Synthesis and Evaluation of 2-Chloro-3-[3-(6-Methyl-1H-Benzimidazol-2-Yl)-4, 5-Dihydro-1H-Pyrazol-5-Yl] Quinolines as Potent Antimicrobial Agents

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ABSTRACT

A new series of 2-chloro-3-[3-(6-methyl-1H-benzimidazol-2-yl)-4,5-dihydro-1H-pyrazol-5-yl]quinoline (Va-k) have been synthesized by the reaction of 3-(2-chloroquinolin-3-yl)-1-(6-methyl-1H-benzimidazol-2-yl)prop-2-en-1-one (IVa-k) with hydrazine hydrate in ethanol and glacial acetic acid. The synthesized compounds were characterized by their IR, 1H NMR and Mass spectral studies. Further, compounds were screened for their antimicrobial activity by cup plate method, using Ciprofloxacin and Fluconazole as a standard drugs. Results of the activities reveal that, compounds exhibited moderate to good antibacterial and antifungal activities.

Keywords: 6-Methylbenzimidazoles, Chalcones, Pyrazolines, Antimicrobial activity.

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Received 01 November 2018, Accepted 16 November 2018
INTRODUCTION

Benzimidazole is a heterocyclic aromatic organic compound. Owing to the vast importance and varied bioactivities exhibited by benzimidazoles, efforts are made from time to time to get libraries of those compounds and screen them for potential biological activities. These observations have encouraged us to synthesize some new products containing the benzimidazole moiety hoping to obtain new compounds with potential biological activity [1]. The benzimidazole has been a crucial pharmacophore and privileged structure in medicinal chemistry. Encompassing a plethora of useful biological activities such as antimicrobial [2], antioxidant[3], antiviral [4], antihypertensive [5], antiprotozoal [6], anti-inflammatory [7] and antifilarial agents [8].

Pyrazolines are well known important nitrogen containing five membered heterocyclic compounds. They possess a wide spectrum of biological activities such as anticancer [9], antioxidant [10], antibacterial [11], antifungal [12], antidepressant [13-15], anti-inflammatory [16], anticonvulsant [17], antitumor [18], analgesic properties [19].

Pyrazolines are used extensively as useful synthon in organic synthesis. Among varied pyrazoline derivatives, 2-Pyrazolines appear to be the foremost often studied pyrazoline type compounds. A classical synthesis of those compounds involves the base catalyzed Claisen-Schmidt condensation of aryl methyl ketones and aldehydes to give chalcones that endure a subsequent cyclization reaction with hydrazines affording 2-Pyrazolines [20].

It is known that 4,5-dihydro-1H-pyrazole and its derivatives exhibit extensive biological and pharmacological activities. Thus considerable efforts are made to design and synthesize functional pyrazoline derivatives over the past few years. Although there are reports of synthesis of these substituted heterocycles, the development of synthetically vital functionalized new pyrazolines remains a challenge and has become a far tried analysis endeavor [21].

Antimicrobial agents are one in every of the foremost necessary weapons in the resistance of infection caused by microorganism strains. In the last few years, increase the resistance of microorganisms toward antimicrobial agents is a serious health problem, so there is a need for safe, effective and novel antimicrobial agents [22].

Therefore, the present study was designed to synthesize and evaluation of 2-chloro-3-[3-(6-methyl-1H-benzimidazol-2-yl)-4, 5-dihydro-1H-pyrazol-5-yl] quinolines as potent antimicrobial agents by adopting the standard procedure.
Scheme

R= (a)-H; (b)-6-CH₃; (c)-7-CH₃; (d)-8-CH₃; (e)-6-Meo; (f)-7-Meo; (g)-8-Meo; (h)-6-Cl;
(i)-7-Cl; (j)-6-Br; (k)-6-F.

Reagents and conditions:- (i) Lactic acid, 4N HCl, MW irradiation 320 minutes       (ii) K₂Cr₂O₇, H₂SO₄ (25% v/v) 2 hrs, (iii) 10% NaOH, 2-chloroquinoline-3-carbaldehydes, Ethanol, 0.5 hrs, (iv) Hydrazine hydrate, Ethanol, Glacial acetic acid, 4 hrs.

