**Reviewer’s Comments**

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**Green, rapid, simple, and an efficient one-pot multicomponent protocol for Synthesis of novel dihydropyrano[2,3-*c*]pyrazol-6-amines in Aqueous Medium**

**Abstract:** In the present study, a series of new dihydropyrano[2,3-*c*]pyrazol-6-amines are synthesized by a one-pot four component reaction of hydrazine hydrate, araldehydes, ethyl acetoacetate, and phenylacetonitrile in presence of Sodium hydrogen sulphate as a catalyst in good yields. All the synthesized compounds were characterized by FT-IR, 1H-NMR and 13C-NMR spectroscopic techniques.



**Key words:**Pyrano[2,3-*c*]pyrazol-6-amines, Hydrazine hydrate, fluorophenylacetonitrile, Araldehydes, Ethyl acetoacetate, Water.

**Introduction:**

In the last two decades, the growing environmental concern in chemistry has turned spotlight on the multicomponent reactions as new trends in organic chemistry.1 Multicomponent reactions (MCRs) are very important for the construction of many heterocyclic compounds,2 using this strategy many biologically active substances and natural products have been synthesized.3 The synthesis of nitrogen heterocycles is of great interest because they constitute an important class of natural and synthetic products, many of which exhibit useful biological activity and find application in pharmaceutical preparations.4‒7

The need of development the concept of green chemistry to help safeguard human life started after the first chemical revolution, which changed modern life with excellent amenities and services, but also created the serious problem of environmental pollution. Thus, The core principle of this concept is to protect the environment, not by cleaning it up, but by discovery of new chemistry and pharmaceutical industries to concern the effect on human life when new chemicals are introduced into our society.8,9 Water appears to be a better option compared to others green solvents because of its abundant, non-toxic, non-corrosive, and non-inflammable nature. In addition, water can be contained because of its relatively high vapour pressure as compared to organic solvents, making it a green and sustainable alternative.10, 11 Water offers several benefits such as control over exothermic reactions, salting out and salting in, as well as variation of pH.12

Recently, organic reactions in water without use of harmful organic solvents have drawn much more attention, because water is cheap, safe and environmentally benign solvent.13, 14

Dihydropyrano[2,3-*c*]pyrazole scaffold represents an interesting template in medicinal chemistry, and play an essential role as biological active molecules.15 Many of the pyrano[2,3-*c*]pyrazoles are known for their antimicrobial,16insecticidal,17 anti-inflammatory,18 anticancer19 and molluscicidal activities.20 During the last few years, synthesis of dihydropyrano[2,3-*c*]pyrazoles has received great interest.21Pyranopyrazoles are also used as pharmaceutical ingredients and biodegradable agrochemicals.22

Dihydropyrano[2,3-*c*]pyrazole derivatives possess useful biological and pharmacological properties 23. Only a few reports are available on the synthesis of dihydropyrano[2,3-*c*]pyrazol-6-amines 24, 25. A Four-Component Domino Combinatorial Synthesis in presence of DIPEA is reported by Kanchithalaivan et al. 26  In continuation of our efforts to find and develop a new methods for the synthesis of biologically active heterocyclic compounds using inexpensive, readily available, and environment friendly catalysts,27‒32 herein, we wish to report a mild, efficient method for the synthesis of some novel and simple one-pot four-component synthesis of dihydropyrano [2, 3-*c*] pyrazol-6-amines using green chemistry principles. In the present study, a series of novel dihydropyrano[2,3-*c*]pyrazol-6-amines are synthesized by a one-pot four-component reaction of hydrazine hydrate, araldehydes, ethyl acetoacetate, and 4-fluoro phenylacetonitrile in water using sodium hydrogen sulphate as a catalyst in good yields as shown in the following **scheme**. 

