**Microwave assisted one –pot synthesis of 3, 4-dihydro-1-aryl-(1, 3)oxazino(5,6-h)quinolin-3-one**

Monika Gupta\*, Anamika Singh, Rajesh Kumar Pandey

Ashish kumar

Department of Chemistry, Babu Banarasi Das University, Lucknow, U.P. 2260 28, India

Corresponding Author: Monika Gupta

**ABSTRACT**

In this book chapter we have described an efficient one –pot synthesis for the preparation of 3, 4-dihydro-1-aryl-(1,3)oxazino(5,6-h)quinolin-3-one derivatives (1-6 )in three component cyclocondensation reaction of 8-quinolinol, aromatic aldehydes and urea under solvent-free condensation and microwave assisted conditions.

With our continuous investigation on the methodology of green synthesis we have described the synthesis, mass spectral analysis and biological activities of 3,4-dihydro-4-phenyl-(1,3)oxazino(5,6-h)quinolin-2-one **(1)**, 3,4-dihydro-4-(4-nitrophenyl)-(1,3)oxazino(5,6-h)quinolin-2-one **(2)**, 3,4-dihydro-4-(hydroxyphenyl)-(1,3)oxazino(5,6-h)quinolin-2-one **(3)**, 3,4-dihydro-4-(2,4-dihydroxyphenyl)-(1,3)oxazino(5,6-h)quinolin-2-one **(4)**, 4-(3-ethoxy-2-hydroxyphenyl)-3,4-dihydro-(1,3)oxazino(5,6-h)quinolin-2-one **(5)**, 4-(4-(dimethylamino)phenyl)-3,4-dihydro-(1,3)oxazino(5,6-h)quinolin-2-one (6).

**KEYWORDS:** ρ-TSA, 3, 4-dihydro-1, 3-oxazin-2-one, Quinoline, Anti-Convulsant activity, pharmacologically active

**INTRODUCTION**

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry, because the strategies of MCR offer significant advantages over conventional linear type synthesis. MCRs leading to interesting heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of drug like molecules for biological screening, since the combination of three or more small molecular weight building blocks in a single operation leads to high combitorial chemistry.

In recent years, organic synthesis involving environmentally friendly protocol under solvent free condition is being explored world wide due to stringent environment and economic regulation. The presence of quinoline skeleton in the frameworks of pharmacologically active compounds and natural products has spurred on developments of different strategies for their synthesis. Quinoline derivatives have long been known for their wide range of biological activities1 and chemotherapeutic activities.2 In addition they are used as dyestuffs and photographic sensitizers.3 They are valuable reagents for the synthesis of nano and mesostructures with enhanced electronic and photonic properties.4 The quinoline nucleus is the backbone of many natural products and pharmacologically significant compounds displaying a broad range of biologically activity. Many functionalized quinolines are widely used as antimalarial, antiasthmatic, anti-inflammatory agents, and antibacterial, antihypertensive and tyrosine kinase PDGF-RTK inhibiting agents.6 Oxazinone derivatives have received considerable attention due to interesting pharmacological properties associated with this heterocyclic scaffold. Example -naphthooxazinone derivatives have been reported to acts as antibacterial agents, or Efavirenz (Sustiva), a benzoxazinone derivative, is a non-nucleoside reverse transcriptase inhibitor that has been approved by the FDA in 1998 and is presently in clinical use for the treatment of AIDS. Therefore numerous methods for the synthesis of aromatic oxazinone derivatives exist in literature. To the best of our knowledge, there are no reports in the literature for the preparation of 1, 2-dihydro (5, 6)-quinolin-3-one derivatives via condensation of 6-quinolinol, aldehyde and urea. Then several aromatic aldehydes with 8-quinolinol and urea under solvent-free condition using ρ-TSA at 1500C reacted to afford the corresponding products in good yields. High yields were obtained using aromatic aldehydes carrying electron-donating or electron withdrawing substituent. Under the same condition, with aliphatic aldehydes the yields of reaction notably decreased (20%, with butanal or hexanal), probably due to possible aldol condensation side reaction. In the absence of ρ-TSA, the products were obtained in low yields (less than 20%), when the reaction were carried out in solvent-free condition at 1500C.

