# A review on the antibacterial potential of cantabiline-based derivatives

**Noora Thamer Abdulaziz, Yasser Fakri Mustafa***

*Pharmaceutical Chemistry Department, College of Pharmacy, Mosul University, Nineveh, Iraq.*

*Corresponding author: Dr.yassermustafa@uomosul.edu.iq

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## ABSTRACT

**Objective:** The target of this review study is to highlight the importance of cantabiline and its derived compound as antibacterial agents. Also, to take into consideration the characteristic structural features that can enhance the capability of these compounds to fight pathogenic bacteria.

**Methods:** The recently available reports concerning the antibacterial activity of cantabiline-derived compounds have been reviewed efficiently. The outcomes of these reports have been also analyzed to detect the proper substituents that can enhance the target activity.

**Results:** The hand-availability of antibacterial agents, as well as their inadvisable utilization, resulted in a mounting health problem named multi-drug resistant bacterial strains. To handle this emerging issue, the design and synthesis of agents with a powerful ability to fight such bacterial strains is becoming a pressing need.

**Conclusion:** This review study has concluded that cantabiline and its derived compounds may represent hopeful antibacterial agents. Also, they can address several mechanisms acquired by bacteria for resisting the currently-available antibacterial agents.

**Keywords:** Coumarin, pathogenic bacteria, cantabiline, antibacterial activity.

**مراجعة حول الإمكانات المضادة للبكتيريا للمشتقات القائمة على الكانتابلين**


**الخلاصة**

**الغاية من الدراسة:** ان الهدف من هذه الدراسة الاستعراضية هو تسليط الضوء على أهمية الكانتابلين ومركباته المشتقة كعوامل مضادة للجراثيم. أيضًا ، لمراعاة السمات الهيكلية المميزة التي يمكن أن تعزز قدرة هذه المركبات على محاربة البكتيريا المسببة للأمراض.

**طريقة العمل:** تمت مراجعة التقارير المتوفرة مؤخرًا بشأن النشاط المضاد للبكتيريا للمركبات المشتقة من الكانتابلين بكفاءة. تم تحليل نتائج هذه التقارير أيضًا لاكتشاف البدائل المناسبة التي يمكن أن تعزز النشاط المستهدف.

**النتائج:** أدى التوافر اليدوي للعوامل المضادة للبكتيريا بالإضافة إلى استخدامها غير المرغوب فيه إلى مشكلة صحية متزايدة تسمى السلالات البكتيرية المقاومة للأدوية المتعددة. للتعامل مع هذه المشكلة الناشئة ، أصبح تصميم وتوليف العوامل ذات القدرة القوية على محاربة هذه السلالات البكتيرية حاجة ملحة.

**الاستنتاج:** خلصت هذه الدراسة المراجعة إلى أن الكانتابلين ومركباته المشتقة قد تمثل عوامل مضادة للجراثيم مأمولة. أيضًا ، يمكنهم معالجة العديد من الآليات التي اكتسبتها البكتيريا لمقاومة العوامل المضادة للبكتيريا المتوفرة حاليًا.



**الكلمات المفتاحية:** الكومارين ، البكتيريا المسببة للأمراض ، الكانتابلين ، النشاط المضاد للبكتيريا.


## Introduction

Infections caused by pathogenic bacteria are the most frequently observed type of infectious diseases worldwide. The mortality and morbidity because of bacterial infections are mountingly increasing, and this is considered as one of the most alerting issues [1]. Many Gram-negative (GN) and Gram-positive (GP) infectious bacteria such as *Staphylococcus aureus* (GP-Sa), *Streptococcus pneumonia* (GP-Sp), *Escherichia coli* (GN-Ec), and *Pseudomonas aeruginosa* (GN-Pa) are accountable for the most documented infectious issues of the hospital and community [2]. Based on WHO data released in 2017, the infection of the highest disease burden is *Mycobacterium tuberculosis*, which was results in

approximately 1.8 million deaths every year [3].

Coumarin-derived products constitute a large family of natural and synthetic compounds that sharing the chemical nucleus made of fused benzene fused with alpha-pyrone ring [4]. Many compounds holding this chemical moiety in their structures have displayed encouraging biological activities. These potentials involving antitumor [5], antibacterial [6], antifungal [7], anticoagulant [8], estrogenic [9], vasodilator [10], sedative [11], analgesic and hypothermic activity [12], and anti-inflammatory [13] effects.

Derivatives of 7-hydroxy-4-methyl coumarin (Cantabiline, Figure 1) have been of mounting interest in pharmaceutical chemistry, particularly because of their roles as potent antibacterial and antifungal agents [14].

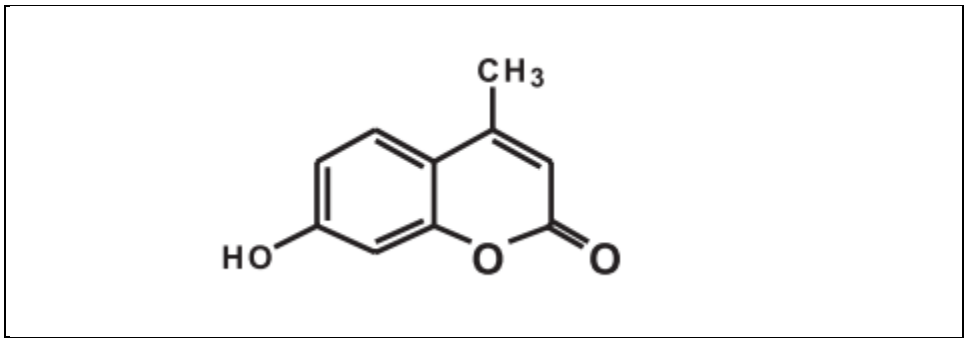
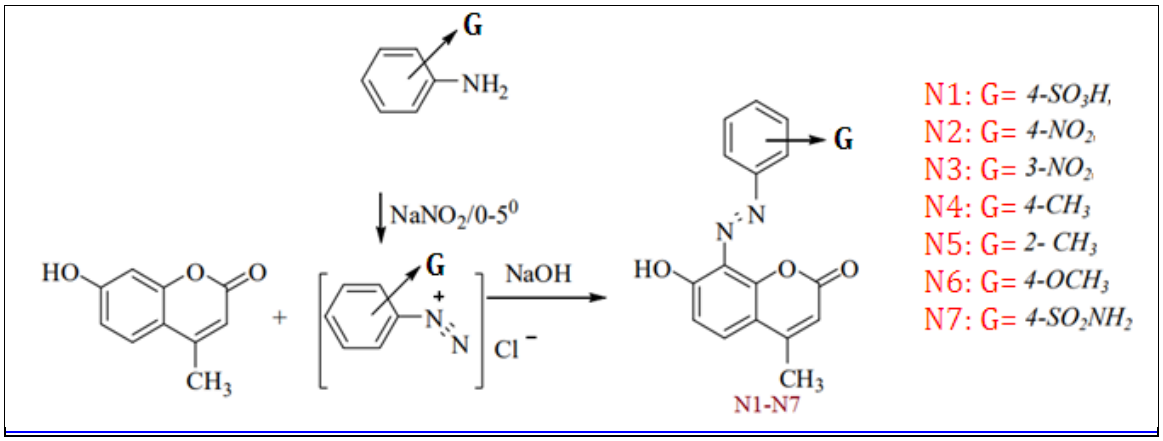