 **Scheme 1**

**Methodology:**

|  |
| --- |
|  |

**Results and Discussion**

 Initially, to identify the optimum reaction conditions, a representative reaction between 3-methoxy, 4-hydroxy benzaldehyde (vanillin), ethylacetoacetate, 4-fluoro phenylacetonitrile and hydrazine hydrate (1 m mol each) was considered. To begin with, the reaction was carried out in the absence of any catalyst in ethanol, at room temperature, ultrasonic and microwave irradiation which didnot afford desired product. This test reaction was then investigated using different catalysts (**Table 1**) in refluxing ethanol which gave different product yields. In the presence of NaHSO4, the reaction afforded better yield of % after when compared to other catalysts (**Table 1, entry 4**). After selection of catalyst for the reaction, investigation for an appropriate solvent was performed. The representative reaction was carried out in solvents such as ethanol, water, acetonitrile and water: ethanol (1: 1) mixture (**Table 1, entries 5-7**). As seen from the data in Table 1, Water-ethanol(1:1) was found to be the ideal solvent for this reaction which afforded maximum yield of the product.

The reaction template, with NaHSO4 as catalyst and Water-ethanol(1:1) as a solvent system, was applied to a different substituted araldehydes to prepare a library of compounds. The template works well for all the araldehydes to give corresponding products (**Table 3**) The template failed for aliphatic aldehydes (Table 3, entries 11-12) and the ,-unsaturated aldehydes such as cinnamaldehyde (Table 3, entry 13) did not give any product even after the reaction was carried out for longer duration.

**Table 1**: Selection of suitable catalyst and solvent for the synthesis of (**5d)a.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Entry | Catalyst (10 mol%)  | Solvent | Time(min) | Yielda(%) |
| 1 | Imidazole | Ethanol | 120 | 45 |
| 2 | NaOH | Ethanol | 140 | 50 |
| 3 | Ba(OH)2 | Ethanol | 130 | 45 |
| 4 | NaHSO4 | Ethanol | 120 | 55 |
| 5 | NaHSO4 |  Water | 120 | 50 |
| 6 | NaHSO4 | Water-ethanol(1:1) | 65 | 87 |
| 7 | NaHSO4 | Acetonitrile | 120 | 40 |

a isolated yields

To select a best catalyst and solvent, we carried out the reaction between 3-methoxy, 4-hydroxy benzaldehyde (vanillin), ethylacetoacetate, 4-fluoro phenylacetonitrile and hydrazine hydrate (1 m mol each) was considered in the presence of 10 mol% of different basic catalysts such as Ba(OH)2, imidazole, NaOH and NaHSO4 and ethanol as solvent. We found that, imidazoledid not afford the product in good yield and reaction time was very long, similar results were obtained with Ba(OH)2. The yield of the desired product improved to a very less extent when NaOH was used as a basic catalyst and the product was a sticky mass. When the same reaction was carried out in the presence of NaHSO4, and different solvent such as ethanol, water, water : ethanol in the ratio 1 : 1 and acetonitrile, we found the product of the desired product improved to a very less extent when ethanol solvent was used but the time still little long then it was not improved when pure water used as solvent, whilst the product yield obtained in very high yield 87% within 65 mins, when ethanol-water in the ratio 1 : 1 . In presence of acetonitrile has been used the very poor yield of product has been obtained in long duration time of the reaction. The results of this study are presented in (**Table 1**).

We have also varied the amount of NaHSO4 from 5, 7, 10 to 12 mol% and the results revealed that, 10 mol% gives excellent yield of the product in a short duration as shown in **Table 2**.

**Table 2** Effect of the amount of NaHSO2 on the synthesis of (**5e**)a.

|  |  |  |
| --- | --- | --- |
| Entry | NaHSO4(mol %) | Yield(%) |
| 1 | 5 | 50 |
| 2 | 7 | 65 |
| 3 | 10 | 89 |
| 4 | 12 | 89 |

aReactions are performed on a 1 mmol scale of the reactants.

After optimizing the conditions, the generality of this method was examined by the reaction of different substituted aldehydes with ethyl acetoacetate, meldrums acid and hydrazine hydrate in the presence of 10 mol% NaHSO4 in ethanol-water (1:1) under reflux; and the results of this study are shown in the table 3.