EXPERIMENTAL

By open capillary tube method, melting points were checked and are uncorrected. By using TLC plates, TLC analysis was performed. By using KBr method, on a Shimadzu FTIR 8400S
spectrometer IR spectra were recorded. On Bruker Avance II of 400 MHz NMR spectrometer, NMR spectra and Mass spectra on a Waters, Q-TOF Micro ma SS spectrometer.

**Synthesis of 1-(6-methyl-1H-benzimidazol-2-yl)ethanol (II)**

4-methyl-o-phenylenediamine (0.01,mole) (I) was mixed with Lactic acid (0.01 mole) and 4N hydrochloric acid under Phillips conditions and heated to reflux in a synthetic microwave system, at an intensity of 65% (450 W) for 320 minutes. TLC was monitored, after completion of reaction period; cooled mixture was neutralized by sodium bi carbonate. The solid was separated, filtered and recrystallization was carried out from absolute alcohol. m.p-186-88°C [23-25].

**Synthesis of 1-(6-methyl-1H-benzimidazol-2-yl)ethanone (III)**

To a solution of 1-(6-methyl-1H-benzimidazol-2-yl)ethanol (II) (8.8g, 50 mmole) in dilute H$_2$SO$_4$ (5%, 40 ml) was added a solution of K$_2$Cr$_2$O$_7$ (44g, 150 mmole) in dilute H$_2$SO$_4$ (25%, 80 ml) with constant stirring, drop wise for 20 minutes at an ambient temperature. The stirring further continued for 2 hours. On completion of reaction period (TLC monitored), separated solid (a chromium complex) dispersed in water and adjusted a pH up to 6 to 6.5 with aqueous ammonia (1:1). Solid product then washed, dried and recrystallized by ethyl acetate to obtain a purified compound. m.p-195-97°C [26-27].

**Synthesis of 3-(2-chloroquinolin-3-yl)-1-(6-methyl-1H-benzimidazol-2-yl) prop-2-en-1-one (IVa-k)**

1-(6-methyl-1H-benzimidazol-2-yl)ethanone (III) (10 mm ole, 1.74g) and substituted 2-chloroquinoline-3-carbaldehydes (10 mm ole, 1.91g) were mixed in 30 ml of aqueous Na OH (10%). Continuing stirring up to 30 minutes, TLC was checked for completion of reaction. Solid filtered was dried. In addition, purified by recrystallization from a suitable solvent [28-34].

Similarly, **3-(2-chloroquinolin-3-yl)-1-(6-methyl-1H-benzimidazol-2-yl) prop-2-en-1-one (IVa-k)** were synthesized.

**IVb: yield 77%, m.p-250-52°C; IR (KBr): 3275, 3064, 2918, 1658, 1579, 1427, 1217, 763 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.52 (s, 3H, CH$_3$), 2.79 (s, 3H, CH$_3$), 5.14 (s, 1H, NH-benzimidazole), 6.63 (d, 1H, 1-ethylene), 7.73 (d, 1H, 1-ethylene), 7.10-7.68 (m, 3H, benzimidazole), 7.29-8.52 (m, 4H, quinoline). MS: $m/z$ 361.80 (M••).**

**IVe: yield 86%, m.p-262-64°C; IR (KBr): 3271, 3192, 2848, 1664, 1554, 1234, 804 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.49 (s, 3H, CH$_3$), 3.92 (s, 3H, OCH$_3$), 5.14 (s, 1H, NH-benzimidazole), 6.63 (d, 1H, 1-ethylene), 7.73 (d, 1H, 1-ethylene), 7.07-7.37 (m, 3H, benzimidazole), 7.52-8.53 (m, 4H, quinoline). MS: $m/z$ 377.80 (M••).**
IVh: yield 88%, m.p-278-80°C; IR (KBr): 3282, 2850, 1660, 1413, 1334, 802,719 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 2.30 (s, 3H, CH₃), 5.21 (s, 1H, NH-benzimidazole), 6.58 (d, 1H, 1-ethylene), 7.18 (d, 1H, 1-ethylene), 7.04-7.49 (m, 3H, benzimidazole), 7.67-8.23 (m, 4H, quinoline). MS: m/z 382.20 (M⁺ +1).