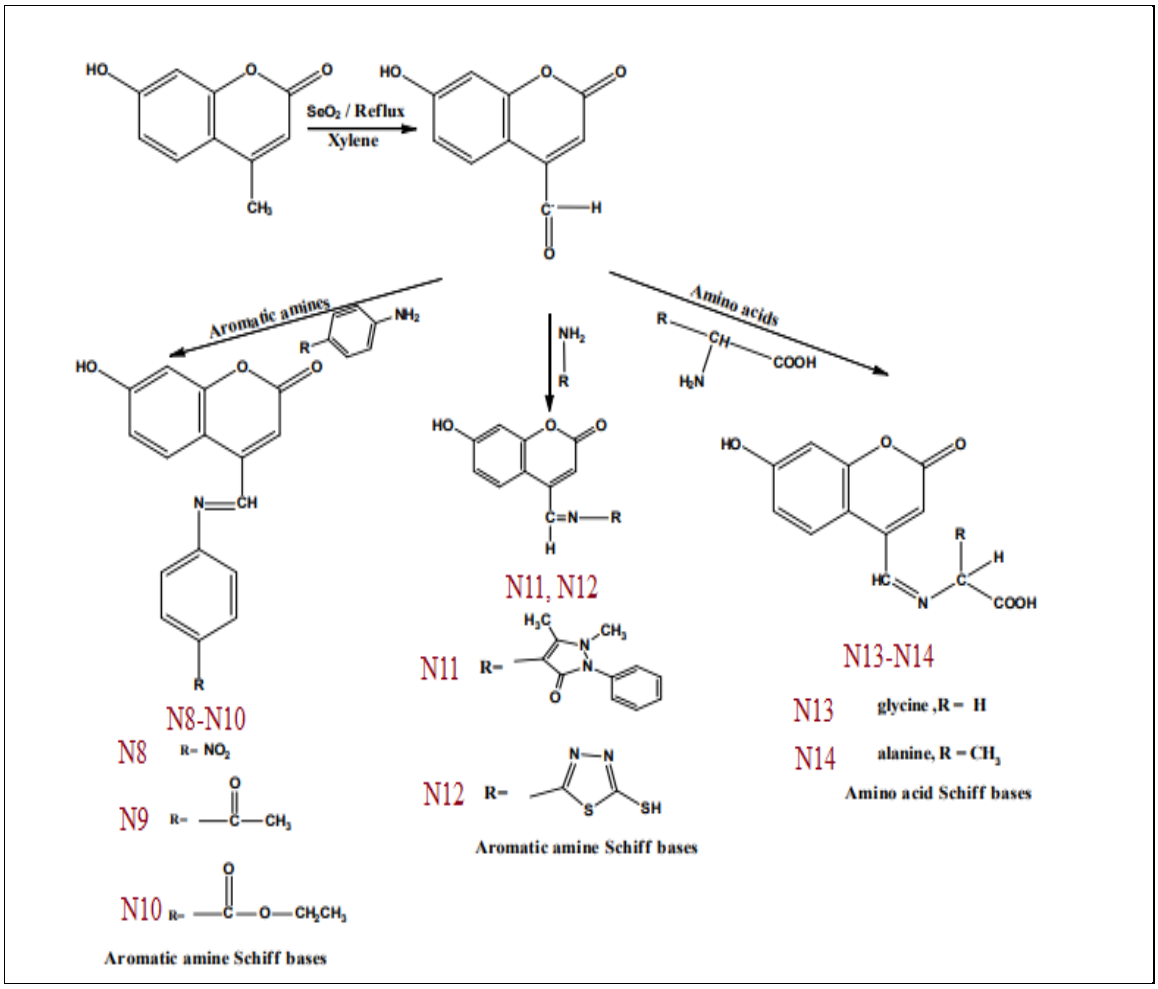

**Figure 1: Chemical backbone of 7-hydroxy-4-methyl coumarin (cantabiline).**

Sudhir *et al* have prepared a panel of novel cantabiline derivatives (Scheme 1), herein designated as **N1**-**N7**. The authors have investigated the antibacterial activity of these newly synthesized compounds versus four standard bacterial strains; namely *Bacillus subtilis*, GN-Ec, GN-Pa, and GP-Sa. The results of this investigation showed that these cantabiline derivatives exhibited acceptable antibacterial activity versus all the test pathogenic standard bacterial strains. Besides, compound **N7** revealed the most potent effect. The authors have concluded that the presence of an azo bond as well as sulfonamide substituents on the cantabiline nucleus may increase the antibacterial potential of these compounds [15].




**Scheme 1: Synthetic route of N1-N7 compounds as proposed by Sudhir *et al.***

Hussein *et al.* have recorded, as displayed in Scheme 2, the design and preparation of seven new Schiff-bases using cantabiline as a precursor. These new derivatives, herein designated as **N8-N14**, have been examined for their antibacterial activity versus many GP and GN bacterial strains. The results revealed that these cantabiline derivatives have good activity. Besides, compound **N14** exhibited the best potential versus GP-Sa, *Micrococcus luteus*, and GN-Ec [16].




**Scheme 2: Synthesis of seven novel cantabiline-Schiff base conjugates as recorded by Hussein *et al.***

Prabhakara *et al.* have synthesized a group of metal complexes derived from cantabiline-Schiff base hybridization. These novel complexes, herein designated as **N15**-**N17** (Figure 2), have been evaluated for their antibacterial effect versus two pathogenic standard bacterial strains, including GN-Pa and *Proteus mirabilis*. The authors revealed that all the newly prepared metal chelates exhibited a hopeful antibacterial activity. The cupper (**$Cu^{+2}$**) complexes showed a more potent effect than those of cobalt (**$Co^{+2}$**) and nickel (**$Ni^{+2}$**) complexes [17].