**Table 3: Synthesis of novel dihydropyrano [2,3-*c*]pyrazol-6-amines from various aldehydes,hydrazine hydrate, ethyl acetoacetate, and 4-chloro phenylacetonitrile and NaHSO4 in ethanol-water (1:1) solvent .**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Entry** | **Aldehyde (1)** | **Product** | **Time (min)** | **Yielda (%)** | **MP(C)** |
| **found** |
| 1. | 3-NO2C6H4CHO | **5a** | 120 | 85 | 185−187 |
| 2. | 4-HOC6H4CHO | **5b** | 120 | 82 | 236−239 |
| 3. | 4-ClC6H4CHO | **5c** | 120 | 80 | 199−200 |
| 4. | 3-MeO,4-HOC6H3CHO | **5d** | 80 | 87 | 260−263 |
| 5. | 3-MeOC6H4CHO  | **5e** | 80 | 89 | 195−197 |
| 6. | 3,4,5-(MeO)3C6H2CHO  | **5f** | 90 | 80 | 180−184 |
| 7. | 4-NO2C6H4CHO | **5g** | 90 | 82 | 271−273 |
| 8. | 2,4-Cl2C6H3CHO | **5h** | 120 | 80 | 205−207 |
| 9. | 3,4-(MeO)2C6H3CHO  | **5i** | 120 | 80 | 175−178 |
| 10. | 2-HOC6H4CHO  | **5j** | 90 | 82 | 200−204 |
| 11. | HCHO | **5k** | 240 | ND | - |
| 12. | CH3CHO | **5l** | 240 | ND | - |
| 13. | C6H5CH=CHCHO |  **5m** | 240 | ND | - |

aisolated yields. ND: not detected

**Experimental:**

All chemicals used were commercial and without further purification. The progress of the reaction was monitored on TLC (eluent;2 : 8 ethyl acetate–petroleum ether). The melting points were measured in open capillary tubes and are uncorrected. Melting points were determined using Raaga, melting point apparatus, Indian make. FT-IR spectra were recorded on SHIMADZU FT-IR-8400s spectrophotometer. 1H NMR and 13C NMR spectra of the products were recorded on Bruker AMX 400 MHz and 100 MHz respectively in DMSO-*d6*as solvent and TMS as internal standard.

**General procedure for the preparation of dihydropyrano[2,3-*c*]pyrazol-6-amines :**

The aromatic aldehyde (1 m mol), malononitrile (1 m mol), ethyl acetoacetate (1 m mol) hydrazine hydrate (1 m mol) and NaHSO4 (0.5 m mol) were taken in ethanol-water (1:1) (~5 ml) and heated at 80 C for ----minutes. The progress of the reaction was monitored using Silica gel-G TLC plates with a mixture of petroleum ether (60−80°C) and ethyl acetate (20:80) as eluent. After the completion of the reaction, the mixture was cooled to room temperature and the precipitated solid was filtered, washed with water to get nearly pure product.

***SPECTRAL DATA***

***5- (4-flourophenyl)-3-methyl-4-(3-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazol-6-amine***

 **(5a)**:

 Yellow crystalline solid (85 %, 0.590 g); mp 185-187ºC: IR (KBr) ν:3387 (br), 3065 (ws) 2968 (s), 1694 (vs), 1622 (s), 1375 (s), 1236 (s), 1173 (vs), 1033 (s) cm-1;

1HNMR (400 MHz, DMSO-*d6*): δ 2.48 (2H, NH2), 3.29 (s, 3H, Me), 4.89 (s,1H, CH), 6.85 – 6.38 (d,d, *J* = 8.4 Hz, 4H, Ph), 7.84 – 8.87 (m, 4H, Ph), 10.74 (s, 1H, NH);

13CNMR (100 MHz, DMSO-*d6*): δ 160.0 (O-**C**=N), 157.0 , 153.0, 148.1, 135.0, 134.4, 130.0, 122, 115.1 (all Ar**C**), 144.0 (C-**C**=N pyrazole), 133.5(O­**C**=C pyrazole), 115.1 (C=**C**pyrazole), 105.3. (C=**C** pyrano), 25.1 (**C**H), 11.1(**C**H3).