In order to decrease the reaction time, microwave irradiation in the presence of different catalyst such as ρ-TSA, HOAc, FeCl3, ZnCl2, SnCl2 was used. In the course of study it was found that HOAc is the most effective catalyst in terms of yield. It is clear that using microwave irradiation the reaction time decreased from 2-2.5 h to 4 min in the presence of catalytic amount of HOAc. In addition to decrease of reaction time, the yields in all cases are reasonable.12 According to the results, and as in numerous classical multi-component reaction can be mechanistically considered to proceed through acylamine intermediate14 formed in-situ by condensation reaction of aldehyde with urea.15 High yields were obtained in good yields obtained using aromatic aldehydes carrying electron- donating or electron-withdrawing substituents. It is well known that quinoline derivatives exhibit a wide range of biological activities, pharmaceutical and therapeutic properties such as antiviral, antibacterial anti-inflammatory activities, preparation of this heterocyclic nucleus has great important in organic synthesis.

In this chapter we have described an efficient one –pot synthesis for the preparation of 3, 4-dihydro-1-aryl-(1,3)oxazino(5,6-h)quinolin-3-one derivatives **(1-6)** in three component cyclocondensation reaction of 8-quinolinol, aromatic aldehydes and urea under solvent-free condensation and microwave assisted conditions. The following compounds are given below in Table 1.



**Table 1. Substituted Quinoline derivatives are given below:**

|  |  |  |  |
| --- | --- | --- | --- |
| **COMPOUND NO** | **-R1** | **-R2** | **-R3** |
| 1 | -H | -H | -H |
| 2 | -H | -H | -NO2 |
| 3 | -H | -H | -OH |
| 4 | -OH | -H | -OH |
| 5 | -OH | -OC2H5 | -H |
| 6 | -H | -H | -N(CH3)2 |

 **Synthesis of 3, 4-dihydro-4-phenyl-(1, 3) oxazino (5, 6-h) quinolin-2-one (1)**

3,4-dihydro-4-phenyl-(1,3)oxazino(5,6-h)quinolin-2-one **(1)** has been synthesized by the cyclocondensation of benzaldehyde, 8-quinolinol and urea under solvent free condition using ρ-TSA at 1500C reacted to afford the corresponding products in good yields. The mass spectrum of (1) has shown the molecular ion peak at m/e 276 (C17H12N2O2). Other important peaks have been found at m/e 225(C14H11NO2), 200(C11H18N2O2), 175(C10H9NO2), 149(C8H7NO2), 99(C4H5NO2). 1HNMR spectrum of **(1)** has shown one singlet for NH proton at δ 8.0.One multiplet in the range of δ 7.06-7.14 for aromatic proton. One doublet has found at δ 6.16 for proton of heterocyclic ring adjacent to NH proton. One multiplet is also found in the range of δ 7.14-8.86 for protons of quinoline nucleus.

 **Synthesis of 3, 4-dihydro-4-(4-nitrophenyl)-(1,3)oxazino(5,6-h)quinolin-2-one(2)**

3,4-dihydro-4-(4-nitrophenyl)-(1,3)oxazino(5,6-h)quinolin-2-one **(2)** has been synthesized by the cyclocondensation of 4-nitrobenzaldehyde, 8-quinolinol and urea under solvent free condition using ρ-TSA at 1500C reacted to afford the corresponding products in good yields. The mass spectrum of **(2)** has shown the molecular ion peak at m/e 321 (C17H11N3O4). Other important peaks have been found at m/e 276(C17H12N2O2), 220(C10H8N2O4), 175(C10H9NO2), 149(C8H7NO2), 99(C4H5NO2). 1HNMR spectrum of **(2)** has shown one singlet for NH proton at δ 8.0.One multiplet is found in the range of δ 7.32-8.07-for aromatic proton which is strongly deshielded by nitro group. One doublet has found at δ 6.16 for proton of heterocyclic ring adjacent to NH proton. One multiplet is also found for aromatic proton at δ 7.14-8.86 situated in quinoline nucleus.

 **Synthesis of 3,4-dihydro-4-(hydroxyphenyl)-(1,3)oxazino(5,6-h)quinolin-2-one (3)**

3,4-dihydro-4-(hydroxyphenyl)-(1,3)oxazino(5,6-h)quinolin-2-one has been synthesized by the cyclocondensation of 4-hydroxybenzaldehyde, 8-quinolinol and urea under solvent free condition using ρ-TSA at 1500C reacted to afford the corresponding products in good yields. The mass spectrum of **(3)** has shown the molecular ion peak at m/e 292 (C17H12N2O3). Other important peaks have been found at m/e 276(C17H12N2O2), 241(C14H11NO3), 200(C11H18N2O2), 191(C10H9NO3), 175(C10H9NO2), 149(C8H7NO2), 99(C4H5NO2). 1HNMR spectrum of **(3)** has shown one singlet for NH proton at δ 8.0.One multiplet is found in the range of δ 6.61-6.89 for aromatic proton which is strongly deshielded by hydroxyl group. One doublet has found at δ 6.16 for proton of heterocyclic ring adjacent to -NH proton. One multiplet is also found for aromatic proton at δ 7.14-8.86 situated in quinoline nucleus.