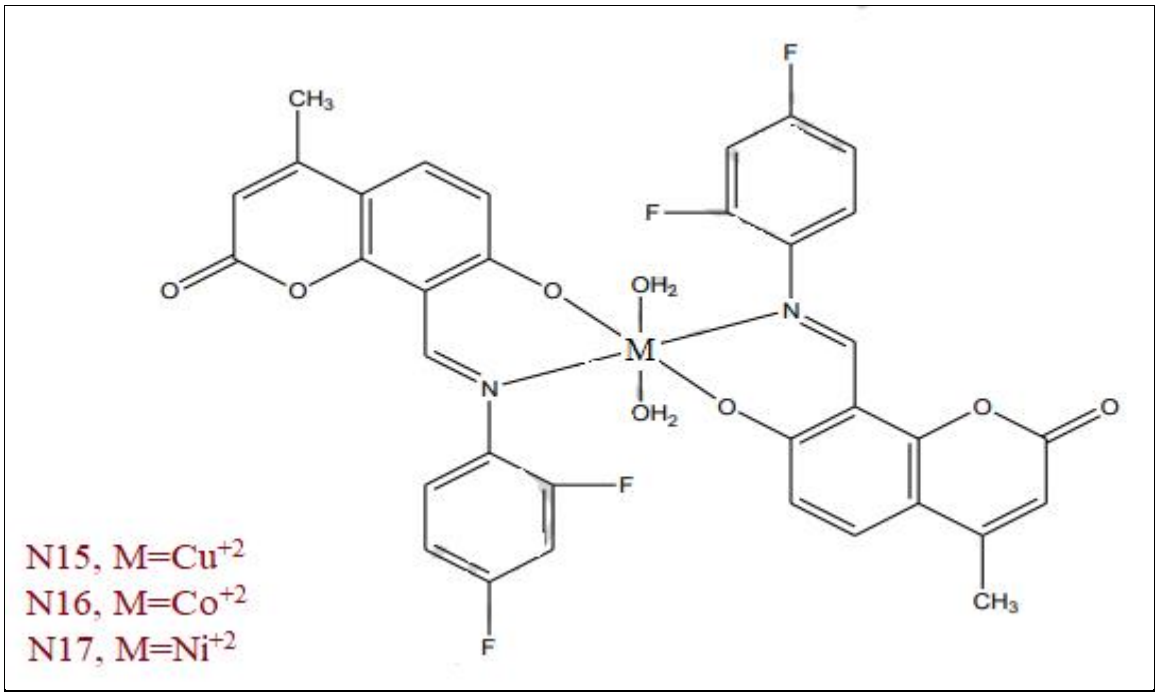



**Figure 2: Proposed chemical structure of metal chelates prepared by Prabhakara *et al.***

Kraljević *et al*. have designed and synthesized a panel of 1,2,3-triazole-cantabiline conjugates by ecologically-friend technique. The authors have tested the synthesized coumarins for their antibacterial effect versus GP bacteria including GP-Sa, *Enterococcus faecalis, Enterococcus faecium* resistant to vancomycin, and GN bacteria including GN-Ec, *Acinetobacter baumannii*, GN-Pa, and β-lactamase-releasing *Klebsiella pneumonia*. The examined compounds revealed some activity against the test pathogenic bacterial strains. Compound **N18** (Figure 2) containing piperazine and morpholine substituents revealed remarkable effect versus many bacterial strains, especially GN-Pa. Compound **N19** (Figure 2) that is coupled to butylene revealed a good effect versus *methicillin-resistant* GP-Sa [18].

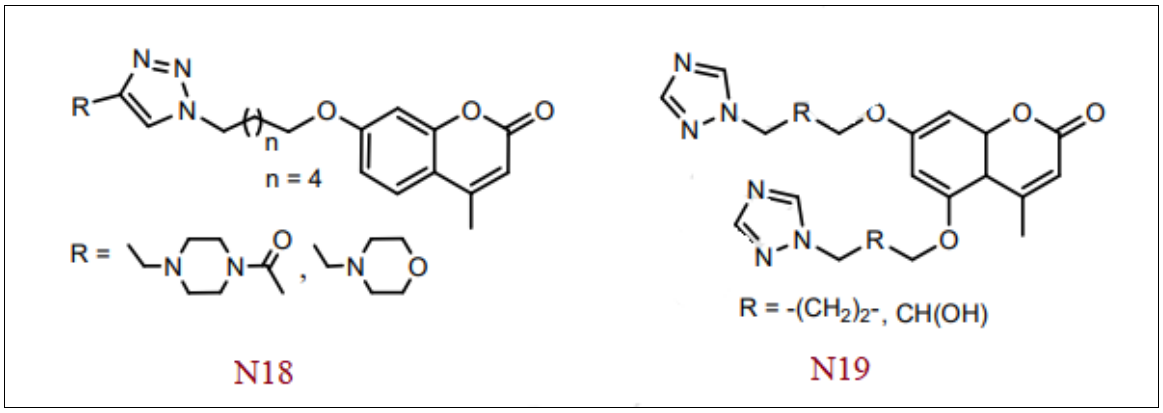
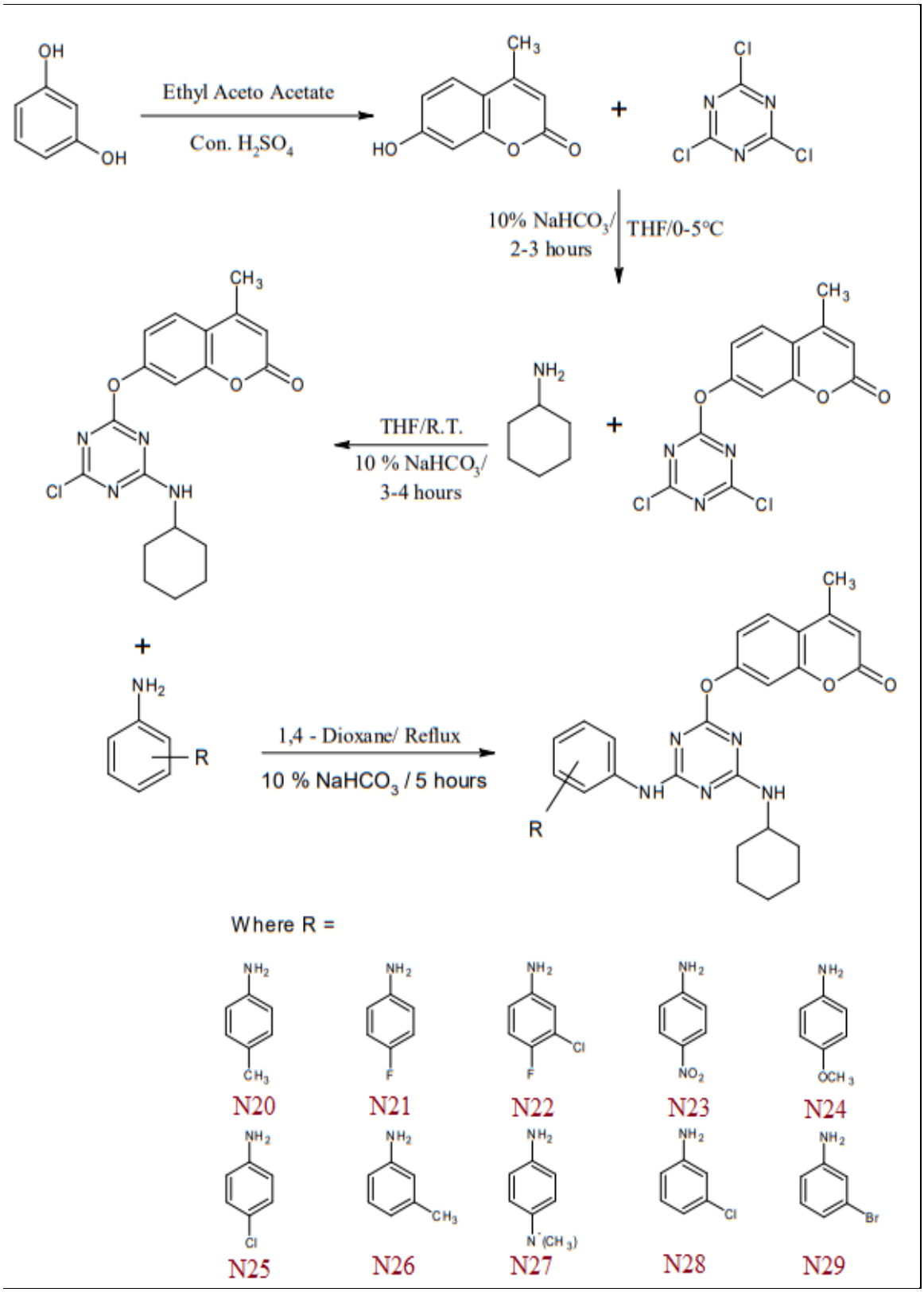