***4-(6-amino-5-(4-flourophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-4-yl)phenol (5b)****:*

 White crystalline solid (82 %, 0.570 g); mp 236-239ºC: IR (KBr) ν:3534 (br), 3343 (br), 3065 (ws) 2968 (s), 1684 (s), 1598 (s), 1375 (s), 1236 (s), 1173 (vs), 1033 (s), 834 (s) cm-1;

1HNMR (400 MHz, DMSO-*d6*): δ 2.00 (2H, NH2), 2.48 (s, 3H, Me),4.09 (s, 1H, OH), 5.0 (s,1H, CH), 6.85 – 6.38 (d,d, *J* = 8.4 Hz, 2H, Ph), 6.85 – 6.38 (d,d, *J* = 8.4 Hz, 4H, Ph ), 10.04 (s, 1H, NH).

***4-(4-chlorophenyl)-5-(4-flourophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine*** (**5c**):

*White amorphous solid* (80 %, 0.560 g); mp 199-200ºC: IR (KBr) ν:3378 (br), 3047 (ws) 2968 (s), 1684 (s), 1623 (s), 1400 (s), 1235(s), 1163 (vs), 1053 (s), 821 (vs), 653(s ) cm-1;

13CNMR (100 MHz, DMSO-*d6*): δ 160.5 (O-**C**=N), 154.5 , 151.5, 143.9, 132.5, 129.0, 120.9, 116.9, 115.6 (all Ar**C**), 143.0 (C-**C**=N pyrazole), 135.9 (O­**C**=C pyrazole), 108.7 (C=**C**pyrazole), 104.7 (C=**C** pyrano), 23.1 (**C**H), 11.1(**C**H3).

***4-(6-amino-5-(4-flourophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-4-yl)-2-methoxyphenol*** (**5d**):

*Pale orange crystalline solid* (87 %, 0.598 g); mp 260-263ºC: IR (KBr) ν:3534 (br), 3452 (s), 3363 (s), 3225 (b), 3065 (ws) 2968 (s), 1680 (s), 1591 (s), 1455 (s), 1423 (s), 1107 (s), 1055 (s), 802 (s), 622 (s) cm-1;

1HNMR (400 MHz, DMSO-*d6*): δ 2.23 (2H, NH2), 2.49 (s, 3H, Me),3.82 (s, 3H, OCH3), 5.10 (s, 1H, OH), 5.65 (s,1H, CH), 6.85 – 6.87 (d,d, *J* = 8.4 Hz, 4H, Ph), 7.23 – 7.53 (d,d, *J* = 8.4 Hz, 2H, Ph ), 7.44 (s, 1H, Ph), 8.57 (s, 1H, NH);

13CNMR (100 MHz, DMSO-*d6*): δ 161.5 (O-**C**=N), 158.6 , 150.8, 148.8, 146.6, 134.9, 126.3, 124.4, 116.4 (all Ar**C**), 140.0 (C-**C**=N pyrazole), 130.0 (O­**C**=C pyrazole), 110.9 (C=**C**pyrazole), 90.4 (C=**C** pyrano), 56.4 (O**C**H3), 23.6 (**C**H), 12.1(**C**H3).