 **Synthesis of 3,4-dihydro-4-(2,4-dihydroxyphenyl)-(1,3)oxazino(5,6-h)quinolin-2-one (4)**

3,4-dihydro-4-(2,4-dihydroxyphenyl)-(1,3)oxazino(5,6-H) quinolin-2-one has been synthesized by the cyclocondensation of 2,4-dihydroxybenzaldehyde, 8-quinolinol and urea under solvent free condition using ρ-TSA at 1500C reacted to afford the corresponding products in good yields. The mass spectrum of **(4)** has shown the molecular ion peak at m/e 309 (C17H12N2O4). Other important peaks have been found at m/e 292(C17H12N2O3), 276(C17H12N2O2), 207(C10H9NO4), 200(C11H18N2O2), 175(C10H9NO2), 149(C8H7NO2), 99(C4H5NO2). 1HNMR spectrum of **(4)** has shown one singlet for NH proton at δ 8.0.One multiplet in the range of δ 6.08-6.72 for aromatic proton. One doublet has found at δ 6.16 for proton of heterocyclic ring adjacent to NH proton. One multiplet is also found in the range of δ 7.14-8.86 for protons of quinoline nucleus. Another prominent singlet is observed at δ 5.0 for proton of hydroxyl group (-OH).

 **Synthesis of 4-(3-ethoxy-2-hydroxyphenyl)-3,4-dihydro-(1,3)oxazino(5,6-h)quinolin-2-one(5)**

4-(3-ethoxy-2-hydroxyphenyl)-3,4-dihydro-(1,3)oxazino(5,6-h)quinolin-2-one has been synthesized by the cyclocondensation of 2-hydroxy-3-ethoxyhydroxybenzaldehyde, 8-quinolinol and urea under solvent free condition using ρ-TSA at 1500C reacted to afford the corresponding products in good yields. The mass spectrum of **(5)** has shown the molecular ion peak at m/e 336 (C19H16N2O4). Other important peaks have been found at m/e 320(C19H16N2O3), 292(C17H12N2O3), 276(C17H12N2O2), 287(C16H17NO4), 235(C12H13NO4), 200(C11H8N2O2), 99(C4H5NO2).1HNMR spectrum of **(5)** has shown one singlet for NH proton at δ 8.0. One multiplet is found in the range of δ 6.41-6.59 for aromatic proton which is strongly deshielded by ethoxy group. One doublet has found at δ 6.16 for proton of heterocyclic ring adjacent to NH proton. One multiplet is also found for aromatic proton at δ 7.14-8.86 situated in quinoline nucleus, strongly deshielded by electronegative atom (N). Another prominent singlet is observed at δ 5.0 for proton of hydroxyl group (-OH). 1HNMRSpectrum shows that one quartet for methylene proton and one triplet for methyl proton at δ3.98 and 1.33 respectively.

 **Synthesis of 4-(4-(dimethylamino)phenyl)-3,4-dihydro-(1,3)oxazino(5,6-h)quinolin-2-one (6)**.

4-(4-(dimethylamino)phenyl)-3,4-dihydro-(1,3)oxazino(5,6-h)quinolin-2-one has been synthesized by the cyclocondensation of 4-dimethylaminobenzaldehyde, 8-quinolinol and urea under solvent free condition using ρ-TSA at 1500C reacted to afford the corresponding products in good yields. The mass spectrum of **(6)** has shown the molecular ion peak at m/e 319 (C19H17N3O2).Other important peaks have been found at m/e 276(C17H12N2O2), 268(C16H16N2O2), 200((C11H8N2O2), 175(C10H9NO2), 149(C8H7NO2), 99(C4H5NO2). 1HNMRspectrum of **(6)** has shown one singlet for NH proton at δ 8.0. One doublet has found at δ 6.16 for proton of heterocyclic ring adjacent to NH proton. The spectrum illustrates that two aryl proton are coupled to give a pair of doublets at δ 6.47-6.88 deshielded by dimethylamino group. One multiplet is also found for aromatic proton at δ 7.14-8.86 situated in quinoline nucleus.