**Figure 3: Chemical structures of the synthetic conjugates N18 and N19 that have potent antibacterial activity.**

Parmar *et al.* have recorded the preparation of several cantabiline-based derivatives, as displayed in Scheme 3. These novel derivatives, herein designated as **N20-N29**, have been examined for their *in-vitro* antibacterial effect versus four standard pathogenic bacterial strains, including; *Bacillus subtilis* and GP-Sa, GN-Ec, and GN-Pa. The authors revealed that these cantabiline derivatives exhibited a good antibacterial effect against the test bacterial strains. Among these derivatives, compounds **N25** and **N27** were the best [19].




**Scheme 3: Synthetic pathway of the novel cantabiline derivatives as recorded by Parmar *et al.***

Tataringa *et al.* have recorded the synthesis of a panel of compounds using cantabiline as a precursor. These novel derivatives have been examined for their potential as antibacterial products versus many infectious bacterial strains. The researchers revealed that all the newly synthesized derivatives showed high antibacterial activity versus GP-Sa, excellent activity versus *Sarcina lutea*, and good activity versus GN-Pa. This potential activity could be attributed to the presence of methyl substituent on carbon number 4 of the coumarin chemical nucleus [20].

Darla *et al.* have recorded a modern technique for the synthesis of twelve 7-hydroxycoumarin derivatives substituted at position 8 from cantabiline as a starting material. These novel cantabiline derivatives have been examined for their antibacterial effect. The authors revealed that two of these new compounds designated as **N30** and **N31** (Figure 3) exhibited a noticeable antibacterial effect versus GP-Sa, GN-Ec, and GN-Pa [21].

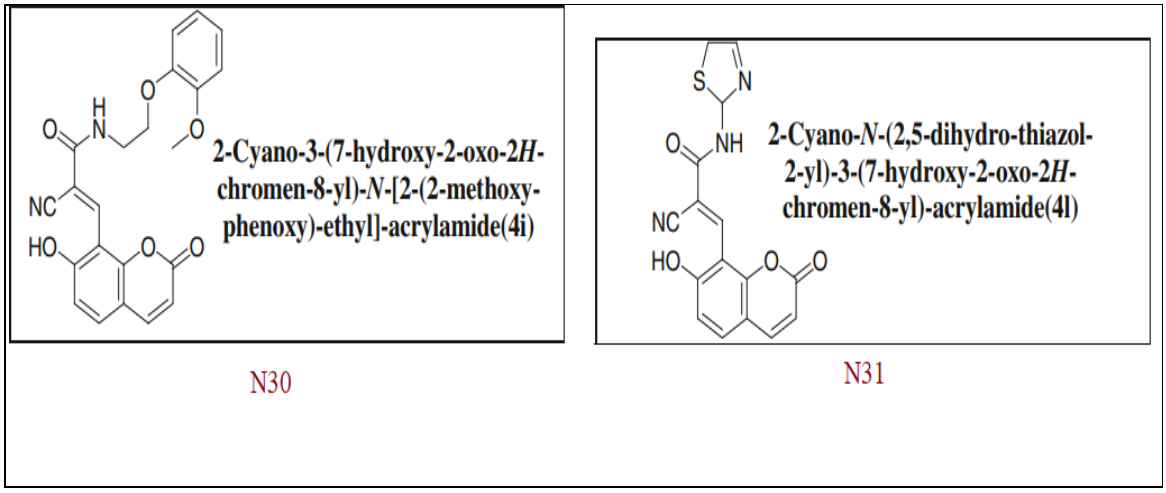
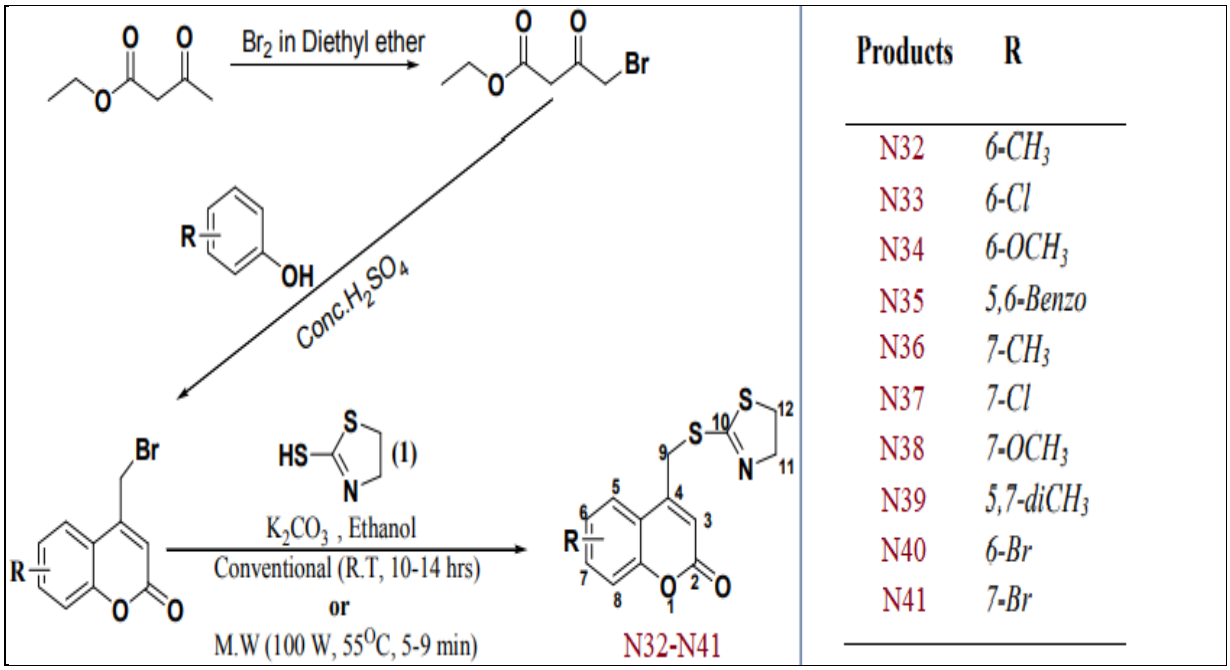



**Figure 4: Chemical structures of N30 and N31 compounds**

Hosamani *et al.* have recorded the synthesis of ten cantabiline-thiazoline conjugates by applying the microwave irradiation technique, as displayed in Scheme 4. The newly synthesized compounds, herein designated as **N32-N41**, have been tested for their anti-tubercular effect and DNA cleavage. The researchers have revealed that compound **N33** showed a high anti-tubercular activity, which may be attributed to the good DNA




**Scheme 4: Synthetic route of N33-N41 conjugates as recorded by Hosamani *et al.***

cleavage activity exhibited by compound [22]. Jogi *et al.* have recorded the preparation of six new cantabiline-based azo compounds, as displayed in Figure 4. These novel compounds, herein designated as **N42-N47**, have been tested for their potential as effective antibacterial products against certain pathogenic standard bacteria. The results showed that these cantabiline-based azo compounds exhibited an antibacterial activity similar to those of streptomycin and ampicillin [23].