Synthesis of 2-chloro-3-[3-(6-methyl-1H-benzimidazol-2-yl)-4, 5-dihydro-1H-pyrazol-5-yl]quinoline (Va-k)

To a solution of 3-(2-chloroquinolin-3-yl)-1-(6-methyl-1H-benzimidazol-2-yl)prop-2-en-1-one (3.68g, 0.01 mole) was dissolved in ethanol (40 ml) and glacial acetic acid (10 ml). Hydrazine hydrate (0.75g, 0.015 mol) was then added and the reaction mixture refluxed for 4 hrs on a water bath. The solvent was reduced to half its volume. The crystalline product which separated out on cooling was filtered, washed with water, dried and crystallized from ethanol [35]. Similarly, 2-chloro-3-[3-(6-methyl-1H-benzimidazol-2-yl)-4, 5-dihydro-1H-pyrazol-5-yl]quinoline (Va-k) were synthesized.

Vb : Yellow solid, yield 55%, m.p-168-70°C; IR (KBr): 3190, 3053, 1664, 1579, 1479, 1228, 767 cm⁻¹; ¹H NMR(CDCl₃, 400 MHz): δ 1.89 (d, 2H, methylene), 2.63 (s, 3H, CH₃), 2.74 (s, 3H, CH₃), 3.59 (d, 1H, methine), 5.44 (d, 1H, NH-benzimidazole), 7.04 (s, 1H, hydrazid) 7.37-7.55 (m, 3H, benzimidazole), 7.69-8.80 (m, 4H, quinoline). MS: m/z 375.80 (M⁺).

Vd: Brown solid, yield 60%, mp 174-76°C; IR (KBr): 3217, 3047, 1658, 1543, 1479, 1228, 767 cm⁻¹; ¹H NMR(CDCl₃, 400 MHz): δ 2.03 (d, 2H, methylene), 2.18 (d, 3H, CH₃), 2.38 (s, 3H, CH₃), 3.75 (d, 1H, methine), 5.29 (d, 1H, NH-benzimidazole), 7.03 (s, 1H, hydrazid) 7.35-7.46 (m, 3H, benzimidazole), 7.70-8.35 (m, 4H, quinoline). MS: m/z 375.82 (M⁺).

Vf: Brown solid, yield 64%, mp 183-85°C; IR (KBr): 3216, 3086, 1624, 1570, 1448, 1288, 763 cm⁻¹; ¹H NMR(CDCl₃, 400 MHz): δ 2.17 (d, 2H, methylene), 2.40 (s, 3H, CH₃), 3.73 (s, 3H, OCH₃), 3.92 (s, 1H, methine), 5.31 (d, 1H, NH-benzimidazole), 7.01 (s, 1H, hydrazid) 7.53-7.80 (m, 3H, benzimidazole), 8.12-8.54 (m, 4H, quinoline). MS: m/z 391.83 (M⁺).

Vh: Brown solid, yield 52%, mp 190-92°C; IR (KBr): 3227, 3066, 1627, 1570, 1427, 1217, 806, 736 cm⁻¹; ¹H NMR(CDCl₃, 400 MHz): δ 2.17 (d, 2H, methylene), 2.48 (s, 3H, CH₃), 3.73 (d, 1H, methine), 5.34 (d, 1H, NH-benzimidazole), 7.04 (s, 1H, hydrazid) 7.37-7.53 (m, 3H, benzimidazole), 7.58-8.24 (m, 4H, quinoline) MS: m/z 397.25 (M⁺ +1).
Table 1: Physical Characterization of 2-chloro-3-[3-(6-methyl-1H-benzimidazol-2-yl)-4, 5-dihydro-1H-pyrazol-5-yl] quinoline (Va-k)

