# COMPARATIVE ANALYSIS OF SOLVENT FREE, KHSO4 AND CE(SO4)2 CATALYZED MICROWAVE-ASSISTED SYNTHESIS OF 1, 3-DIAZACYCLOPENTA-2, 4-DIENES AND EVALUATION OF ITS ANTI-BACTERIAL ACTIVITY

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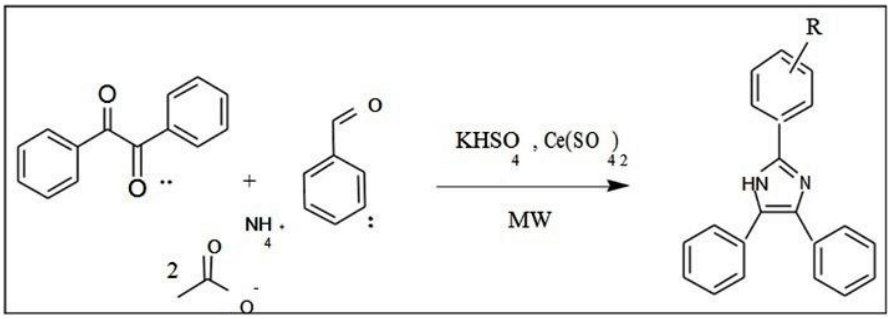
**ABSTRACT:** The presented research demonstrated solvent free, microwave-assisted one-pot synthesis of derivatives of 1, 3-diazacyclopenta-2, 4-diene. The targeted moiety being a dynamic class of N-heterocycles had remained at the forefront of biological and medicinal chemistry throughout since they were important pharmacophores encompassing vast significant activities. Owing to the potency and wide applicability of this moiety, a diversity-oriented convergent synthesis through multi-component cyclocondensation of dicarbonyl substrates with numerous aryl aldehydes and ammonium acetate was carried out by employing two active catalysts individually. In addition, the catalytic performance in the synthesis of the desired compounds was also successfully evaluated and the compounds were also tested again two bacterial strains. This protocol produced pure products in high yield within a short period having the enhancing features of easy work-up and a high degree of atom economy.




**KEYWORDS:** One-pot synthesis, microwave-assisted synthesis, 1, 3-diazacyclopenta-2, 4-diene, multi-component reaction, cyclocondensation.

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## INTRODUCTION

Microwave-assisted high-speed chemistry has much to propose to the synthestic chemist due to its multiple advantages. The influence of micro-waves on stereo selectivity, regioselectivity and chemoselectivity along with the enormous accelerations resulting in speedy molecular interactions causing higher yield and purity as well are attributes that cannot be overlooked without contemplation (Jayabharathe *et al*., 2015). A merit of such distinguished attributes has empowered this technique to successfully carry out all formerly conventional synthesis along with those reactions that are incompatible with conventional heating. Thus, microwave-assisted organic transformations are an influential mean of rapidly exploring "chemistry space" and constructing structurally diverse libraries of active compounds (Gupta and Paul, 2012).

In addition, green approach has revolutionized the synthetic chemistry by focusing on the intrinsic hazards of a chemical and attempting to eliminate the use and generation of such perilous substances. Based on a set of 12 principles, green chemistry targets from the environmental protection to the energy efficiency and atom economy of a protocol thus contributing to overcome the debt to mother nature in terms of pollution (Teimouri and Chermahini, 2011).

Owing to the emergence of previously unknown complicated diseases, deadly infections and a drug-resistance to old plagues, a global public health dilemma has been created. In an effort to overcome it and formulate exotic potential medicinal molecules for the augmentation of new drugs, novel synthetic strategies for complex scaffolds from readily accessible reagents through convergent technique has been a subject of immense interest. In this regard, multicomponent one-pot reaction holds a valuable status in modern organic synthesis and pharmaceuticals and has come to the limelight as a powerful tool in drug discovery. These so-called complexity generating reaction results in the

speedy generation of an assorted library of complex molecules utilizing diversity oriented synthetic protocols (Heravi *et al*., 2012).

Nature is full of extraordinary resources that have benefitted the human race in one way or other. Numerous alkaloids containing the 1,3-diazacyclopenta-2,4-diene motif is one such asset that has jeopardized the researchers since their discovery owing to the fact that this nucleus is a compelling rudimentary pharmacodynamics nub, likely to be the finest molecular frame in nature. As a result, there has been a never ending hunt for naturally occurring derivatives of 1, 3-diazacyclopenta-2,4-diene (Safari and Zarnegar, 2013).