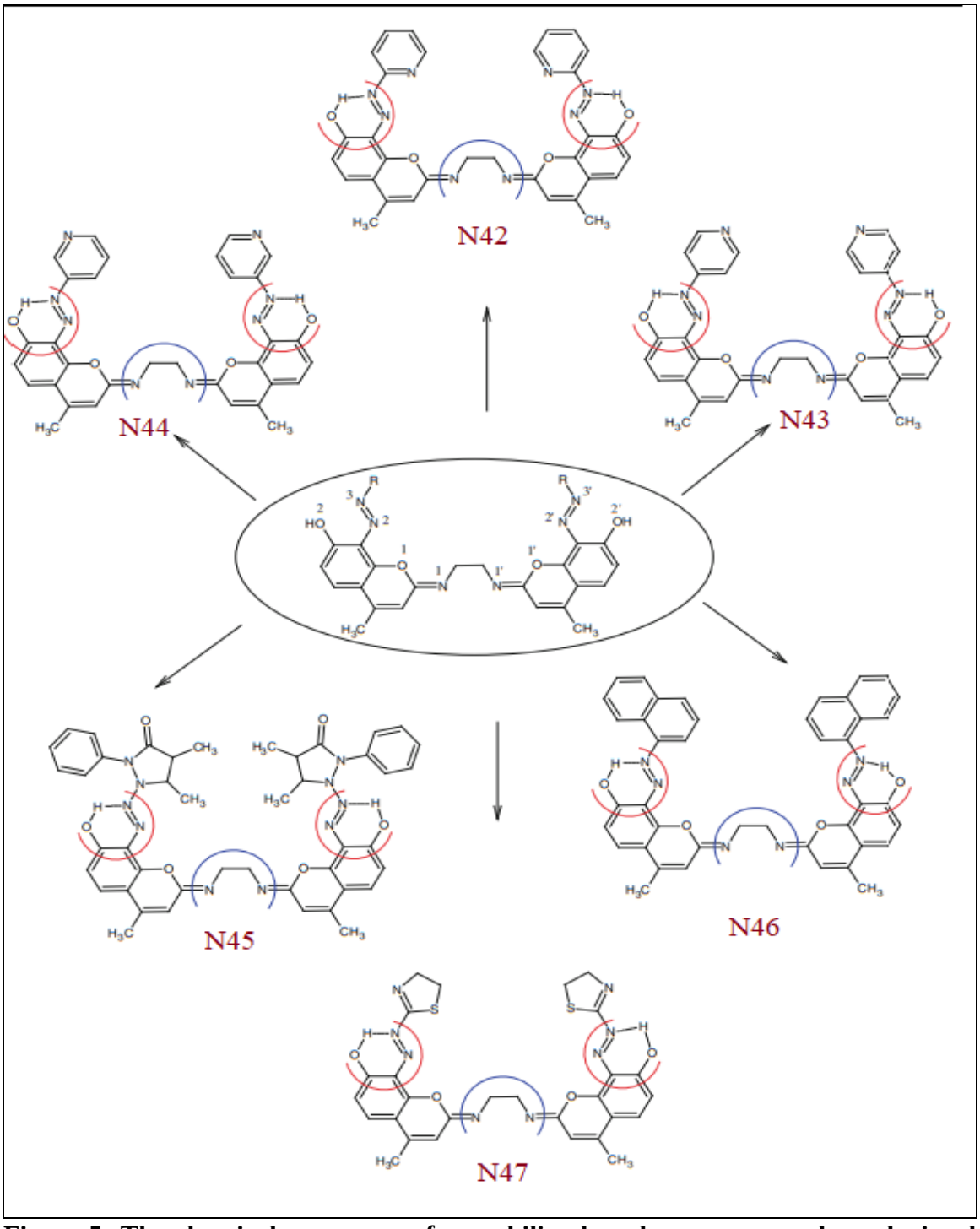
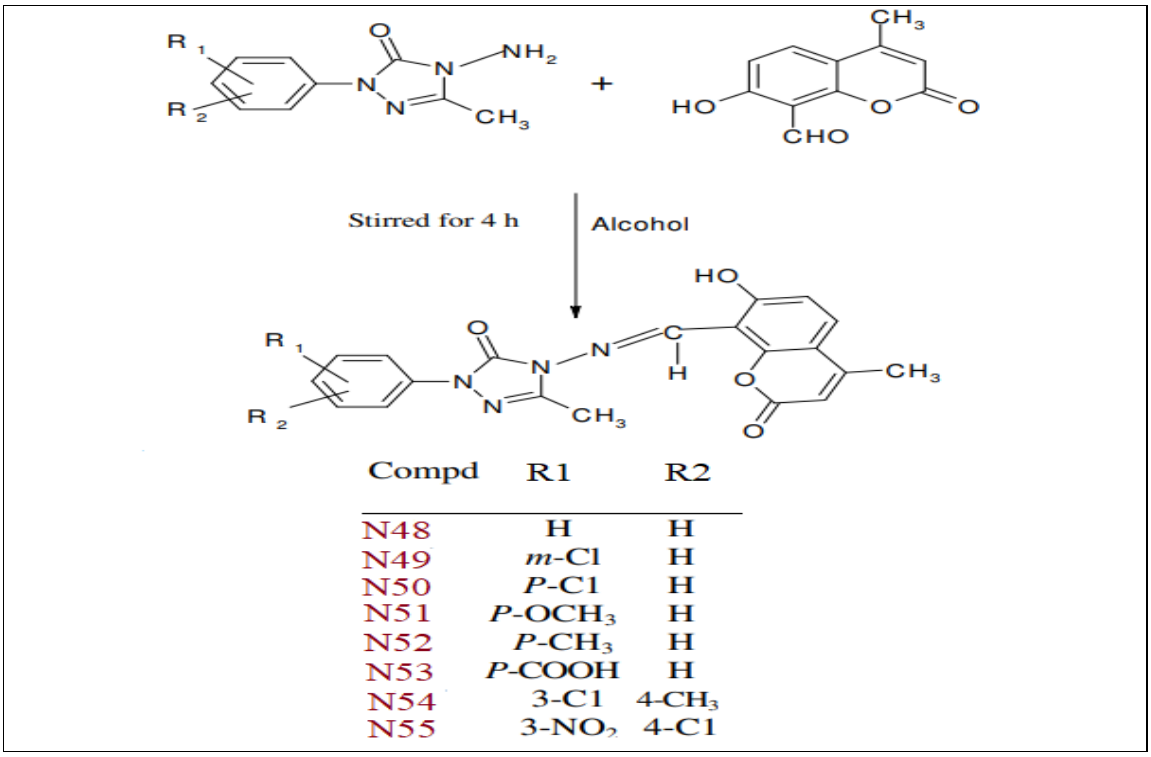



**Figure 5: The chemical structures of cantabiline-based azo compounds as depicted by Jogi *et al*.**

A panel of cantabiline-based Schiff bases was synthesized by Lamani *et al*. by the condensation of 8-formyl-cantabiline with 3-methyl-

5-oxo-1,2,4-triazoles, as displayed in Scheme 5. These new condensates, herein designated as **N48**-**N55**, have been examined for their antibacterial activity versus *Bacillus subtilis* and GN-Ec. The authors revealed that these compounds showed promising antibacterial effect versus the test pathogenic strains [24].