| Sl. No | Compound Code | R     | Molecular Formula      | Molecular Weight | M.P °C | % Yield |
|--------|---------------|-------|------------------------|-----------------|--------|---------|
| 1      | Va            | H     | C_{20}H_{16}ClN_{5}    | 361.82          | 162-164| 50      |
| 2      | Vb            | 6-CH3 | C_{21}H_{18}ClN_{5}    | 375.85          | 168-170| 55      |
| 3      | Vc            | 7-CH3 | C_{21}H_{18}ClN_{5}    | 375.85          | 171-173| 57      |
| 4      | Vd            | 8-CH3 | C_{21}H_{18}ClN_{5}    | 375.85          | 174-176| 60      |
| 5      | Ve            | 6-Ome | C_{21}H_{18}ClN_{5}O   | 391.85          | 180-182| 67      |
| 6      | Vf            | 7-Ome | C_{21}H_{18}ClN_{5}O   | 391.85          | 183-185| 64      |
| 7      | Vg            | 8-Ome | C_{21}H_{18}ClN_{5}O   | 391.85          | 187-189| 59      |
| 8      | Vh            | 6-Cl  | C_{20}H_{15}Cl_{2}N_{5} | 396.27     | 190-192| 52      |
| 9      | Vi            | 7-Cl  | C_{20}H_{15}Cl_{2}N_{5} | 396.27     | 194-196| 54      |
| 10     | Vj            | 6-Br  | C_{20}H_{15}BrClN_{5}  | 440.72         | 204-206| 70      |
| 11     | Vk            | 6-F   | C_{20}H_{15}ClFN_{5}   | 379.81         | 198-200| 62      |

Biological Evaluation [36-41]

Antibacterial activity:
The synthesized compounds are tested for antibacterial activity against two Gram-positive bacteria viz., *Bacillus subtilis*, *Staphylococcus aureus*, and two Gram-negative bacteria viz., *Proteus Mirabilis* and *Escheria coli*. The standard drug used was antibiotic Ciprofloxacin and DMSO as a solvent. Test compounds and the standard drug were used at a concentration 100µg/ml and 50µg/ml. The zones of inhibition of compounds were recorded once incubation of twenty four hours at 37°C.
The results of the antibacterial activity reveals that, the compounds Vb, Vd and Vf displayed relatively high antibacterial activity, while compounds Vc, Ve, Vh and Vi showed reasonable antibacterial activity. Va, Vj and Vk showed moderate activity and the remaining compound Vg showed low activity.

Antifungal activity:
The antifungal activity of the products has been screened against two fungi viz., *Aspergillus Niger* and *Candida albicans* by cup-plate method. Fluconazole was used as a standard drug and DMSO as a solvent. Test compounds and standard drug were used at a concentration of 100µg/ml and 50µg/ml. The zones of inhibition of compounds were recorded once incubation of forty eight hours at 25°C.
Further from antifungal activity results, compounds Vb, Vd and Vf showed excellent results for antifungal activity, while the compounds Vc, Ve, Vh and Vi also showed high antifungal activity. Va, Vj and Vk showed moderate activity and remaining compound Vg exhibited low activity.
Table 2: Antibacterial and antifungal activity of synthesized compounds (Va-k)

| Compound | Antibacterial activity a, b |  |  |  |  |
|----------|----------------------------|----------------|----------------|----------------|----------------|
|          | B. subtilis | S. aureus | P. mirabilis | E. coli | A. niger | C. albicans |
| Va       | 12/10 | 11/09 | 10/08 | 11/10 | 08/06 | 09/07 |
| Vb       | 24/22 | 25/24 | 23/21 | 24/23 | 18/16 | 19/17 |
| Vc       | 17/15 | 16/14 | 15/14 | 16/15 | 14/12 | 15/13 |
| Vd       | 25/23 | 24/21 | 22/21 | 25/23 | 17/15 | 18/16 |
| Ve       | 18/16 | 17/14 | 14/13 | 15/14 | 13/11 | 14/12 |
| Vf       | 23/22 | 22/20 | 24/22 | 22/20 | 18/16 | 17/15 |
| Vg       | 07/05 | 08/05 | 10/07 | 09/06 | 06/03 | 07/04 |
| Vh       | 18/16 | 17/15 | 16/14 | 19/17 | 13/10 | 12/11 |
| Vi       | 17/16 | 17/15 | 19/17 | 18/16 | 14/13 | 13/11 |
| Vj       | 11/09 | 10/08 | 10/09 | 10/07 | 09/07 | 08/06 |
| Vk       | 13/11 | 11/10 | 12/09 | 12/10 | 10/08 | 09/07 |
| Ciprofloxacin b | 26 | 26 | 26 | 26 | - | - |
| Fluconazole b | - | - | - | - | 23 | 23 |

a Zone of inhibition at 100µg/ml.
b Zone of inhibition at 50µg/ml.