The potency and extensive applicability of the 1, 3-diazacyclopenta-2, 4-diene pharmacophore can be certified to its hydrogen bond donor-acceptor capability along with its elevated attraction for metals such as Zn, Fe and Mg reported by (Nagargoje *et al*., 2012).

The potency and extensive applicability of the 1, 3-diazacyclopenta-2, 4-diene pharmacophore can be certified to its hydrogen bond donor-acceptor capability along with its elevated attraction for metals such as Zn, Fe and Mg reported by (Nagargoje *et al*., 2012).

Moreover, the imidazole motif can undergo substitution at four different positions giving rise to a diverse library of biologically active compounds. The citing and nature of these substituents plays a vital role in shaping the biological and medicinal properties of these compounds (Safari *et al*., 2012).

1, 3-diazacyclopenta-2, 4-diene derivatives when N-substituted with amide group increase pharmacological characteristics namely bronchodilatery, calcium antagonist, antiepileptic, anti- convulsant and antiparkinsonism. Similarly, the 2, 4, 5 trisubstituted 1, 3-diazacyclopenta-2, 4-diene containing thiosemicarbazide group are found to show remarkable biological activities against microbes. Moreover, the 1, 2, 4, 5 tetrasubstituted imidazole derivatives are strong inhibitors of thromboxane A2 synthase and also hold back against p38 MAP kinase, cyclooxygenase-2 (COX-2) and (TGF-b1) type 1 activin receptor like kinase (ALK5) (Nikalje *et al*., 2015).

The miracle motif of imidazole is not only renowned for its pharmacological and medicinal properties but is also widely known as a key tool in various new technologies such as biological imaging, fluorescence labeling agents, as light sensitive materials in photography and as chromophores for non-linear optic systems. They have also found application as a ligand in coordinate chemistry (Jourshari *et al*., 2013).

In recent years, KHSO4 has been the center of much attention for catalyzing different organic reactions due to its experimental simplicity, ease of operation, cost effectiveness and exceptional solubility in organic solvents (Karimi-Jaberi and Barekat, 2013). Cerium sulphate, on the other hand being a good oxidizing agent, has invoked enormous interest as a potential catalyst capable of building carbon-carbon and carbon-heteroatom bond in a number of organic transformations. In addition to its easy availability, its cheap and non-toxic characteristics have highlighted its use for organic transformations (Mekheimer *et al*., 2009).

Thus, in view of the pronounced effect of microwave-assisted catalyzed synthetic routes, a systematic work for the generation of multi-purpose derivatives of 1, 3-diazacyclopenta-2, 4-diene was carried out.

## MATERIALS AND METHODS

**Synthesis of derivatives of 1, 3-diazacyclopenta-2, 4-dienes using KHSO4 (2a-8a):** Benzil (0.1 g/1 mM) was ground using a pestle and mortar until a fine powder was formed. Aryl aldehyde (0.1 ml/1 mM) and ammonium acetate (0.154 g/2 mM) were added along with KHSO4 (0.274 g/2 mM) as catalyst. The reaction mixture was irradiated with microwaves (Microwave oven DW-180 MHz, 950 W) for 40 to 90 seconds. After completion of reaction as indicated by TLC and a slight change in color, the product was extracted with ethanol and recrystallized.

**Synthesis of derivatives of 1, 3-diazacyclopenta-2,4-dienes using Ce(SO4)2 (2b-8b):** Benzil (0.1 g/1 mM) was ground using a pestle and mortar until a fine powder was formed. Aryl aldehyde (0.1 ml/1 mM) and ammonium acetate (0.154 g/2 mM) were added along with Ce(SO4)2 (0.236 g/ 1 mM) as catalyst. The reaction mixture was then irradiated with microwaves for 50 to 150 seconds. After slight change in color, the product was extracted with ethanol and recrystallized.

**Antibacterial activity:** The newly synthesized compounds have been screened in vitro against an assortment of two bacterial strains namely *Staphylococcus aureus* and *Pseudomonas* using agar well-diffusion method at concentrations of 1000µg/ml, 500 µg/ml, 250 µg/ml, 100 µg/ml in nutrient agar media. Screening results are summarized in (Table 1). All the synthesized compounds were prepared in dimethylsulphoxide.