**MASS SPECTRAL STUDIES**

The commonly used technique for obtaining the mass spectrum of an organic compound is by electron impact. The techniques are used as for compounds which are volatile. The compound is introduced by vaporization followed by ionization by electron impact. Mass spectral studies of substituted quinoline derivatives 1-6, 3, 4-dihydro-4-phenyl-(1,3)oxazino(5,6-h)quinolin-2-one has been described in the Table 2.

**Table 2. Mass spectral fragmentation of substituted quinoline derivatives 3, 4-dihydro-4-phenyl-(1,3)oxazino(5,6-h)quinolin-2-one given below.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Compound no: | -R1 | -R2 | -R3 | -X | m/e |
| 1 | -H | -H | -H | -O | 276,225,200,175,149,99 |
| 2 | -H | -H | -NO2 | -O | 321,276,270,220,200,175,149,99 |
| 3 | -H | -H | -OH | -O | 292,276,241,191,175,149,99 |
| 4 | -OH | -H | -OH | -O | 309,292,276,200,207,149,99 |
| 5 | -OH | 0C2H5- | -H | -O | 336,320,292,276,287,235,200,99 |
| 6 | -H | -H | -N(CH3)2 | -O | 319,276,268,200,175,149,99 |

**RESULTS AND DISCUSSIONS**

Although the molecular ion formed by the initial electron ionization usually undergoes extensive fragmentation but m/e value of ion is of course, molecular weight of compound.

The mass spectrum of **3,4-dihydro-4-phenyl-(1,3)oxazino(5,6-h)quinolin-2-one (Figure 1)** has shown major peaks at m/e 276, 225, 200, 175, 149 and 99.The most intense molecular ion peak is observed at m/e 276 **(1).** A characteristic fragmentation is cleavage of pyridine nucleus often leads to most abundant ion at m/e 225 **(1.1)** in the mass spectrum of compound. The most intense base peak is found at m/e 200(**1.2**). The typical peak found at m/e 175 **(1.3)** showing the loss of quinoline moiety. There is one more significant peak is found at m/e 99 **(1.5)** due to formation of 3, 4-dihydro-1, 3-oxazin-2-one nucleus which is more stable.

Fragmentation pattern of **3,4-dihydro-4-(4-nitrophenyl)-(1,3)oxazino(5,6-h)quinolin-2-one(Figure 2)**  has shown molecular ion peak is observed at 321**(2).** Other important peaks are 321, 276,200, 175, 149, 99**.** The spectrum also showed the characteristic peak at m/e 276showing the nucleus of nitro group. Another ion at m/e 220 **(2.2)** is prominent in the mass spectrum of compounds, due to fragmentation of quinoline nucleus. The fragment at m/e 200**(2.3)** may be attributed to be formed due to cleavage of nitrobenzene nucleus, showing the loss of 123 units. The base peak has been observed at m/e 99**(2.5)** due to formationof3, 4-dihydro-1, 3-oxazin-2-one nucleus.

The mass spectrum of **3,4-dihydro-4-(hydroxyphenyl)-(1,3)oxazino(5,6-h)quinolin-2-one (Figure 3)** has shownthe major peaks at m/e 292, 276, 241, 200, 191, 175, 149,99.The most intense molecular ion peak is found at m/e 292 **(3)**. A characteristic fragmentation is found at m/e 276 **(3.1)** due to loss of hydroxyl group showing the loss of 17 units. The typical peak is found at m/e 200 **(3.3)** showing the loss of -C6H5OH group. The peak at m/e 175 **(3.5**) comprises of fragmentation of quinoline nucleus. The most significant base peak is found at m/e 99 **(3.7)** due to formation of 3, 4-dihydro-1,3-oxazin-2-one nucleus which is more stable.

In the mass spectrum of **3,4-dihydro-4-(2,4-dihydroxyphenyl)-(1,3)oxazino(5,6-h)quinolin-2-one (Figure 4)**, the fragment molecular ion peak at m/e 309 together with ion peaks at m/e 292, 276, 200, 207, 149, 99 are suggestive of the presence of substituted benzaldehyde and 3,4-dihydro-1,3-oxazin-2-one nucleus. The most intense molecular ion peak is found at m/e 309 **(4).**The other fragment at m/e 292 **(4.1)** confirms the removal of –OH group, showing the loss of 17 units. The spectrum also showed the characteristic peak at m/e 276 **(4.2)** showing the removal of both hydroxyl group substituted on benzaldehyde. Another ion at m/e 200 **(4.3)** is prominent in the mass spectrum of compounds, due to fragmentation of -C6H5 (OH)2. The fragment at m/e 207 **(4.4)** may be attributed to be formed due to cleavage of quinoline nucleus. The base peak has been observed at m/e 99**(4.6)** due to formationof3, 4-dihydro-1, 3-oxazin-2-one nucleus.

