*Available on line www.jocpr.com*

# *Journal of Chemical and Pharmaceutical Research*

*J. Chem. Pharm. Res., 2010, 2(1): 489-496*

**ISSN No: 0975-7384**

# Synthesis and biological evaluation of some dibenzazepine analogs

**Gopal Krishna Rao[a*], Ranjit Kaur*and PN Sanjay Pai [b]**

*[a]Department of Pharmaceutical Chemistry, Al-Ameen College of Pharmacy, Hosur Road, Near Lalbagh Main Gate, Bangalore-560027*
*[b]Department of Quality Assurance, Al-Ameen College of Pharmacy, Hosur Road, Near Lalbagh Main Gate, Bangalore-27*

---

## Abstract

Dibenzazepines and analogs exhibit a wide variety of biological activities like antidepressant, anticonvulsant, antipsychotic, antioxidant, antimicrobial etc.In the present study we have synthesized new analogs of dibenzazepines. The structures of these synthesized compounds were confirmed by IR, NMR, Mass and CHN analysis. All the values and results of this spectral and elemental analysis were found to be in the normal range. These compounds were evaluated for antimicrobial activity.

**Key words**: 5H-dibenzo(b,f)azepine-5-{4-benzylidene-2-methylimidazole-5-one}-carboxamide, characterization, antimicrobial activity.

---

## Introduction

Drug development has been one of the most prominent research areas in the field of pharmaceutical industry. Consequently, the development of methodologies useful for the assembly of molecules containing heterocyclic templates continues to attract the attention of both the academic and industrial communities. There is always need for the safer antibacterial agents and research efforts are going on for developing safer antibacterial agents. The synthesis of newer class of anti-bacterial and anti-fungal agents is in need of time, especially against drug-resistant bacteria and fungi, such as gram-positive and gram-negative strains, which are responsible for a number of serious infections in the acute and chronic care units in hospitals.

There is a continuous need for the development of new compounds capable of interacting with neurotrophin receptors and which shows physicochemical properties different from the neurotrophins[1]. One such class of drugs bearing tricyclic moiety, a privileged structure with number of successful molecules have been described as useful building blocks for the assembly of various heterocyclic rings. According to literature, majority of tricyclics and related compounds are known for their potential biological and pharmacological properties viz antidepressants, antihistamines, anticonvulsants, sedatives etc [2,3,4].

Synthesis of imidazoline from oxazolin-5(4H)-ones and primary amines under different experimental conditions has been reported. Imidazolones and their derivatives are known for their potential biological and pharmacological properties. Imidazolidinones have been also reported to possess potent CNS depressant activity. Some imidazoles and substituted imidazolones have been reported to possess MAO inhibitory and anticonvulsant activities. Some new imidazolinone derivatives bearing sulphonamide moiety have been synthesized by the condensation of some known sulpha drugs with oxazolones of different aromatic aldehydes. The therapeutic importance of imidazolinones has been reported [5,6]. These observations prompted us to synthesize the title compounds with presumption that incorporation of substituted imidazole moiety would produce new compounds with significant antimicrobial activity.

## Experimental Section

***Antibacterial activity: [7,8]***

The method followed was Agar Diffusion method. The standard cultures of gram positive *Staphylococcus aureus* (ATCC 9144) and *Streptococcus fecalis* (ATCC 35550) and gram negative *Escherichia coli* (ATCC 25322) and *Pseudomonas pneumoniae* (ATCC 15380) were used for determining the antibacterial activity of all the synthesized compounds. The results are calculated as zone of inhibition in mm and tabulated **(Table-1).**

***Antifungal activity: [7,8]***

The antifungal activity was tested against two strains of fungi namely
*Candida Albicans* (ATCC 2091) and *Aspergillus Fumigatis* (ATCC 13073) using agar diffusion method.
The results are calculated as zone of inhibition in mm and tabulated **(Table-2).**