## RESULTS AND DISCUSSION

Measurements of "zones of inhibition" of the compounds were measured in mm and the results showed that compounds possessed antimicrobial activity against the tested strains. The highest activity was found at the highest dilution that is 100 µg/ml because the higher molecular weight of the compounds restricted it to diffuse further in the agar medium when concentration was increased. However, all the bacteria were killed in the well and the immediate surrounding when higher

concentrations were used. Thus, the dilutions played a significant role in the antibacterial measurements.

**Table-1: An illustration of antibacterial activity.**

| Compounds | Diameter of zone of inhibition (mm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *Staphylococcus aureus* | | | | *Pseudomonas* | | | |
| | 1000µg/ Ml | 500µg/ ml | 250µg/ ml | 100µg/ Ml | 1000µg /ml | 500µg/ ml | 250µg/ ml | 100µg/ ml |
| **Compound 1 (a)** | 7 | 9 | 9 | 10 | 9 | 9 | 11 | 13 |
| **Compound 2 (a)** | 9 | 9 | 10 | 12 | 9 | 10 | 10 | 13 |
| **Compound 7 (a)** | 10 | 12 | 13 | 15 | 11 | 11 | 13 | 16 |
| **Chloroamphenicol** | 25 | - | - | - | 26 | - | - | - |
| **Control DMSO** | - | - | - | - | - | - | - | - |

The bacterial strains were provided by the Botany department, Lahore College for Women University, Lahore. The bacteria were stored at -70ºC prior to re-culturing.

The Percentage yield, reaction time and the melting points of the fabricated compounds by the use of both catalysts namely KHSO4 and Ce(SO4)2 were recorded (Table 2 and Table 3 respectively).