***5-(4-flourophenyl)-4-(3-methyoxyphenol)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine***  *(****5e****):*

*Pale yellow amorphous solid* (89 %, 0.614 g); mp 195-197ºC: IR (KBr) ν:3484 (w), 3354 (w), 3222 (w), 3014 (ws) 2935 (s), 1675 (s), 1604 (s), 1454 (s), 1387 (s), 1150 (s), 1043 (s), 764 (s) cm-1;

1HNMR (400 MHz, DMSO-*d6*): δ 2.48 (2H, NH2), 3.40 (s, 3H, Me),3.80 (s, 3H, OCH3), 4.89 (s,1H, CH), 7.07 – 7.09 (d,d, *J* = 8.4 Hz, 4H, Ph), 7.38 – 7.45 (m, 3H, Ph ), 8.67 (s, 1H, Ph), 10.03 (s, 1H, NH);

13CNMR (100 MHz, DMSO-*d6*): δ 161.3 (O-**C**=N), 159.4 , 151.5, 145.9, 138.8, 135.1, 129.9, 125.1, 117.4 (all Ar**C**), 144.4 (C-**C**=N pyrazole), 134.0 (O­**C**=C pyrazole), 112.4 (C=**C**pyrazole), 88.8 (C=**C** pyrano), 55.1 (O**C**H3), 23.1 (**C**H), 11.1(**C**H3).

***5-(4-flourophenyl)-4-(3,4,5-trimethyoxyphenol)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine***(**5f**):

*Paleorange crystalline solid (80%, 0.560 g); mp 180–184ºC: IR (KBr) ν:* 3484 (w), 3354 (w), 3222 (w), 3014 (ws) 2986 (s), 1675 (s), 1622 (s), 1438 (s), 1413 (s), 1342 (s), 1234 (s), 1130 (s), 1053 (s), 993 (s), 765 (s), 619 (s) cm-1;

1HNMR (400 MHz, DMSO-*d6*): δ 2.48 (2H, NH2), 3.29 (s, 3H, Me),3.72 (s, 3H, OCH3), 3.83 (s, 6H, 2OCH3), 4.64 (s,1H, CH), 7.2 (s, 1H, Ph), 8.06 – 8.08 (d,d, *J* = 8.4 Hz, 4H, Ph), 8.64 (s, 1H, Ph), 10.09 (s, 1H, NH);

13CNMR (100 MHz, DMSO-*d6*): δ 161.1 (O-**C**=N), 155.4 , 153.2, 144.5, 136.4, 132.1, 129.2, 122.1, 120.1 (all Ar**C**), 144.5 (C-**C**=N pyrazole), 132.1 (O­**C**=C pyrazole), 105.5 (C=**C**pyrazole), 88.9 (C=**C** pyrano), 60.1(O**C**H3), 55.1 (2O**C**H3), 23.1 (**C**H), 11.9(**C**H3).

***5-(4-flourophenyl)-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazol-6-amine*** (**5g**):

*Pale orange crystalline solid (82 %, 0.570 g); mp*271-273 *ºC:* : IR (KBr) ν:3484 (w), 3354 (w), 3222 (w), 3114 (ws) 2925 (s), 1675 (s), 1620 (s), 1596 (s), 1523(vs),1454 (s), 1346 (vs), 1161 (s), 1014 (s), 844 (s) cm-1;

1HNMR (400 MHz, DMSO-*d6*): δ 2.48 (2H, NH2), 3.29 (s, 3H, Me), 4.84 (s,1H, CH), 8.14 – 8.16 (d,d, *J* = 8.4 Hz, 4H, Ph), 8.35 – 8.37 (d,d, *J* = 8.4 Hz, 4H, Ph), 10.05 (s, 1H, NH).

**4-(2,4-dichlorophenyl)-5-(4-flourophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine** *(****5h****):*

*White crystalline solid (80 %, 0.560 g); mp*205-207*ºC:* : IR (KBr) ν:3448 (w), 3354 (w), 3222 (w), 3089 (ws) 2935 (s), 1733 (ws), 1616 (s), 1583 (s), 1319 (s), 1139 (s), 1053 (s), 885 (s), 786 (s) cm-1;

1HNMR (400 MHz, DMSO-*d6*): δ 2.48 (2H, NH2), 3.28 (s, 3H, Me), 4.89 (s,1H, CH), 7.54 – 7.56 (d,d, *J* = 8.4 Hz, 4H, Ph), 8.14 – 8.16 (d,d, *J* = 8.4 Hz, 2H, Ph), 8.96 (s, 1H, Ph), 11.08 (s, 1H, NH);