Minimum inhibitory concentration was found at 40µg/ml concentration.

RESULTS AND DISCUSSION

All compounds were screened for their antibacterial activity against two Gram-positive bacteria viz., Bacillus subtilis, Staphylococcus aureus, and two Gram-negative bacteria viz., Proteus Mirabilis and Escheria coli by the Cup-plate method using standard drug Ciprofloxacin. Similarly all the synthesized compounds were also screened for their antifungal activity against two fungi viz., Aspergillus Niger and Candida albicans by standard procedure using standard drug Fluconazole. Compounds Vb, Vd and Vf displayed relatively high antibacterial and antifungal activity. Minimum inhibitory concentration (MIC) was determined by broth dilution method and it was found at 40µg/ml concentration.

CONCLUSION

A new series of compounds of 2-chloro-3-[3-(6-methyl-1H-benzimidazol-2-yl)-4, 5-dihydro-1H-pyrazol-5-yl]quinoline (Va-k) were synthesized and characterized. The synthesized compounds were also screened for antimicrobial activity. The results of antimicrobial testing revealed the compounds Vb, Vd and Vf have shown promising antimicrobial activity. Therefore, this work would be fruitful matrix for the development of novel class of antimicrobial agents.

ACKNOWLEDGEMENT

The authors thank the Rajiv Gandhi University of Health Sciences, Bangalore for financial support.
and also the Principal and management of the BLDEA SSM College of Pharmacy and Research Center, Vijayapur, Karnataka for the provision of facilities.

REFERENCES

1. Gayathri B, Hipparagi SM, Ramjith US and Jacob CM. Microwave assisted synthesis of fluoro, chloro 2-substituted benzimidazole thiazine derivatives for antibacterial and analgesic activities. International Journal of Research in Pharmacy and Science. 2012; 2 (3): 146-158.

2. Joshi CK, Jain R, Dandia A and Sharma K. Synthesis of [1,2,4] triazino[4,3-a] benzimidazol-4(10h)-ones as antimicrobial agents. Indian Journal of Chemistry. 1989; 28 (B): 698-701.

3. Shivakumar B, Anil Kumar KK, Madawali IM, Hugar S and Kalyane NV. Synthesis and antioxidant activity of new pyrazoles of 6-methylbenzimidazoles. World Journal of Pharmaceutical Research. 2018; 7 (16): 1017-1028.

4. Pandey VK, Gupta VD and Tiwari DN. 1,2-disubstituted benzimidazoles as potential antiviral agents. Indian Journal of Heterocyclic Chemistry. 2005; 14: 217-220.

5. Kumar JR, Jawahar J and Pathak DP. Synthesis of benzimidazole derivatives: as anti-hypertensive agents. E-Journal of chemistry. 2006; 3 (4): 278-285.

6. Valdez J, Cedillo R, Hernandez-Campos A, Yepez LN, Hernandez-Luis F, Navarrete-Vazquez G et al. Synthesis and antiparasitic activity of 1H-benzimidazole derivatives. Bioorganic and Medicinal Chemistry Letters. 2002; 12: 2221–2224.

7. Narayan reddy A, Patnaik S, Kalyane N and Reddy VM. Synthesis of some substituted imidazolino-[3,4-a]-2,3-dihydroimidazoles/benzimidazoles as possible non steroidal, non-acidic anti-inflammatory agents. Indian Journal of Heterocyclic Chemistry. 2003; 12: 347-350.

8. Divakar KJ, Rao MK, Shrivastava R and Reddy AB. Synthesis and anti filarial activity of benzimidazole-2-carbamates carrying an amino acid side chain at the 5(6)-position. Indian Journal of Chemistry. 1989; 28 (B): 252-260.