**Table-1: Antibacterial studies of 5H-dibenzo(b,f)azepine-5-{4-benzylidine-2-methylimidazo le -5-one}-carboxamide.**

| Compd. code | Zone of Inhibition (mm) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *E. coli* | | | *K.pneumoniae* | | | *S. aureus* | | | *S.fecalis* | | |
| | 25 | 50 | 75 | 25 | 50 | 75 | 25 | 50 | 75 | 25 | 50 | 75 |
| | Concentration in µg/ ml | | | | | | | | | | | |
| 4a | - | - | - | - | - | - | - | - | 10 | - | - | - |
| 4b | - | - | - | - | - | 12 | 12 | 18 | 20 | - | - | - |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4c | - | 15 | 20 | - | - | - | - | 15 | 20 | - | 20 | 30 |
| 4d | - | - | - | - | - | - | - | - | - | - | - | - |
| 4e | - | - | - | - | 12 | 18 | - | - | 12 | - | - | 12 |
| 4f | - | - | - | - | 10 | 12 | - | - | - | - | - | - |
| 4g | 12 | 18 | 20 | - | - | 20 | - | - | 12 | - | - | - |
| 4h | - | - | - | - | 10 | 22 | - | - | 15 | - | 20 | 25 |
| 4i | - | - | 12 | - | - | - | - | 10- | 12 | - | - | - |
| 4j | - | - | - | - | - | 8 | - | - | 14 | - | - | - |

(-) Nil activity
Ciprofloxacin and flucanazole were used as standard drugs.

**Table-2: Antifungal studies of 5H-dibenzo(b,f)azepine-5-{4-benzylidine-2-methylimidazole-5-one}-carboxamide.**

| **Compd. code** | **Zone of Inhibition (mm)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ***Candida Albicans*** | | | | | ***Aspergillus Fumigatis*** | | | | |
| | **5** | **10** | **25** | **50** | **75** | **5** | **10** | **25** | **50** | **75** |
| | **Concentration in µg/ ml** | | | | | | | | | |
| 4a | - | - | - | 10 | 16 | - | - | 8 | 10 | 12 |
| 4b | - | - | - | 11 | 15 | - | 8 | 11 | 15 | 19 |
| 4c | - | - | 10 | 15 | 20 | 6 | 8 | 11 | 17 | 20 |
| 4d | - | - | - | 10 | 15 | - | - | 8 | 11 | 15 |
| 4e | - | - | - | 8 | 10 | - | - | - | - | - |
| 4f | - | - | - | 7 | 11 | - | - | 7 | 13 | 15 |
| 4g | - | - | 6 | 15 | 17 | - | - | - | 10 | 12 |
| 4h | - | - | 14 | 15 | 17 | 6 | 10 | 11 | 12 | 15 |
| 4i | - | - | - | - | - | - | 7 | 10 | 16 | 17 |
| 4j | - | - | - | - | 6 | 5 | 8 | 10 | 15 | 17 |

(-) Nil activity

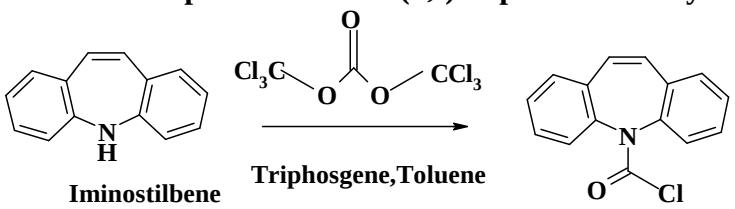
**Table-3: MIC values of selected compounds expressed in µg/ ml**

| **Compound code** | **Concentration expressed in µg/ ml** | | | | | |
|---|---|---|---|---|---|---|
| | ***K.pneumoniae*** | ***E.coli*** | ***S.fecalis*** | ***S.aureus*** | ***Candida*** | ***A.Fumigatis*** |
| **4c** | 50 | 100 | >100 | >100 | 1.6 | 50 |
| **4g** | 100 | 50 | 100 | >100 | 6.25 | 50 |