The mass spectrum of **4-(3-ethoxy-2-hydroxyphenyl)-3,4-dihydro-(1,3)oxazino(5,6-h)quinolin-2-one (Figure 5)** has shownthe major peaks at m/e 336, 320, 292, 287, 235, 200,99. The most intense molecular ion peak is found at m/e 336 **(5)**. A characteristic fragmentation is found at m/e 320 **(5.1)** due to loss of hydroxyl group showing the loss of 17 units. The typical peak is found at m/e 292 **(5.2)** showing the loss of –OC2H5 group. The peak at m/e 276 **(5.3**) indicates fragmentation of hydroxyl and ethoxy group. The fragment at m/e 235 **(5.5)** may be attributed to be formed due to cleavage of quinoline nucleus. The most significant base peak is found at m/e 99 **(5.7)** due to formation of 3,4-dihydro-1, 3-oxazin-2-one nucleus which is more stable.

The mass spectrum of **4-(4-(dimethylamino)phenyl)-3,4-dihydro-(1,3)oxazino(5,6-h)quinolin-2-one (Figure 6)**  has shown the molecular ion peak at m/e 219 (6).Other important peaks are 268, 276, 200,175, 149, 99. Fragmentation pattern has shown that dimethylamino group got fragmented showing the mass spectral peak at m/e 276 **(6.1).**The peak at m/e 200 **(6.3)** has shown that -C6H5 (NCH3)2 has been fragmented showing the loss of 121 units. The spectrum also showed the characteristic peaks at m/e 175 **(6.4)** and 149**(6.5)**.The most significant base peak is found at m/e 99 **(6.6)** due to formation of 3,4-dihydro-1,3-oxazin-2-one nucleus which is more stable.













**EXEPERIMENTAL**

Melting points were taken in an electrically heated melting apparatus and are uncorrected. Compounds were routinely checked for their purity on silica gel TLC plates and spots were visualized by iodine vapours. PMR spectra were recorded on Bruker DRX 300 MHz FT NMR spectrometer using TMS as internal reference and chemical shift values are expressed in δ units. Signals were designated as follows s singlet, d doublet, t triplet, m multiplet. Mass spectra were run on Jeol SX-102 spectrometer. All the reactions were monitored by thin layer chromatography over silica gel-G and basic alumina coated TLC plates. The structure of products 1-6 were characterized by 1H NMR and mass spectra.

**GENERAL PROCEDURE**

A mixture of 8 quinolinol (1.0mmol), aldehyde (1.0 mmol), and urea (1.5mmol) and ρ-TSA were finally mixed together. The reaction mixture was placed in a Pyrex test tube and irradiated for 4 min with a power of 700W. After cooling, the reaction mixture was washed with water and then recrystallized from EtOH or hexane to afford pure product. According to the results, and as in numerous classical multicomponent reaction can be mechanistically considered to proceed through the acylamine intermediate formed in-situ by condensation reaction of aldehyde with urea.The subsequent addition of 8-quinolinol to the acylamine, followed by the cyclisation of intermediate afforded cyclisation products.

**5.4.1. Synthesis of3, 4-dihydro-4-phenyl-(1,3)oxazino(5,6-h)quinolin-2-one (1)**

3,4-dihydro-4-(hydroxyphenyl)-(1,3)oxazino(5,6-h)quinolin-2-one has been synthesized by the cyclocondensation of hydroxybenzaldehyde (106mg), 8-quinolinol (145mg) and urea(60mg) under solvent free condition using ρ-TSA at 150 0C reacted to afford the corresponding products in good yields. White power, **Yield:** 143mg. **mp:** above 200 0C **1HNMR (DMSOd6)** δ 8.0 (s, 1H, NH), 7.25-8.86 (m, 5H, ArH), 7.06-7.14(m, 5H, ArH), 6.16 (d, 1H, CH).**MS(m/e):** 276(C17H12N2O2), 225(C14H11NO2), 200(C11H8N2O2), 175(C10H9NO2), 149(C8H7NO2), 99(C4H5NO2). **Anal.**: (C17H12N2O2) Calc:C, 73.90; H, 4.30; N, 10.14.Found: C, 73.84; H, 4.26; N, 10.10 %