13CNMR (100 MHz, DMSO-*d6*): δ 162.2 (O-**C**=N), 158.1 , 143.7, 141.3, 134.6, 133.1, 130.4, 128.1, 127.7 (all Ar**C**), 143.7 (C-**C**=N pyrazole), 130.1 (O­**C**=C pyrazole), 114.4 (C=**C**pyrazole), 88.9 (C=**C** pyrano), 23.1 (**C**H), 11.1(**C**H3).

***5-(4-flourophenyl)-4-(3,4-dimethyoxyphenol)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine*** *(****5i****):*

*Orange crystalline solid (80%, 0.560 g); mp 175–178ºC: IR (KBr) ν:* 3484 (wbr), 3421 (w), 3222 (w), 3002 (ws) 2942 (s), 1675 (s), 1623 (s), 1508 (s), 1421 (s), 1344 (s), 1271 (s), 1157 (s), 1018 (s), 867 (s), 754 (s) cm-1;

1HNMR (400 MHz, DMSO-*d6*): δ 2.48 (2H, NH2), 3.42 (s, 3H, Me),3.81 (s, 6H, 2OCH3), 4.82 (s,1H, CH), 7.05 – 7.07 (d,d, *J* = 8.4 Hz, 4H, Ph), 7.35 – 7.37 (d,d, *J* = 8.4 Hz, 2H, Ph), 8.62 (s, 1H, Ph), 10.09 (s, 1H, NH);

13CNMR (100 MHz, DMSO-*d6*): δ 160.6 (O-**C**=N), 157.5 , 151.5, 148.9, 143.3, 135.3, 131.4, 126.6, 123.3 (all Ar**C**), 140.0 (C-**C**=N pyrazole), 117.5 (O­**C**=C pyrazole), 115.4 (C=**C**pyrazole), 88.8 (C=**C** pyrano), 55.5 (O**C**H3), 55.3 (O**C**H3), 23.1 (**C**H), 11.1 (**C**H3).

***2-(6-amino-5-(4-flourophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-4-yl)phenol (5j)****:*

*White crystalline solid(82 %, 0.570 g); mp 200-204ºC: IR (KBr)* ν:3534 (br), 3343 (br), 3065 (ws) 2968 (s), 1684 (s), 1598 (s), 1375 (s), 1236 (s), 1173 (vs), 1033 (s), 834 (s) cm-1;

1HNMR (400 MHz, DMSO-*d6*): δ 2.00 (2H, NH2), 2.48 (s, 3H, Me),4.09 (s, 1H, OH), 5.0 (s,1H, CH), 6.94 – 6.96 (d,d, *J* = 8.4 Hz, 2H, Ph), 7.37 – 7.41 (t,d, *J* = 16 Hz, 2H, Ph ), 7.67 – 7.69 (d,d, *J* = 8.4 Hz, 2H, Ph ), 11.09 (s, 1H, NH).

13CNMR (100 MHz, DMSO-*d6*): δ 163.2 (O-**C**=N), 159.1, 155.5, 150.3, 149.7, 136.7, 133.7, 131.3, 120.0 (all Ar**C**), 143.3 (C-**C**=N pyrazole), 118.6 (O­**C**=C pyrazole), 117.0 (C=**C**pyrazole), 89.9 (C=**C** pyrano), 23.0 (**C**H), 11.1 (**C**H3).

**Conclusions:**

To conclude, we have reported a new, rapid, simple, and an efficient one-pot multicomponent protocol for the expedient synthesis of dihydro-pyrano[2,3-*c*]pyrazol-6-amines. The noteworthy advantages of this protocol include easily available starting materials, simple procedure, and easier separation of products by filtration. The reaction is facile, simple and environment-friendly.