9. Nimavat KS, Popat KH and Joshi HS. Synthesis, anticancer, anti tubercular and antimicrobial activity of 1-substituted 3-aryl-5-(3’-bromophenyl)-pyrazo lines. Indian Journal of Heterocyclic Chemistry. 2003; 12: 225-28.
10. Venkatesh P, Hari Prasath K, Sharfudeen S, Soumya V, Spandana V, Priyanka J. Synthesis of coumarin fused pyrazoline-5-one derivatives and screening for their antimicrobial and antioxidant activity. Journal of Pharm Research. 2012; 5 (5): 2875-77.

11. Seham YH. Synthesis, Antibacterial and antifungal activity of some new pyrazoline and pyrazole derivatives. Molecules. 2013; 18: 2683-711.

12. Shailesh HS and Pankaj SP. Synthesis and biological activity of some novel phenyl pyrazoline derivatives. Chem Sci Trans. 2012; 1 (3): 632-37.

13. Palaska E, Aytemir M, Uzbay T and Dilek E. Synthesis and antidepressant activities 3,5-diphenyl-2-pyrazolines. European Journal of Medicinal Chemistry. 2001; 36: 539-43.

14. Rajendra Prasad Y, Lakshmana Rao A, Prasoona L, Murali K and Ravi Kumar P. Synthesis and antidepressant activity of some 1,3,5-triphenyl -2-pyrazolines and 3- (2-hydroxynaphthalen-1-yl) -1,5-diphenyl-2-pyrazolines. Bioorganic and Medicinal Chemistry Letters. 2005; 15: 5030-34.

15. Palaska E, Erol D and Demirdamar R. Synthesis and antidepressant activities of some 1,3,5- triphenyl-2-pyrazolines. European Journal of Medicinal Chemistry. 1996; 31: 43-47.

16. Ozdemir Z, Kandilici BH, Gumucel B, Calis U and Bilgin AA. Synthesis and studies on antidepressant and anticonvulsant activities of some 3-(2-furyl)-pyrazoline derivatives. European Journal of Medicinal Chemistry. 2007; 42: 373-79.

17. Ramesh B and Sumana T. Synthesis and anti-inflammatory activity of pyrazolines. E-Journal of Chemistry. 2010; 7 (2): 514-16.

18. Jainey PJ and Bhat IK. Antitumor, analgesic, and anti-inflammatory activities of synthesized pyrazolines. Journal of Young Pharm. 2012; 4 (2): 82–7.

19. Sridhar S and Rajendra prasad Y. Synthesis and analgesic studies of some new 2-pyrazolines. E-Journal of Chemistry. 2012; 9 (4): 1810-15.

20. Ragini G, Neetu G and Anshu J. Improved synthesis of chalcones under ultrasonic irradiation. Indian Journal of Chemistry. 2010; 49 (B): 351-355.

21. Tiwari AK, Fatma S, Bishnoi A, Srivastava A, Tripathi CKM, Banerjee B. Synthesis characterization and in vitro antimicrobial activity of some novel 4,5-dihydro-1H-pyrazoline derivatives. Indian Journal of Chemistry. 2017; 56 (B): 317-324.

22. Indira MM, Navanath VK, Gaviraj EN and shivakumar B. Synthesis and antimicrobial activity of some new pyrimidines of 6-chlorobenzimidazoles. Oriental Journal of Chemistry. 2018; 34 (3): 1633-1637.
23. Reddy VM and Reddy KR. Synthesis and biological evaluation of some novel-3-(5-substituted benzimidazol-2-yl)-5-arylisoxazolines. Chinese Chemical Letters. 2010; 21: 1145-1148.

24. Wang Z. Phillips-Ladenburg Benzimidazole Synthesis, In: Comprehensive Organic Name Reactions and Reagents. 2010; 496: 2197-2199.

25. Sharmila AG, Shivakumar B and Gaviraj EN. Synthesis and evaluation of new pyrazolines of benzimidazole as potent analgesic and anti-inflammatory agents. Der Pharma Chemica. 2016; 8 (5): 33-37.