 **Synthesis of3,4-dihydro-4-(4-nitrophenyl)-(1,3)oxazino(5,6-h)quinolin-2-one (2)**

3,4-dihydro-4-(4-nitrophenyl)-(1,3)oxazino(5,6-h)quinolin-2-one **(2) h**as been synthesized by the cyclocondensation of 4-nitrobenzaldehyde(151mg), 8-quinolinol(145mg) and urea(60mg) under solvent free condition using ρ-TSA at 1500C reacted to afford the corresponding products in good yields. White power, **Yield**: 143mg**. mp**: above 200 0C **1HNMR(DMSOd6)** δ 8.0(s, 1H, NH), 7.32-8.02(m, 4H, ArH), 7.25-8.86 (m, 5H, ArH), 6.16 (d, 1H, CH). **MS (m/e)**: 321 (C17H11N3O4), 276(C17H12N2O2), 270(C14H10N2O4), 220(C10H8N2O4), 200(C11H8N2O2), 175(C10H9NO2), 149(C8H7NO2), 99(C4H5NO2). **Anal.**: (C17H11N3O4)Calc: C, 63.55; H, 3.45; N, 13.08.Found: C, 63.14; H, 3.26; N, 13.00 %

 **Synthesis of 3,4-dihydro-4-(hydroxyphenyl)-(1,3)oxazino(5,6-h)quinolin-2-one**

3,4-dihydro-4-(hydroxyphenyl)-(1,3)oxazino(5,6-h)quinolin-2-one **h**as been synthesized by the cyclocondensation of 4-hydroxybenzaldehyde(122mg), 8-quinolinol(145mg) and urea(60mg) under solvent free condition using ρ-TSA at 1500 C reacted to afford the corresponding products in good yields. White power, Yield: 143mg. **mp**: above 200 0C .**1HNMR(DMSOd6)** δ 8.0(s, 1H,NH), 7.14-8.86 (m, 5H, ArH) ,6.61-6.89(m, 4H, ArH), 6.16 (d,1H, CH), 5.0(s, 1H, OH) MS(m/e): 292 (C17H12N2O3), 276(C17H12N2O2) , 241(C14H11NO3), 200(C11H8N2O2), 175(C10H9NO2), 149(C8H7NO2), 99(C4H5NO2). **Anal.:** (C17H12N2O3) Calc:C, 69.86; H, 4.14; N, 9.58.Found C, 69.14; H, 4.12; N, 9.50%

 **Synthesis of 3,4-dihydro-4-(2,4-dihydroxyphenyl)-(1,3)oxazino(5,6-h)quinolin-2-one (4)**

3,4-dihydro-4-(2,4-dihydroxyphenyl)-(1,3)oxazino(5,6-h)quinolin-2-one has been synthesized by the cyclocondensation of 2,4-dihydroxybenzaldehyde(138mg), 8-quinolinol(145mg) and urea (60mg)under solvent free condition using ρ-TSA at 150 0C reacted to afford the corresponding products in good yields. White power, **Yield:** 143mg. **mp**: above 200 0C .**1HNMR (DMSOd6)** δ 8.0(s, 1H, NH), 7.14-8.86 (m, 5H, ArH), 6.16 (d, 1H, CH), 6.08-6.72(m, 3H, ArH), 5.0(s, 1H, OH). **MS (m/e):** 336(C19H16N2O4), 292 (C17H12N2O3), 276(C17H12N2O2), 207(C10H9NO4), 200(C11H8N2O2), 175(C10H9NO2), 149(C8H7NO2), 99(C4H5NO2). **Anal.:** (C17H12N2O4)Calc: C, 66.23; H, 3.92; N, 9.09. Found C, 66.14; H, 3.89; N, 9.00%

 **Synthesis of 4-(3-ethoxy-2-hydroxyphenyl)-3,4-dihydro-(1,3)oxazino(5,6-h)quinolin-2-one(5)**

4-(3-ethoxy-2-hydroxyphenyl)-3,4-dihydro-(1,3)oxazino(5,6-h)quinolin-2-one has been synthesized by the cyclocondensation of 2-hydroxy-3-ethoxyhydroxybenzaldehyde(166mg), 8-quinolinol(145mg) and urea(60mg) under solvent free condition using ρ-TSA at 150 0C reacted to afford the corresponding products in good yields. White power, Yield: 143mg. mp: above 200 0C .**1HNMR (DMSOd6)** δ 8.0(s, 1H, NH), 6.41-6.59(m, 3H, ArH), 7.14-8.86 (m, 5H, ArH), 6.16 (d, 1H, CH), 5.0(s, 1H, OH) 3.98(q, 2H, CH2), 1.33(t, 3H, CH3). **MS (m/e):** 336(C19H16N2O4) 292 (C17H12N2O3), 276(C17H12N2O2), 287(C16H17NO4), 200(C11H8N2O2), 235(C12H13NO4), 149(C8H7NO2), 99(C4H5NO2). **Anal.:** (C19H16N2O4) Calc:C, 67.85; H, 4.79; N, 8.33.Found C, 67.14; H, 4.69; N, 8.20 %.