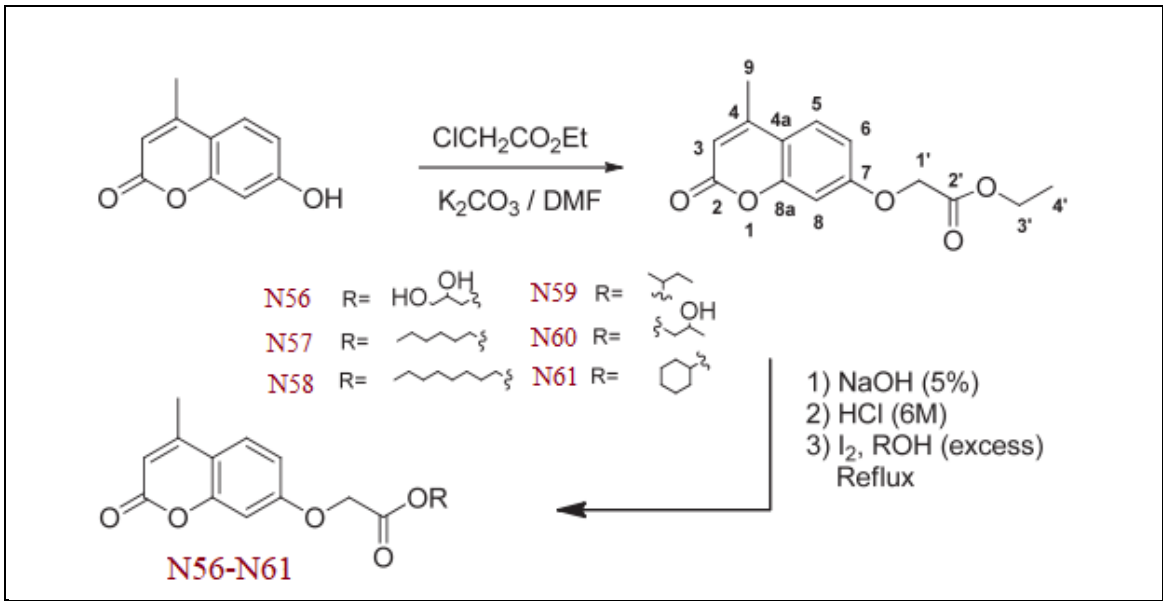



| Compd | R1 | R2 |
|---|---|---|
| N48 | H | H |
| N49 | *m*-Cl | H |
| N50 | *P*-C1 | H |
| N51 | *P*-$OCH_3$ | H |
| N52 | *P*-$CH_3$ | H |
| N53 | *P*-COOH | H |
| N54 | 3-C1 | 4-$CH_3$ |
| N55 | 3-$NO_2$ | 4-C1 |

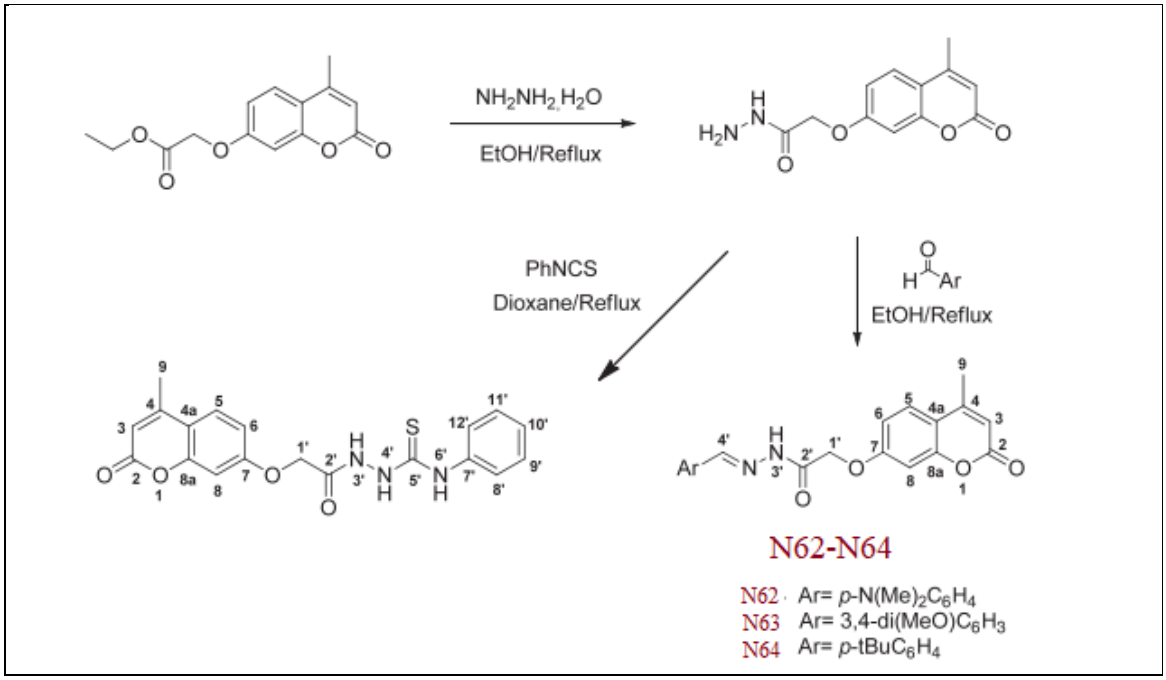
**Scheme 5: The preparation of cantabiline-based Schiff bases as recorded by Lamani *et al.***

Zayane *et al.* have designed and several novels cantabiline-based derivatives, as displayed in Scheme 6 and 7. The researchers also have been examined the antibacterial activity of these new derivatives, herein designated as **N56**-**N64**, versus many pathogenic microbial strains such as *Pseudomonas huttiensis*, *Pseudomonas savatanoi*, and *Agrobacterium tumefasciens*. The results revealed that these cantabiline-based derivatives displayed an acceptable antibacterial effect versus *Pseudomonas savatanoi*. Besides, compounds **N57** and **N60** were the most active against this bacterial strain. The results have also

displayed that only the derivatives **N62**, **N63**, and **N64** were active versus *Pseudomonas huttiensis*. The authors concluded that the substitution of the aromatic system of cantabiline at para-position with dimethylamine functional group could be the reason behind this improved antibacterial activity [25].