Melting points of the synthesized compounds were determined using Thiele's melting point apparatus and are uncorrected. The IR spectra of the synthesized compounds were recorded using KBr pellets in range of 4000-400 $cm^{-1}$ on a Fourier Transform IR Spectrometer (Shimadzu 8700) and the frequencies are recorded in wave numbers. $^1$H-NMR (400 MHz) spectra were recorded in DMSO-$d_6$ in Amx-400 liquid state PMR spectrometer (Astrazeneca, Bangalore). Chemical shifts *(δ)* are reported in parts per million downfield from internal reference tetramethylsilane (TMS). Mass spectrum was recorded by LC-MS (Shimadzu, Quest, Bangalore). Purity of the compounds was checked by thin layer chromatography. Elemental analysis was found to be within the limits of permissible errors.

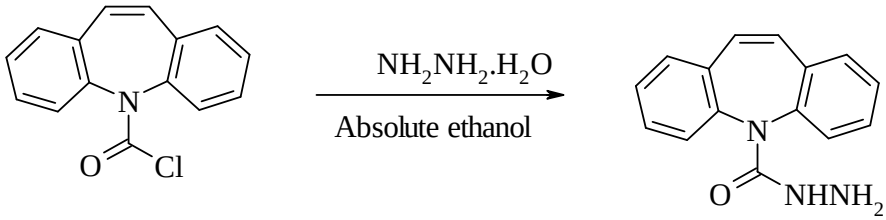
**Scheme**

**Step-1: 5H-dibenzo(b,f)azepine-5-carbonyl chloride (1)**

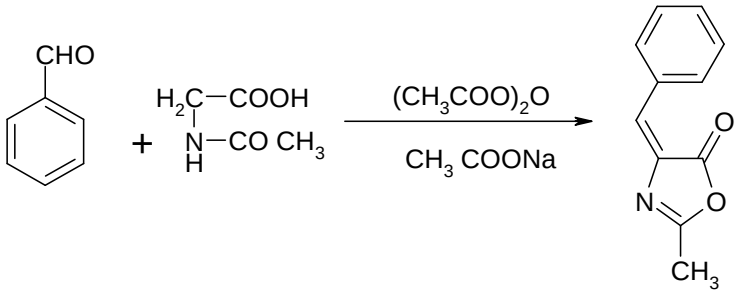



**Iminostilbene** **5H- dibenzo(b,f)azepine-5-carbonyl chloride**

**Step-2 : 5H-dibenzo(b,f)azepine-5-acid hydrazide (2)**




**Step:3 General method for the preparation of oxazolones (3)**




**Step-4: 5H-dibenzo(b,f)azepine-5-{4substituted-benzylidine-2-methylimidazole-5-one}-carboxamide (4a-j)**

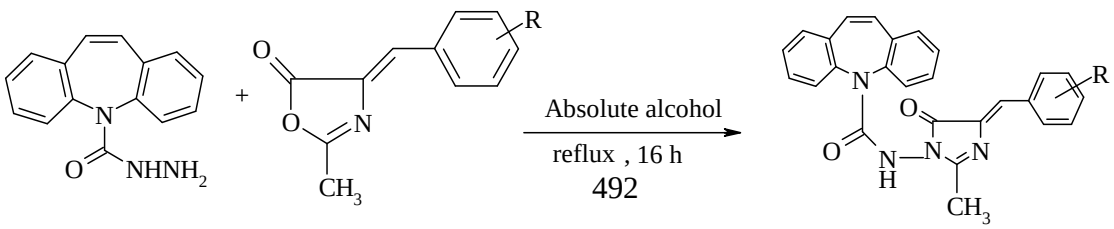
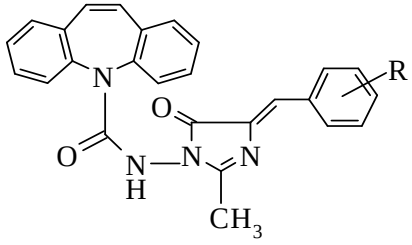