 **Synthesis of 4-(4-(dimethylamino)phenyl)-3,4-dihydro-(1,3)oxazino(5,6-h)quinolin-2-one (6)**.

4-(4-(dimethylamino)phenyl)-3,4-dihydro-(1,3)oxazino(5,6-h)quinolin-2-one has been synthesized by the cyclocondensation of 4-dimethylaminobenzaldehyde(149mg), 8-quinolinol(145mg) and urea(60mg) under solvent free condition using ρ-TSA at 150 0C reacted to afford the corresponding products in good yields. White power, Yield: 133mg. mp: above 2000C. **(1HNMR DMSOd6)**δ 8.0(s, 1H, NH), 7.14-8.86 (m, 5H, ArH), 6.47-6.88(m, 4H, ArH), 6.16 (d, 1H, CH), 2.85(s, 3H, CH3). **MS (m/e):** 319 (C19H17N3O2 m/e 276(C17H12N2O2), 268(C16H16N2O2), 200((C11H8N2O2), 175(C10H9NO2), 149(C8H7NO2), 99(C4H5NO2). **Anal.:** (C19H17N3O2)Calc: C, 81.46; H, 5.37; N, 13.16. Found: C, 81.44; H, 5.29; N, 13.10; %

**BIOLOGICAL ACTIVITY**

 **Anti-inflammatory activity**

The anti-inflammatory activity of compounds **(1 – 6)** was carried out by the procedure described . The activity profile of these compounds is reported in ***Table 3***

**Table 3 Anti-inflammatory activity of substituted 3, 4-dihydro-4-phenyl-(1,3)oxazino(5,6-h)quinolin-2-one derivatives.**

|  |  |  |
| --- | --- | --- |
| **Compound No.** | Mean Difference | **Percent Activity*(100mg/Kg)*** |
| **1** | 22.01 | 45 |
| **2** | 24.35 | 39 |
| **3** | 21.19 | 32 |
| **4** | 17.73 | 49 |
| **5** | 23.18 | 40 |
| **6** | 25.63 | 37 |

**Anti-convulsant activity**

The anti-inflammatory activity of compounds **(1 – 6)** was carried out by the procedure described . The activity profile of these compounds is reported in **Table *4.***

**Table 4. Anti-Convulsant activity ofsubstituted 3, 4-dihydro-4-phenyl-(1,3)oxazino(5,6-h)quinolin-2-one derivatives.**

 **(Dose 60mg/Kg)**

|  |  |
| --- | --- |
| Sl. No | Protection (%)**After 2 hours** |
| Positive controlCarbamazipine | 80 |
| **1** | 40 |
| **2** | 0 |
| **3** | 60 |
| **4** | 20 |
| **5** | 0 |
| **6** | 60 |

 **Cardiovascular Activity**

The anti-inflammatory activity of compounds **(1 – 6)** was carried out by the procedure described . The activity profile of these compounds is reported in ***Table 5.***

**Table 5.** Cardiovascular Activity of **substituted 3, 4-dihydro-4-phenyl-(1,3)oxazino(5,6-h)quinolin-2-one derivatives.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Sl. No.** | **Resting BP***(mmHg)* | **Change in BP** | **Change in HR** | CO |
| Immediate | Delayed |
| **1** | 130 | -50 | -3 | -20 | ↓ |
| **2** | 165 | -40 | 20 | -6 | ↓ |
| **3** | 105 | -30 | -12 | No change | ↓ |
| **4** | 115 | -20 | -52 | No change | ↓ |
| **5** | 170 | -60 | 60 | -8 | ↓ |
| **6** | 130 | -40 | -12 | -24 | ↓ |