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**References:**

1. (a) Zhu, J.; Bienayme, H. In Multicomponent Reactions, Wiley: Weinheim, **2005**; (b)
 Beck, B.; Hess, S.; Dömling, A. Bioorg. Med. Chem. Lett. **2000**, 10, 1701.

2. Pandey, G.; Singh, R. P.; Singh, V. K. Tetrahedron Lett. **2005**, 46, 2137.

3. Ugi I. Pure Appl.Chem, **2001**, 73, 187.

4. Hermecz, I.; Vasvari-Debreczy, L.; Matyus, P. In Comprehensive Heterocyclic
 Chemistry; Katritzky, A. R., Rees, C. W., Scriven, E. V. F., Eds. Pergamon: London,
**1996**; Chapter 8.23, p 563.

5. (a) Jayaraman, M.; Fox, B. M.; Hollingshead, M.; Kohlhagen,G.; Pommier,Y.; Cushman,
 M. J. Med. Chem. **2002**, 45, 242. (b) Goldberg, D. R.; Butz, T.; Cardozo, M. G.; Eckner,
 R. J.; Hammach, A.; Huang, J.; Jakes, S.; Kapadia, S.; Kashem, M.; Lukas, S.; Morwick,
 T. M.; Panzenbeck, M.; Patel, U.; Pav, S.; Peet, G. W.; Peterson, J. D.; Prokopowicz, A.
 S.III.; Snow, R. J.; Sellati, R.; Takahashi, H.; Tan, J.; Tschantz, M. A.; Wang, X. J.;
 Wang, Y.; Wolak, J.; Xiong, P.; Moss, N. J. Med. Chem. **2003**, 46, 1337. (c) Griffin, R.
 J.; Fontana, G.; Golding, B. T.; Guiard, S.; Hardcastle, I. R.; Leahy, J. J. J.; Martin, N.;
 Richardson, C.; Rigoreau, L.; Stockley, M.; Smith, G. C. M. J. Med. Chem. 2005, 48,
 569. (d) Gold brunner, M.; Loidl, G.; Polossek, T.; Mannschreck, A.; von Angerer, E. J.
 Med. Chem. **1997**, 40, 3524.

 6. Ruppert, D.; Weithmann, K. U. Life Sci. **1982**, 31, 2037.

 7. Swinbourne, J. F.; Hunt, H. J.; Klinkert, G. Adv. Heterocycl. Chem. **1987**, 23, 103.

8. Anastas, P.T.; Warner, J.C. Green Chemistry: *Theory and Practice*, Oxford
 University Press, Oxford, 2000.

9. Poliakoff, M.; Licence, P. *Nature*, **2007**, *450*, 810.

10. (a) Clark, J. H. *Green Chem*. **2006**, *8*, 17; (b) Li, C. J.; Chen, L. *Chem. Soc. Rev*.
**2006**, *35*, 68; (c) Polshettiwar, V.; Varma, R. S. *J. Org. Chem*. **2008**, *73*, 7417; (d)
Polshettiwar, V.; Varma, R. S. *J. Org. Chem*. **2007**, *72*, 7420.

11. (a) Polshettiwar , V.; Varma, R. S. *Chem. Soc. Rev*. **2008**, *37*, 1546; (b) Dallinger, D.; Kappe, C. O. *Chem. Rev*. **2007**, *107*, 2563; (c) Pol-shettiwar, V. ; Varma, R. S.
*Alternative Heating for Green Synthesis in Water* (Photo, Ultrasound, and
 Microwave), Hand book of Green Chemistry, ed. Anastas, P. T.; Li, C.-J. Wil
 VCH Verlag GmbH, Weinheim, **2009**; (d) Varma, R. S. *Clean chemical synthesis
 in water*, Org. Chem. Highlights **2007**.