**Table No. 4: Synthesized compounds**



| Compd. code | R |
|---|---|
| 4a | H |
| 4c | 4-OH 3-OCH |
| 4d | 2,4-$(OCH_3)_2$ |
| 4e | 3,4,5-$(OCH_3)_3$ |
| 4f | 4-Cl |
| 4g | 4-$OCH_3$ |
| 4h | 4-OH |
| 4i | 4-$NO_2$ |
| 4j | $C_6H_5CH$=CH- |
| 4k | O-Cl |

**Procedure for synthesis**: [9,10]

*Synthesis of 5H-dibenzo(b,f)azepine-5-carbonyl chloride (1)*
Iminostilbene (0.005 mole) and triphosgene (0.001 mol) were taken in a three-necked flask containing 30 ml of toluene. The mixture was stirred and refluxed under nitrogen over two hours until the solution became light yellow colour. It is then cooled to room temperature. The product obtained was filtered and air dried. Percent yield obtained was 90 and melting point was 148-150 $^{O}C$.

*Synthesis of 5H-Dirbenzo (b,f) azepine-5-acid hydrazide (2)*
A mixture of 5H-dibenzo(b,f) azepine -5-carbonyl chloride (1) (0.01 mole) and hydrazine hydrate (0.01 mole, 80%) in absolute ethanol was stirred for 1hr and then refluxed for 30min. on a water bath. The contents were cooled and product obtained was filtered, washed with cold ethanol, dried and purified by recrystallisation from methanol to give 5H-Dirbenzo (b,f) azepine-5-acid hydrazide. Yield 75%, m.p 178$^0$C. TLC (methanol: toluene, 2:8, $R_f$ (0.20 ).

*General method for the preparation of oxazolones (3)*
A mixture of benzaldeyde (0.05 mole) freshly distilled, acetyl glycine (0.05mol), acetic anhydride (0.1mol) and sodium acetate (0.1mol) was heated on electric hot plate with constant shaking in a conical flask. As soon as the mixture was liquified completely, the flask was heated on a water bath for three hours. The contents of the flask were cooled, ethanol (25mL) was added slowly and and the mixture was kept overnight in the refrigerator. The separated solid was filtered, washed with ice-cold alcohol, dried and recrystallised from alcohol.

Similarily various oxazolones were prepared using different aromatic aldehydes.

*General method for the preparation of 5H-dibenzo(b,f)azepine-5-{4substituted-benzylidine-2-methylimidazole-5-one}-carboxamides (4)*

Oxazolone (0.01mole) was heated with an equimolar quantity of acid hydrazide in absolute alcohol at a temperature between 65-75˚C for 15-16h. The mixture was cooled and poured into crushed ice. The product was filtered and recrystallised from ethanol to give compound **(4a-j)** which is confirmed by the difference in m. p and $R_f$ values. All the title compounds are synthesized by similar procedure and physical constants are tabulated **(Table-5).**

**Table No. 5: Analytical data of the synthesized compounds**

| Compound code | Molecular Formula | Molecular Weight | Melting Point (˚C) | Yield (%) | $R_f$ value* |
|---|---|---|---|---|---|
| 4a | $C_{26}H_{20}N_40_2$ | 420 | 86 | 76 | 0.84 |
| 4c | $C_{27}H_{22}0_4N_4$ | 466 | 110 | 65 | 0.77 |
| 4d | $C_{39}H_{24}O_4N_4$ | 480 | 95 | 64 | 0.81 |
| 4e | $C_{29}H_{29}N_4O_5$ | 511 | 130 | 95 | 0.69 |
| 4f | $C_{26}H_{20}N_4O_2Cl$ | 455 | 120 | 100 | 0.75 |
| 4g | $C_{27}H_{23}N_4O_3$ | 451 | 125 | 72 | 0.75 |
| 4h | $C_{26}H_{21}N_4O_3$ | 437 | 148 | 65 | 0.84 |
| 4i | $C_{26}H_{20}N_4O_4$ | 466 | 120 | 74 | 0.74 |
| 4j | $C_{28}H_{22}N_4O_2$ | 434 | 95 | 76 | 0.74 |