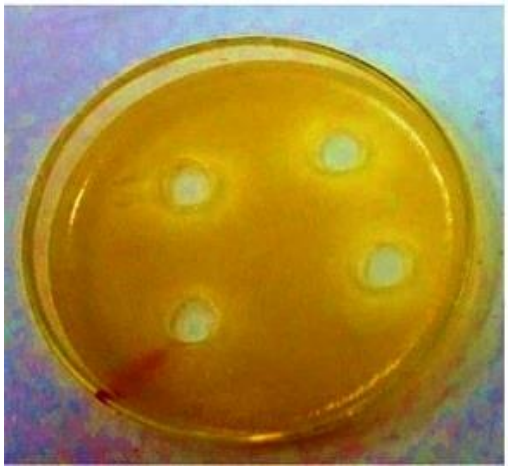


**Figure-1: Staphylococcus aureus Compound (1a)**

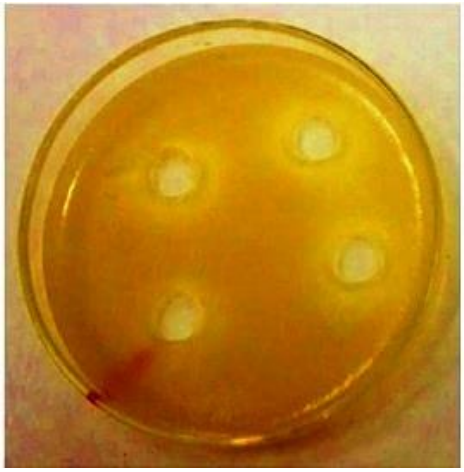


**Figure-2: Pseudomonas Compound (1a)**

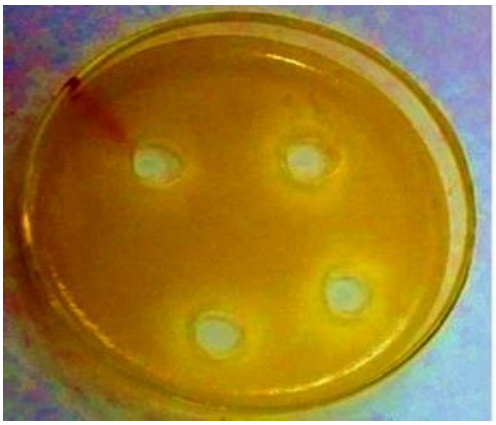


**Figure-3: Staphylococcus aureus Compound (2a)**

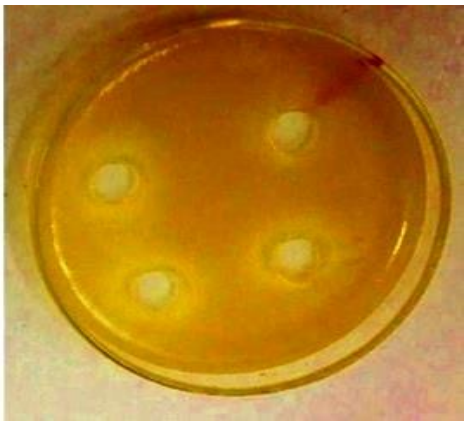


**Figure-4: Pseudomonas Compound (2a)**

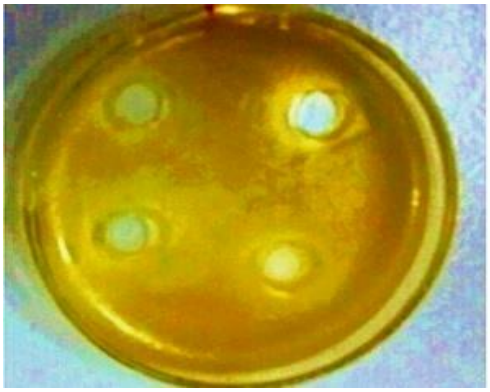


**Figure-5: Staphylococcus aureus Compound (7a)**

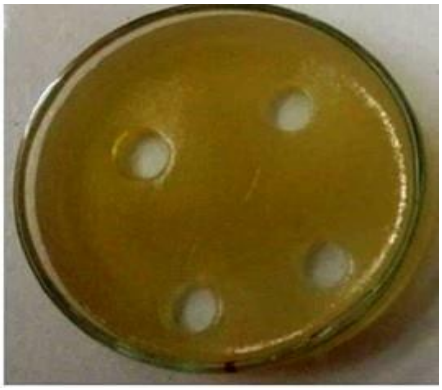
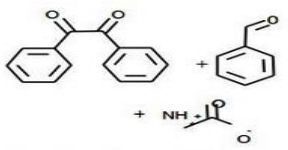
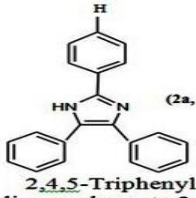
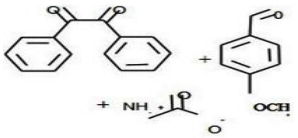
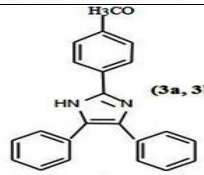
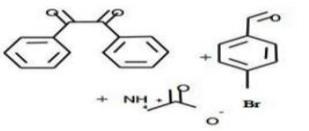
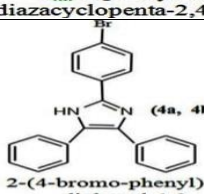
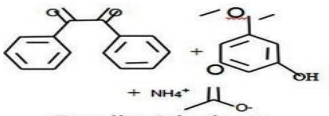
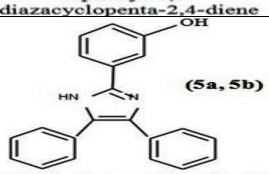
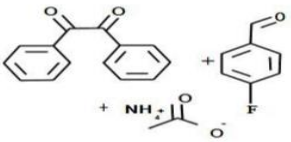
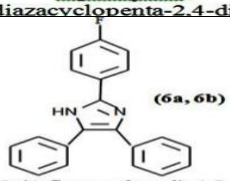