**Scheme 6: Synthetic route of N56-N61 compounds as reported by Zayane *et al.***




**Scheme 7: Synthetic route of N62-N64 compounds as reported by Zayane *et al.***

Gubta *et al*. have recorded the preparation of six new cantabiline derivatives designated as **N65-N70**. These novel coumarin derivatives (Figure 5) have been tested for their antibacterial effect versus two pathogenic standard bacterial strains, namely *Bacillus subtilis* and GN-Ec. The results displayed that all the synthesized derivatives exhibited improved antibacterial activity in comparison with ampicillin. Also, compound **N65** showed the highest activity versus the test bacterial strains [26].

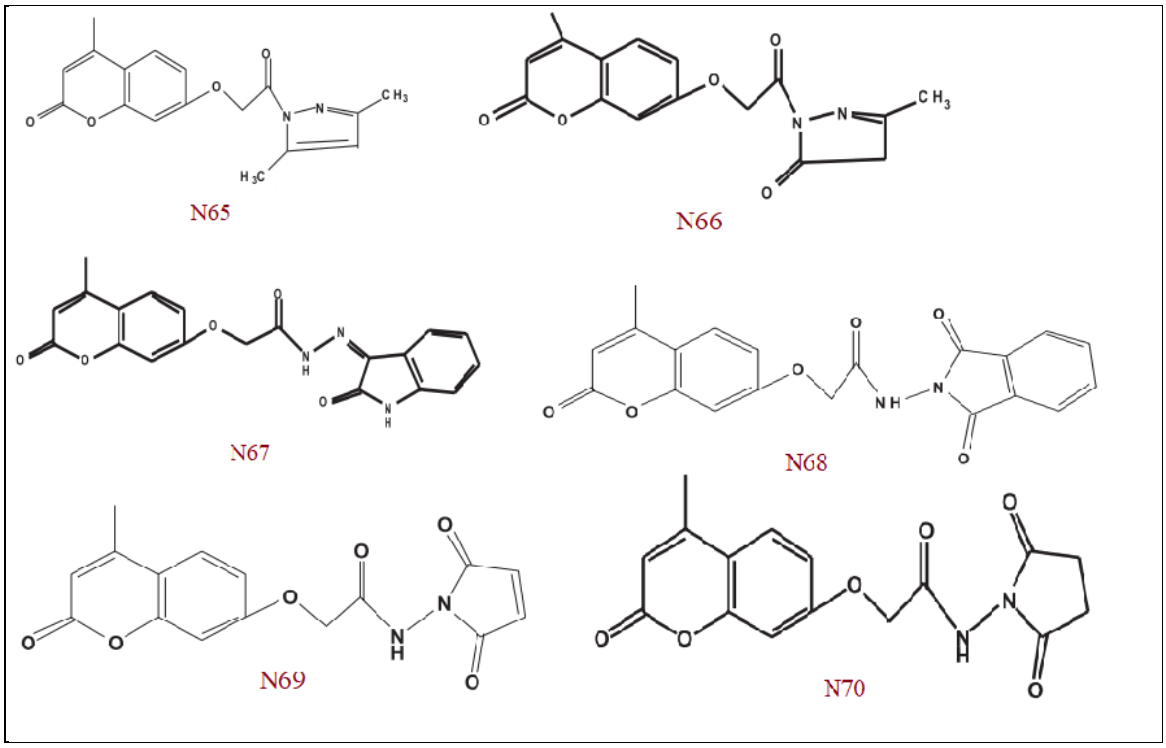



**Figure 6: The chemical structures of the novel compounds prepared by Gubta *et al.***

A panel of cantabiline-based isoxazoline compounds was synthesized by Suresh *et al*. These newly synthesized compounds, herein designated as **N71-N78** (as displayed in Figure 6), have been tested for their antibacterial activity versus two pathogenic bacterial strains, including *GN-Ec* and *GP-Sa*. The results have displayed that these novel coumarin derivatives exhibited a good antibacterial effect versus the test bacterial strains. The researchers concluded that the substitution with an electron-withdrawing functional group could improve the potential of

antibacterial these cantabiline-based isoxazoline compounds as potent antibacterial products [27].

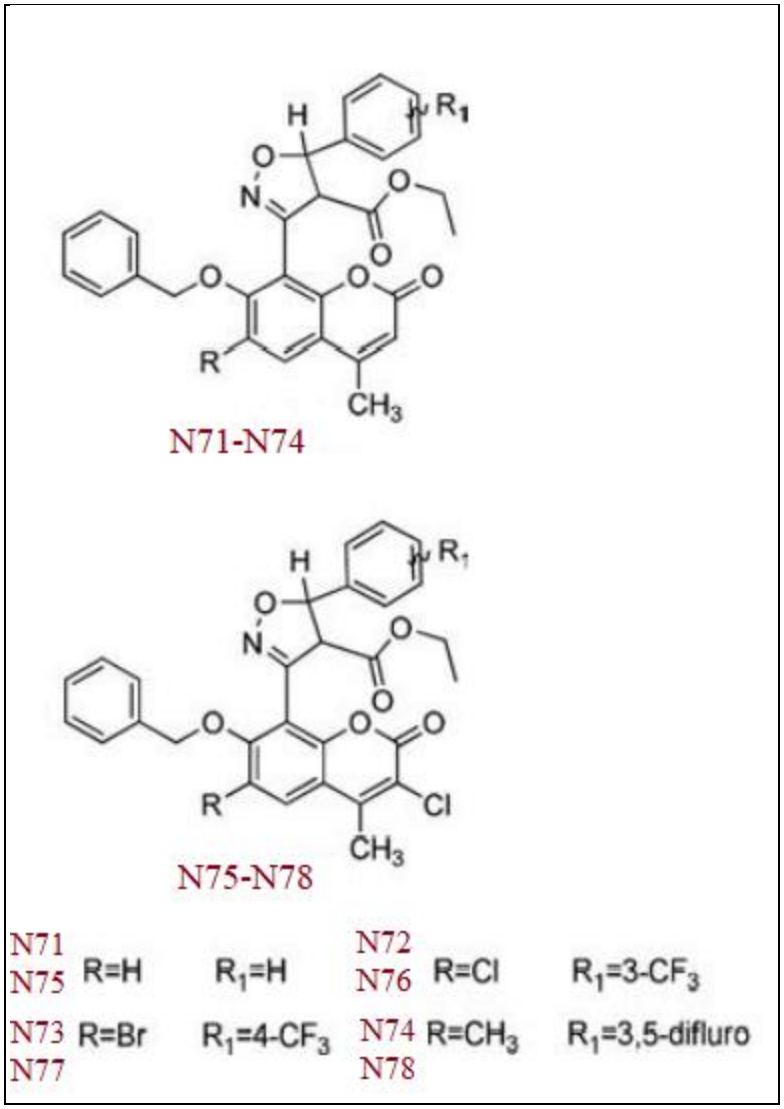



**Figure 7: Chemical structures of the cantabiline-based isoxazoline compounds prepared by Suresh *et al.***

Alghool has synthesized many metal (Ni, Cu, Co, Cd, and Zn) complexes from cantabiline-amine ligand. These complexes have been evaluated for their antibacterial activity versus two GP bacterial strains; namely GP-Sa and *Bacillus subtilis*, and two GN bacterial strains including GN-Ec and GN-Pa. The researchers revealed that the resulted complexes have higher antibacterial activity in comparison

to those of cantabiline-amine ligand and norfloxacin [28].