*cyclohexane:ethyl acetate

**Spectral data**

**4a: IR bands($cm^{-1}$):** 3228(NH), 3047(Ar-H), 2977(C-H), 1782(C=O), 1685(C=O), 1670(C=C), 1242(C-O), 1203(C-C), 1149(C-N) **$^1$H-NMR :**δ7.0-7.8(m, Ar-H, 13H) δ6.3 (s,CONH, 1H) δ3.0(s, $CH_3$, 3H) δ6.7-6.8, (m, -CH=CH-, 2H δ6.5(s, =CH, 1H ). Mass: MS(m/z) 421(M+1) and other peaks are observed at 343 and 340.

**4c: IR bands ($cm^{-1}$):** 3380.02 (N-H and O-H str), 3055.03.61 (ArC-H str), 1647.10 (C=O str), 1589.23 (C=N str), 1330.79 (C-N str), 1167.82 (C-C str).

**4d: IR bands($cm^{-1}$):** 3220.90 (N-H str), 3047.32 (ArC-H str), 1665.42 (C=O str), 1598.88 (C=N str), 1325.01 (C-N str), 1268.11 (C-O str), 1162.03 (C-C str).

**4e: IR bands($cm^{-1}$):** 3378.09 (N-H str), 3052.14 (ArC-H str), 1715.56 (C=O str), 1663.49 (C=N str), 1330.79 (C-N str), 1240.14 (C-O str), 1049.20 (C-C str). **$^1$H-NMR δ:** 8.67 (s, 1H, NH), 8.26 (benzylic C=CH), 6.62-7.67 (m, 10H, ArH), 6.61 (d, 2H, CH=CH), 3.35-3.03 (s, 3x$OCH_3$, 9H ), 2.95 (s, 3H, $CH_3$).

**Elemental analysis**: Calc: C (68.23%), H (5.09%), N (10.98%), Found C (68.66%), H (4.96%), N (11.69%).

**4f: IR bands($cm^{-1}$):** 3228(NH), 3047(Ar-H), 2977(C-H), 1782(C=O),1685(C=O), 1670(C=C), 1242(C-O), 1203(C-C), 1149(C-N).

**4g: IR bands($cm^{-1}$):** 3379.05 (N-H str), 3052.14 (ArC-H str), 1666.36 (C=str), 1583.45 (C=N str), 1330.79 (C-N str), 1273.90 (C-O str), 1109.96 (C-C str). **$^1$H-NMR δ:** 8.49 (s, 1H, NH), 8.25 (benzylic C=CH), 7.35-6.58 (m, 8H, ArH), 6.06 (d, 2H, CH=CH), 3.67-3.36 (s, 1x $OCH_3$, 3H ), 2.95 (s, 3H, $CH_3$).

**4h: IR bands($cm^{-1}$):** 3379.05 (N-H str), 3330.84 (O-H str), 3049.25 (ArC-H str), 1710.74 (C=O str), 1680.85 (C=N str), 1328.86 (C-N str), 114178 (C-C str). **$^1$H-NMR δ:** 9.77 (s, 1H, OH), 8.62 (s, 1H, NH), 8.26 (benzylic C=CH), 7.72-6.61 (m, 12H, ArH + CH=CH), 2.95 (s, 3H, $CH_3$ ).