**Figure-6: Pseudomonas Compound (7a)**

**Table-2: Percentage yield and reaction time of fabricated compounds.**

| Sr. No. | Substrate | Product | KHSO4 Catalyzed | | Ce(SO4)2 Catalyzed | |
|---|---|---|---|---|---|---|
| | | | Time (sec) | Yield % | Time (sec) | Yield % |
| 1 |  Benzil + benzaldehyde + ammonium acetate |  (2a, 2b) 2,4,5-Triphenyl-1,3-diazacyclopenta-2,4-diene | 45 | 89 | 50 | 87 |
| 2 |  Benzil + anisaldehyde + ammonium acetate |  (3a, 3b) 2-(4-methoxy-phenyl)-4,5-diphenyl-1,3-diazacyclopenta-2,4-diene | 45 | 86 | 60 | 83 |
| 3 |  Benzil + 4-bromo benzaldehyde + ammonium acetate |  (4a, 4b) 2-(4-bromo-phenyl)-4,5-diphenyl-1,3-diazacyclopenta-2,4-diene | 90 | 88 | 150 | 87 |
| 4 |  Benzil + 3-hydroxy benzaldehyde + ammonium acetate |  (5a, 5b) 2-(3-hydroxy-phenyl)-4,5-diphenyl-1,3-diazacyclopenta-2,4-diene | 50 | 92 | 60 | 92 |
| 5 |  Benzil + 4-fluoro benzaldehyde + ammonium acetate |  (6a, 6b) 2-(4-fluoro-phenyl)-4,5-diphenyl-1,3-diazacyclopenta-2,4-diene | 40 | 96 | 60 | 93 |

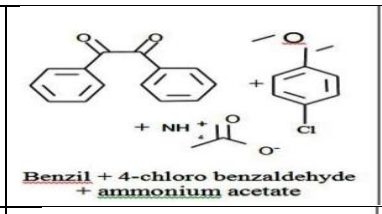
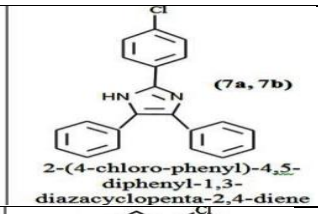
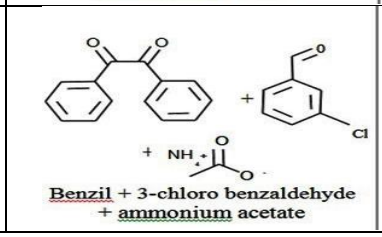
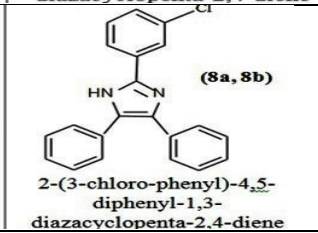
| | | | | | | |
|---|---|---|---|---|---|---|
| 6 |  Benzil + 4-chloro benzaldehyde + ammonium acetate |  (7a, 7b) 2-(4-chloro-phenyl)-4,5-diphenyl-1,3-diazacyclopenta-2,4-diene | 60 | 97 | 100 | 95 |
| 7 |  Benzil + 3-chloro benzaldehyde + ammonium acetate |  (8a, 8b) 2-(3-chloro-phenyl)-4,5-diphenyl-1,3-diazacyclopenta-2,4-diene | 100 | 91 | 140 | 89 |

**Table-3: Melting points of Compounds.**

| Compounds | Melting points (°C) | |
|---|---|---|
| | KHSO4 | Ce(SO4)2 |
| **2 (a, b)** | 274 | 274 |
| **3 (a, b)** | 223 | 224 |
| **4 (a, b)** | 224 | 224 |
| **5 (a, b)** | 226 | 226 |
| **6 (a, b)** | 240 | 241 |
| **7 (a, b)** | 190 | 189 |
| **8 (a, b)** | 199 | 200 |

A comparison of the yields of reported (Aziizi *et al*., 2014) and synthesized compounds is depicted in Fig-2.

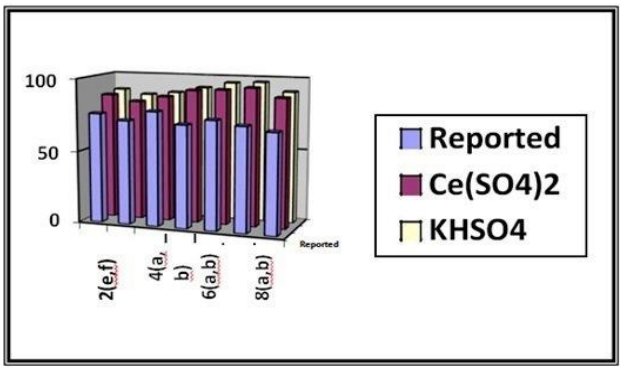



**Figure-2: Comparison of yields of reported and synthesized compounds**

UV spectra were recorded within the range of 200-600 nm on Hitachi U-2800 double beam spectrophotometer (Table 4).