 **REFERENCES**

|  |  |
| --- | --- |
|  | (a) Chauhan, P. M. S.; Srivastava, S. K. Curr. Med. Chem. **2001**, 8, 1535-1542; (b) Balasubramanian, M.; Keay, J. G. In Comprehensive *Heterocylic Chemistry* 2; Kartritzky, A. R., Rees, C. W.; Eds.; Pergamon :New York, NY, **1996**; Vol. 5, p 245. |
|  | Morizava, Y.; Okazoe, T.; Wang, S. Z.; Sasaki, J.; Ebisu, H.; Nishikawa, M.; Shinyama, H. *J. Fluorine Chem*. **2001**, 109, 83-86. |
|  | Ferrarini, P. L.; Mori, c.; Badawneh, M.; Calderone, V.; Greco, R.; Manera, C.; Martinelli, A.; Nieri, P.; Saccomanni, G. Eur. *J. Med. Chem.***2000**, 35, 815-819. |
|  | Dabri, M.; Delbari, a. s., Bazgir, A. *Synlett***2007**, 821. |
|  | SzatmariI.; Hetenyi A.; Lazar L; Funlop F. *J. Heterocyclic. Chem.***2004**, 41, 367. |
|  | Larsen R.D.; Corley E.G.;King A O.; CarrolJ.D.;Davis P.; Verhoeven T. R.; Reiderp.j.; Labelle M.; Gauthier J. Y.; Xiang Y. B.; Zamboni R J. *J. Org.Chem.***1996**, 61, 3398. |
|  | Chen Y. L.; Fang K. C.; Shen J.Y.; Hsu S. L.; Tzeng C. C. *J. Med. Chem.***2001**, 44, 2374. |
|  | (a) Kalluraya B.; Sreenivasa S. Farmaco 1998, 53, 399. (b) Doube D.; Blouin M.; Brideau C.; Chan C .; Desmarias S.; Eithier D.; Falgueyret J. P.; Friesen R. W.; Girrard M.; Girard Y.; Guay J.; Tagari P.; Young R. N*. Bioorg. Med. Chem. Lett*. **1998**, 8, 1255. |
|  | Maguire M. P.; Sheets K. R.; McVety K.; Spada A. P.; Zilberstein A. *J. Med. Chem*. **1994**, 37, 2129. |
|  | Latif N.; Mishriky N.; Assad F. M. Aust. J. Chem. **1982**, 35, 1037. |
|  | Patel M.; Ko S. S.; Mchugh R. J. Jr.; Markwalder J. A.; Srivastava A. S.; Cordova B. C.; Klabe R. M.; Erickson-Viitanen S.; Trainor G. L.; Seitz S. P. *Bioorg. Med. Chem. Lett*. **1999**, 9. 2805. |
|  | Ikeda K.; Morimoto T.; Sekia M. Chem. Pharma. Bull. **1980**, 1178 |
|  | (a) Yadav L. D. S.; Kapoor R. J. Org. Chem. **2004**, 69, 8118. (b) Yadav L. D.S.; Saigal S.; Pal D. R.J.Chem. Res (S) **1998**, 307. |
|  | Cimarelli C.; Palmieri G.; Volpini E. Can. *J. Chem*. **2004**. 82, 1314. |
|  | SzatmariI.; Hetenyi A.; Lazar L; Fulop F. *J. Heterocycl. Chem*. **2004**, 41, 367. |
|  | Dabiri, M.; Delbari, A. S.; Bazgir, A. *Synlett***2007**, 821. |
|  | (a) Kappe, C. O. J. Org. Chem. 1997, 62, 7201. (b) Huang, S.; Pan. Y.; Zhu, Y.; Wu, A. Org. Lett. 2005, 7, 3797. (c) Cristau, P.; Vors, J.; Zhu, J. P. *Tetrahedron Lett*. **2003**, 44, 5575. |
|  | Dondoni, A.; Massi, A.; Minghini, E.; Bertolasi, V. *Tetrahedron***2004**, 60, 2311. |
|  | Waxman L.; Darke P. L. *Antiviral Chem. Chemother*. **2000**, 11, 1. |
|  | Giris A. S. *Phamazie***2000**, 466. |
|  | Patel M.; Mchugh R. J.; Beverly Jr .*Bioorg. Med. Chem. Lett*.**1999**, 9, 3221. |
|  | El-Shafei H. A.; Badr-eldin S. M. Egypt *J. Microbiol*. **1994**, 27,353. |
|  | Noverty, J,; Collins, C, H.; Starts, F. W. *J. Pharm. Sci*. **1974**, 63, 1264-1267. |
|  | Roma, G.; Braccio. M. D.; Grossi, G.; Mattioli, F; Ghia, M. Eur. *J. Med. Chem*. **2000**, 35, 1021-1026. |
|  | Gottlieb, D., Shaw, P D., Eds.; Springer: New York, NY, Antibiotics II, Biosynthesis **1967**; Vol. 2, pp 105 |