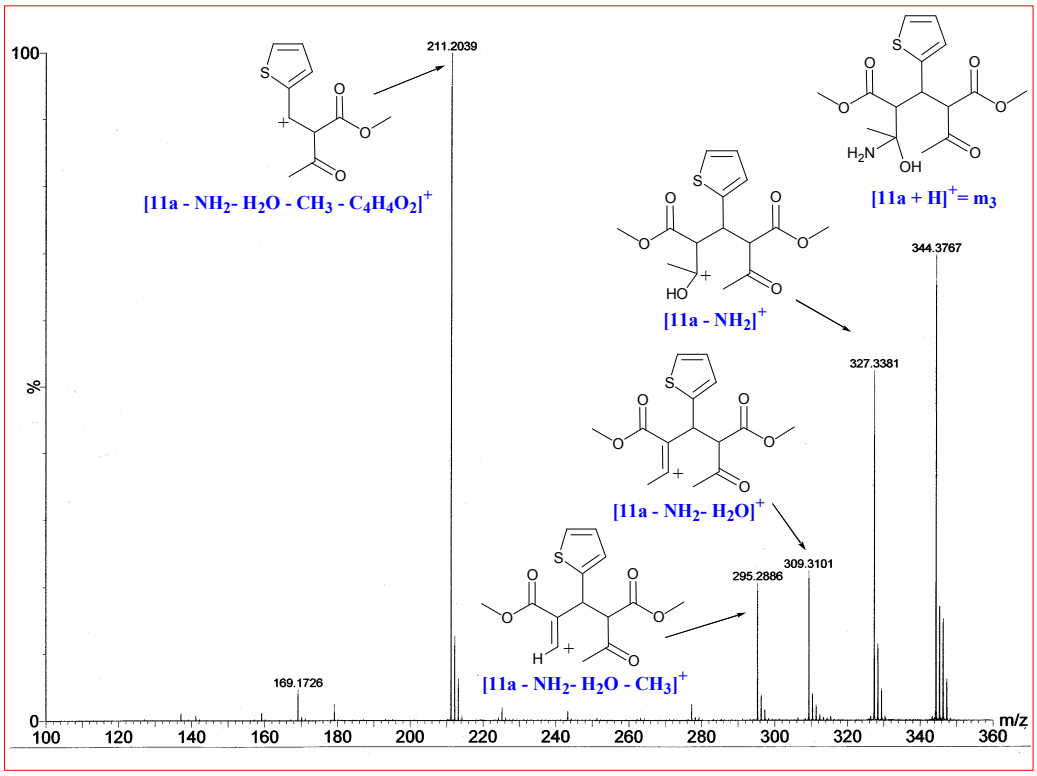


Figure 6. On line Q-TOF, ESI (+) MS/MS of peak m_3 = 344.31 as shown in figure 2.

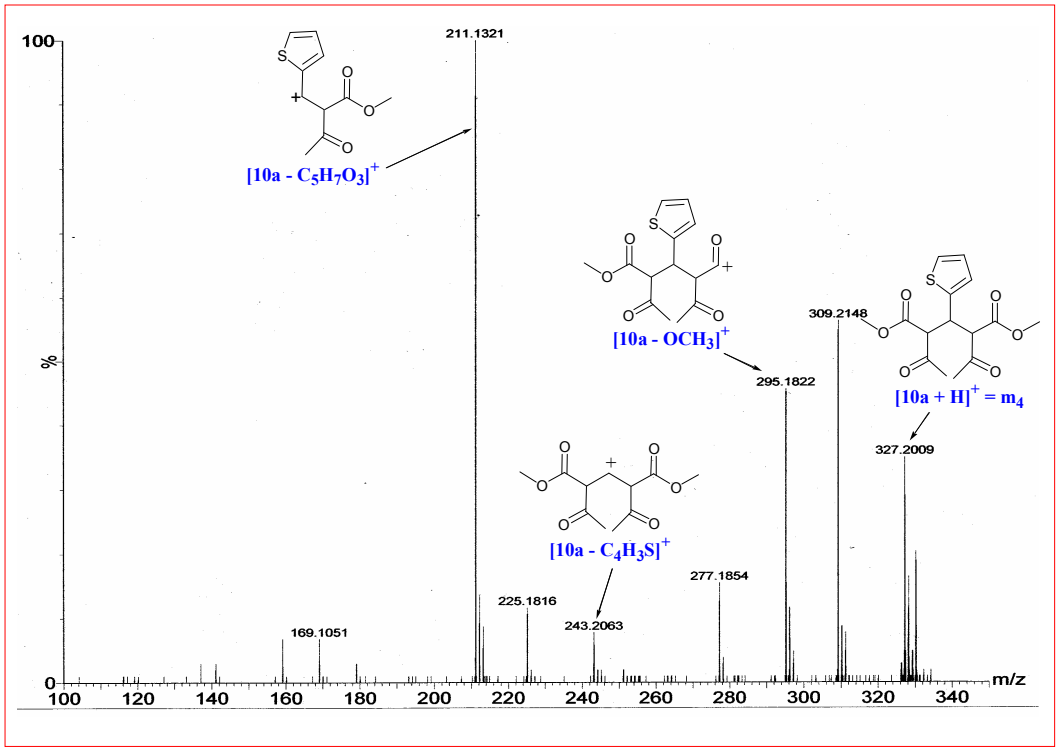


Figure 7. On line Q-TOF, ESI (+) MS/MS of peak m_4 =327.31 as shown in figure 2.