**Table-4: UV-Vis data of synthesized compounds.**

| Compound | KHSO4 catalyzed | Ce(SO4)2 catalyzed |
|---|---|---|
| | λ max (nm) | λ max (nm) |
| **2 (a, b)** | 285 (n-$\pi^*$) | 288 (n-$\pi^*$) |
| **3 (a, b)** | 295 (n-$\pi^*$) | 296 (n-$\pi^*$) |
| **4 (a, b)** | 281(n-$\pi^*$) | 286 (n-$\pi^*$) |
| **5 (a, b)** | 262 (n-$\pi^*$) | 262 (n-$\pi^*$) |
| **6 (a, b)** | 296 (n-$\pi^*$) | 291 (n-$\pi^*$) |
| **7 (a, b)** | 300 (n-$\pi^*$) | 298 (n-$\pi^*$) |
| **8 (a, b)** | 278 (n-$\pi^*$) | 278 (n-$\pi^*$) |

UV-Vis data for derivatives of 1, 3-diazacyclopenta-2, 4-diene synthesized by both catalysts through microwave irradiation were in close approximation with each other and with the reported data. The UV spectra of all compounds 2-8 showed absorption peaks in the region of 262-300 nm which was the result of extended conjugation towards longer wavelength due to n-$\pi^*$ transition. The occurrence of this large red shift is associated with the attachment of the phenyl group with the unsaturated 5-membered ring (Safari *et al*., 2012).

FT-IR analysis was done using Midac FT-IR spectrophotometer (M2000) using KBr disc within the range of 400-4000 $cm^{-1}$ (Table 5).

**Table-5: FT-IR data of compounds synthesized by conventional method**

| Compounds | KHSO4 catalyzed | Ce(SO4)2 catalyzed |
|---|---|---|
| | Wave number ($cm^{-1}$) Absorption Intensity | Wave number ($cm^{-1}$) Absorption intensity |
| **2 (a, b)** | 1324 (C-N), 1448 (>C=C<), 1577 (Ar. Conjugation, 1655 (>N-C), 3063 (Ar. C-H), 3240 (N-H). | 1325 (C-N), 1448 (>C=C<), 1541 (Ar. Conjugation), 1655 (>N-C), 3022 (Ar. C-H), 3297 (N-H). |
| **3 (a, b)** | 1029 (O-CH3), 1294 (C-N), 1492 (>C=C<), 1546 (Ar. Conjugation), 1612 (>N-C), 2964 (Ar. C-H), 3177 (N-H) | 1053 (O-CH3), 1359 (C-N), 1475 (>C=C<), 1581 (Ar. Conjugation), 1620 (>N-C), 2926 (Ar. C-H), 3174 (N-H) |

| | | |
|---|---|---|
| **4 (a, b)** | 499 (C-Br), 1261 (C-N), 1431 (>C=C<), 1500 (Ar. Conjugation), 1600 (>N-C), 2926 (Ar. C-H), 3136 (N-H) | 514 (C-Br), 1259 (C-N), 1427 (>C=C<), 1485 (Ar. Conjugation), 1627 (>N-C), 2929 (Ar. C-H), 3132 (N-H) |
| **5 (a, b)** | 1128 (C-O), 1323 (C-N), 1462 (>C=C<), 1504 (Ar. Conjugation), 1641 (>N-C), 3082 (N-H), 3444 (O-H) | 1178 (C-O), 1261 (C-N), 1485 (>C=C<), 1490 (Ar. Conjugation), 1641 (>N-C), 3178 (N-H), 3448 (O-H) |
| **6 (a, b)** | 1070 (C-F), 1325 (C-N), 1450 (>C=C<), 1492 (Ar. Conjugation), 1639 (>N-C), 3132 (N-H), 3232 (>N-H) | 1000 (C-F), 1320 (C-N), 1469 (>C=C<), 1500 (Ar. Conjugation), 1658 (>N-C), 3085 (N-H), 3350 (>N-H) |
| **7 (a, b)** | 732 (C-Cl), 1325 (C-N), 1435 (>C=C<), 1485 (Ar. Conjugation), 1604 (>N-C), 3130 (N-H), 3417 (>N-H) | 765 (C-Cl), 1361 (C-N), 1408 (>C=C<), 1496 (Ar. Conjugation), 1616 (>N-C), 3132 (N-H), 3446 (>N-H) |
| **8 (a, b)** | 765 (C-Cl), 1323 (C-N), 1442 (>C=C<), 1492 (Ar. Conjugation), 1629 (>N-C), 3134 (N-H), 3446 (>N-H). | 763 (C-Cl), 1325 (C-N), 1442 (>C=C<), 1483 (Ar. Conjugation), 1637 (>N-C), 2926 (N-H), 3500 (>N-H) |