**4i: IR bands($cm^{-1}$):** 3383.87 (N-H str), 3052.14 (ArC-H str), 1708.81 (C=O str), 1588.27 (C=N str), 1487.01 (C-N str), 1337.54 (Ar-$NO_2$ str), 1109.96 (C-C str) **$^1$H-NMR δ:** 8.87 (s, 1H, NH), 8.35 (benzylic C=CH), 7.65- 6.60 (m, 12H, ArH + CH=CH), 2.95 (s, 3H, $CH_3$ ) 1583.45 (C=C str), 1329.83 (C-N str), 1110.92 (C-C str).

**4j**: **IR bands($cm^{-1}$):** 3380.98 (N-H str), 3052.14 (ArC-H str), 1584.41 (C=O str), 1487.98 (C=N str), 1331.76 (C-N str), 1111.89 (C-C str).

## Results and Discussion

The synthesized compounds were screened for antibacterial and antifungal activities by the standard methods.

In the antibacterial screening of the synthesized compounds 4a to 4k, most of them showed very mild activity at various concentrations as compared to the standard. It is seen that these compounds showed some activity against gram negative as compared to gram positive microorganisms. Within the series **4g** with **(p-methoxy)** substitution was found to be the most active against *E.coli*. Among all the compounds **4c & 4g**, the activity is slightly enhanced due to the presence of electron donating groups as compared to electron withdrawing groups. For further confirmations MIC was carried out for the compounds **4c & 4g.** The MIC values reveal that these compounds were more effective against fungus than bacteria as shown in table-2. But both the compounds showed no activity against *K.pneumoniae* and *S.fecalis* and none of the compounds in the series showed activity greater than the standard. Thus based on the above observations we can conclude that only at high concentrations the compound may act as good antibacterial candidate as compared to the standard drug.

In the antifungal screening some of the compounds have shown promising activity as compared to the standard. Among **4a to 4k** compounds **4c** and **4h** showed highest activity against both the species. These observations indicate that electron donating groups enhances the activity as compared to electron withdrawing group. It is also observed that substitution at the para position of the intermediate, oxazolone may affect the activity to a certain extent. Methoxy derivatives have proved to be a better candidate than others.

## Acknowledgement

The authors would like to thank Prof. B. G. Shivananda Principal, Al-Ameen College of Pharmacy, Bangalore for providing support and necessary facilities. Astra Zeneca, Bangalore,

and Quest Research & Training Institute, Bangalore for providing help in obtaining the various spectra. Authors are also thankful to Sangenomics Research Labs Pvt Ltd, Bangalore for providing facilities for biological studies.

## References

[1] www.wikipedia.org accessed on 9th Jan **2010**
[2] LS Tsann; YW Lin; TC Chou; X Zhang; VA Bacherikov; C Ching-Huang. *J. Med. Chem*., **2006,** 49: 3710-18.
[3] H Panwar; RS Verma; VK Srivastava; Ashok Kumar. *Indian .J. Chem*., **2006,** 45B, 2099-104.
[4] S Fustero; J Gonzalez; C Pozo. *Molecules.*, **2006,** 11**,**583.
[5] SA Siddiqui; SR Bhusare; DV Jorikot; RP Pawa; YB Vibhute. *Bull Korean Chem Soc.,* **2001**,22 (9), 1033-1036.
[6] J Hashmukh; P Upadhyay; K Denish; AJ Baxi. Euro J Med Chem., **2003,** 38, 837-840.
[7] JPR Cruikshank; BP Duguid ; RHHS Marmion. *Medical Microbiology*., vol-2, Churchill Livingstone, New York; **1995**:190
[8] A Cremer. *Microbiological methods.* 6th ed. Butterworth and Co., London **1991**;235.
[9] PV Bhatt; PM Patel. *Ind.J.Chem*., **2005,** 44 B, 2082.
[10] CN Prasad; M Khagga; Javed Iqbal. *OCAIJ.*, **2007**,3(3), 112-117.