26. Dubey PK, Ramaiah K, Grossert JS, Hooper DL, and Ramanatham J. Studies on synthesis of 2-acetylbenzimidazole and related benzimidazole derivatives. Journal of Indian Chemical Society. 1999; 76: 140-144.

27. Kumar PK and Dubey PK. Studies on preparation of 2-Acetylbenzimidazole. Der Pharma Chemica, 2012; 4 (3):1292-1295.

28. Dubey PK, Ramanatham J, Kumar R and Kumar RC. Studies on synthesis of 1-alkyl/aryl-2-cinnamoylbenzimidazoles. Indian Journal of Heterocyclic Chemistry. 2000; 9: 259-262.

29. Singh RM and Srivastava A. Vilsmeier-Haack reagent: A facile synthesis of 2-chloro-3-formylquinolines from N-arylacetamides and transformation into different functionalities. Indian Journal of Chemistry. 2005; 44 (B): 1868-1875.

30. Ali MM, Sana SA, Tasneem, Rajanna KC and Saiprakash PK. Ultrasonically accelerated vilsmeier-hak cyclisation and formylation reactions. Synthitic communications. 2002; 32 (9): 1351-1356.

31. Rajakumar P and Raja R. Synthesis and photo physical properties of chiral dendrimers with quinoline surface group via click chemistry Tetrahedron Letters. 2010; 51: 4365-4370.

32. Tabassum S, Kumara THS, Jasinski JP, Millikan SN, Yathirajan HS, Ganapathy PS S. et al. Synthesis, crystal structure, ABTS radical-scavenging activity, antimicrobial and docking studies of some novel quinoline derivatives. Journal of Molecular Structure. 2014; 1070: 10-20.

33. Ramesh E, Sree Vidhya TK and Raghunathan R. Indium chloride/silica gel supported synthesis of pyrano/ thiopyranoquinolines through intra molecular imino Diels–Alder reaction using microwave irradiation. Tetrahedron Letters. 2008; 49: 2810-2814.

34. Nyerges M, Pinter A, Viranyi A, Blasko G and Toke L. Synthesis of pyrrolo[3,4-c] quinolines by 1,5-electrocyclisation of non-stabilised azomethine ylides. Tetrahedron. 2005; 61: 8199-8205.
35. Sawhney SN, Vir D and Gupta A. Synthesis and anti-inflammatory activity of some 2-(5-aryl-4,5-dihydropyrazol-3-yl)- and 2-(2-amino-6-arylpyrimidine-4-yl) benzimidazoles. Indian Journal of Chemistry. 1990; 29 (B): 1107-1112.

36. Kalirajan R, Rathore L, Jubie S, Gowramma B, Gomathy S and Sankar S. Microwave assisted synthesis of some novel pyrazole substituted benzimidazoles and evaluation of their biological activities. Indian Journal of Chemistry. 2011; 50 (B): 1794-1799.

37. Seham YH. Synthesis antibacterial and antifungal activity of some new pyrazoline and pyrazole derivatives. Molecules. 2013; 18: 2683-2711.

38. Radha Y, Manjula A, Madhav Reddy B and Vitthal Rao B. Synthesis and biological activity of novel benzimidazoles. Indian Journal of Chemistry. 2011; 50 (B): 1762-1773.

39. Venkatesan P and Sumathi S. Piperidine mediated synthesis of n-heterocyclic chalcones and their antibacterial activity. Journal of Heterocyclic Chemistry. 2010; 47: 81-84.

40. Malleshappa N, Suresh A, Harun P, Aravind B, Monika G and Azit Z. Synthesis, antimicrobial and cytotoxic activity of novel azetidine-2-one derivatives of 1H-benzimidazole. Arabian Journal of Chemistry. 2014; 7: 219–226.

41. Jayanti R, Janardan Y, Ravindra K and Yogendra KS. Microwave assisted transformation of benzimidazolyl chalcones into N¹- substituted pyrazolines and evaluation of their antimicrobial activities. Indian Journal of Chemistry. 2010; 49 (B): 989-993.