The IR absorption band of the synthesized compounds (2-8) marked a number of peaks on the IR spectra that gave evidence of the formation of the compound. The peaks in the range of 3044-3063 $cm^{-1}$ indicated the C-H stretch of arenas and the presence of the aromatic ring was further confirmed by multiple strong peaks from 1400-1600 $cm^{-1}$ which was a result of the aromatic conjugation and the C=C stretch of the aryl group. Other than this, the peak observed from 1290-1330 $cm^{-1}$ indicated the C-N stretch for secondary nitrogen and the peak at approximately 3300 $cm^{-1}$ showed the N-H stretch which led to the conclusion of existence of amino group. In addition, C=N stretch at 1550-1600 $cm^{-1}$ demonstrated the presence of a tertiary nitro group that indicated the formation of the targeted cyclic compound (Banothu *et al*., 2013).

Other than these common peaks observed for all derivatives, certain specific peaks for individual compounds owing to the presence of certain side groups were also noticed such as 1029-1053 $cm^{-}$ for methoxyl group in compound 3 (a, b), 520 $cm^{-1}$ for bromo group in compound 4 (a, b), 1128-1178 $cm^{-1}$ for hydroxyl group in 5 (a, b), 1000-1070 $cm^{-1}$ for fluoro group in compound 6 (a, b) and 732-765 $cm^{-1}$ for chloro group in 7 (a, b)-8 (a, b) compounds (Nikoofar *et al*., 2015).

Mass spectra of the compounds fabricated by employing KHSO4 were taken by GCMS Schimadzu QP-2010 Spectrometer (Table 6).

**Table-6: Mass spectral data of synthesized compounds.**

| **Compounds** | **Formula** | **GC-MS** |
|---|---|---|
| | | **KHSO4** |
| 3 (a, b) | C22H18N2O | 62, 67, 90, 120, 156, 182, 201, *232*, 270, 329 |
| 4 (a, b) | C21H15N2Br | 60, 79, 85, 124, 150, 226, 245,279, *324*, 366, 385 |
| 5 (a, b) | C21H16N2O | 61, 81, 87, 108, 151, 181, 200, *260*, 291, 382 |
| 6 (a, b) | C21H15N2F | 68, 77, 95, 156, 169, 192, 215, *243*, 278, 310 |
| 7 (a, b) | C21H15N2Cl | 71, 85, 106, 142, 170,192, 232, *248*, 281, 315 |
| 8 (a, b) | C21H15N2Cl | 62, 76, 110, 131, 169, 198, 211, *232*, 280, 341 |

The molecular ion peak is denoted by value in bold while the italic value refers to the base peak. Mass spectra of all compounds from 3a-8a gives base peak at 232 m/z that was originated by the cleavage of phenyl ring from the original molecule and matched the testified standard value. This fragmentation was also accompanied by a peak at 90 m/z owing to the phenyl ring that has been cleaved. A peak at 62 m/z value was also furnished that corresponds to the imidazole ring while the presence of the fragments of substituted imidazoles were confirmed by peaks observed at 156 m/z and 182 m/z. The m/z 120 gave an idea about the presence of methoxyl phenyl group and the other fragment obtained by this partial disintegration resulted in the occurrence of a peak at 201 m/z due to N2C15H11 fragment. Loss of methoxyl from the aromatic ring present on the core molecule gave rise to another signal at 270 m/z. Finally, the molecular ion peak of the fabricated compounds was detected at 329 m/z (Samai *et al*., 2009).

**Conclusion:** The present study demonstrated a novel and efficient one-pot cyclocondensation using two active catalysts. The highlighting feature of this research work was exceptionally high yields, reduced reaction time and generation of pure products without contamination by the catalysts employed. Moreover the compounds showed promising activity against each strain at low concentrations.

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