 12. Gnanasambandam, V.; Kandhasamy, K. Tetrahedron. Lett. **2008**, 49, 5636.

 13 Bigi, F.; Chesini, L.; Maggi, R.; Sartori, G. *J. Org. Chem*. **1999**, *64*, 1033.

 14 Bigi, F.; Conforti, M. L.; Maggi, R.; Piccinno, A.; Sartori, G. Green Chem. **2000**, 2,
 101.

1. Kuppusamy, K.; Kasi, P. *Tetrahedron Lett*. **2010**, *51*, 3312.

 16. El-Tamany, E. S.; El-Shahed, F. A.; Mohamed, B. H.*J Serb.Chem. Soc*. **1999**, *64*, 9.

 17. Ismail, Z. H.; Aly, G. M.; El-Degwi, M. S.; Heiba, H. I.; Ghorab, M. M. *Egypt J. Biot*. **2003**, *13*, 73.

 18. Zaki, M. E. A.; Soliman, H. A.; Hiekal, O. A.; Rashad, A. E. Z. *Natur. forsch. C*.

**2006**, *61*, 1.

 19. Wang, J. L.; Liu, D.; Zhang, Z. J.; Shan, S.; Han, X.; Srinivasula, S. M.; Croce, C.

 M.; Alnemri, E.S.;Huang,Z. *Proc. Natl. Acad. Sci. U. S. A*. **2000**, *97*, 7124.

20. (a)Abdelrazek,F.M.;Metz,P.;Metwally,N.H.;El- Mahrouky, S. F. *Arch. Pharm*. **2006**, *339*, 456;(b)Abdelrazek,F.M.;Metz,P.;Kataeva,O.;Jaeger,A.;El-Mahrouky, S. F. *Arch.
 Pharm*. **2007**, *340*, 543.

21. (a) Sharanin, Y. A.; Sharanina, L. G.; Puzanova, V. V. Zh. *Org. Khim*. **1983**, *19*,2609;

 (b) Rodinovskaya, L. A.; Gromova, A. V.; Shestopalov, A. M.; Nesterov, V. N. *Russ.
 Chem. Bull., Int. Ed*. **2003**, *52*, 2207.

 22. Junek, H.; Aigner, H. *Chem. Ber*. **1973**, *106*, 914.

 23. (a) Zaki, M. E. A.; Soliman, H. A.; Hiekal, O. A.; Rashad, A. E. *Z.Naturforsch.*,
**2006**, *61*, 1; (b) Abdelrazek, F. M.; Metz, P.; Kataeva, O.; Jaeger A.; El-Mahrouky, S.
 F. *Arch. Pharm*., **2007**, *340*, 543; (c) Foloppe, N.; Fisher, L. M.; Howes, R.; Potter,
 A.; Robertson, A. G. S.; Surgenor, A. E. *Bioorg. Med. Chem.,* **2006**, *14*, 4792.

 24. Fadda, A. A. ; Abdel-Rahman, A. A.-H.; Hamed, E. A.; Khalil. E. H.*Am. Jr. Org.
Che.,***2012**, *2*, 7.

25**.**Jaberi, Z. K.; Shams, M. M. R.; Pooladian, B. *ActaChimicaSlovenica*, **2013**,105.

26. Kanchithalaivan, S.; Sivakumar, S.; Kumar, R. R. Elumalai, P.; Ahmed, Q. N.; Padala
 A. K. *ACS Comb. Sci.***2013**, *15*, 631.

27. Madhusudana Reddy, M. B..; M. A. Pasha, Synth. Commun. 2010, 40, 1895.

28. Pasha, M. A.; Jayashankara, V. P. Bioorg. Med. Chem. Lett. 2007, 17, 621.

29. Pasha, M. A.; Jayashankara, V. P. Indian J. Chem. 2007, 46B, 1328.

30. Madhusudana Reddy. M. B.; Pasha, M. A. Chin. Chem. Lett. **2010**, 23, 1025.

31. Pasha, M. A.; Jayashankara, V. P. J. Pharm. Toxic. 2006, 1(6), 573.

32. Pasha, M. A.; Aatika, N. Synth. Commun. 2010, 40, 2864. 26. Aatika, N.; Pasha, M.
 A. J. Saudi Chem. Soc. **2011**, 15, 55.