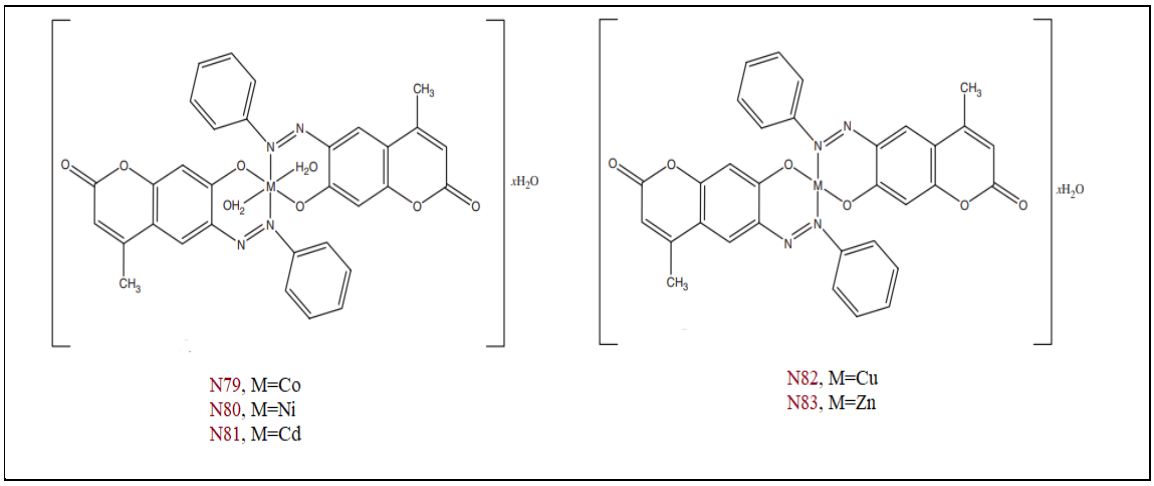
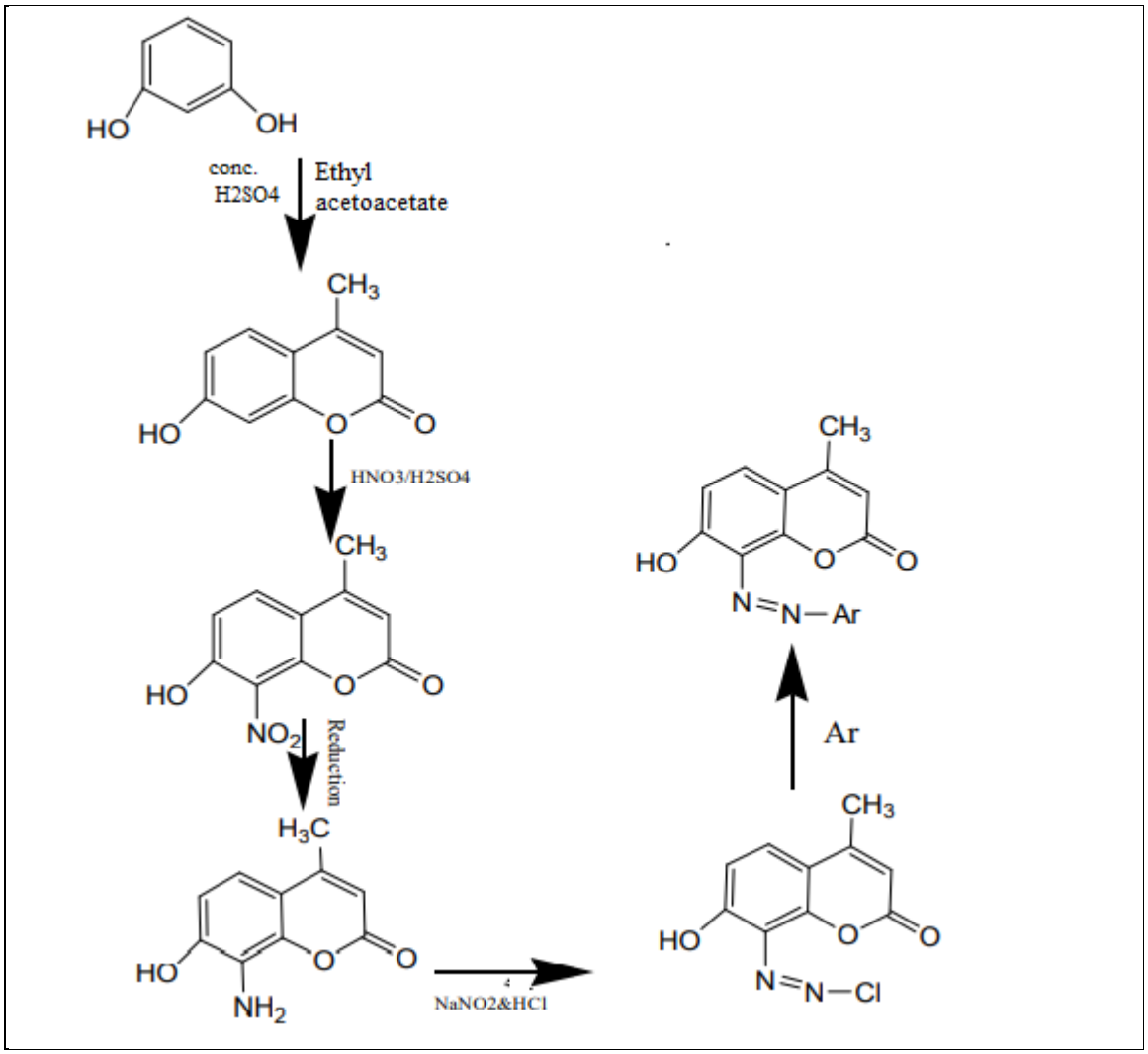



**Figure 8: Chemical structures of the metal complexes prepared by Alghool.**

Gopi C *et al.* have prepared many cantabiline-based compounds by interacting cantabiline with aromatic hydrocarbon. The synthetic route is displayed in Scheme 8. The newly synthesized compounds have been subjected to the antibacterial evaluation versus three pathogenic bacterial strains, including GN-Pa, *Bacillus subtilis*, and GN-Ec. The results displayed that these derivatives exhibited enhanced antibacterial effect versus the test bacterial strains in comparison to the antibiotic ampicillin. The authors concluded that the insertion of the electron-releasing group such as propyl, ethyl methyl, hydroxyl, and the azo-functional group might be responsible for this improved antibacterial potential [29].




**Scheme 8: The synthetic route of the cantabiline-based compounds prepared by Gopi C *et al.***

## Conclusion

This review study has concluded that cantabiline and its derived compounds may represent hopeful antibacterial agents. Also, they can address several mechanisms acquired by bacteria for resisting the currently-available antibacterial agents.

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