Chapter 3
Rationale of Approach

3. RATIONALE OF APPROACH

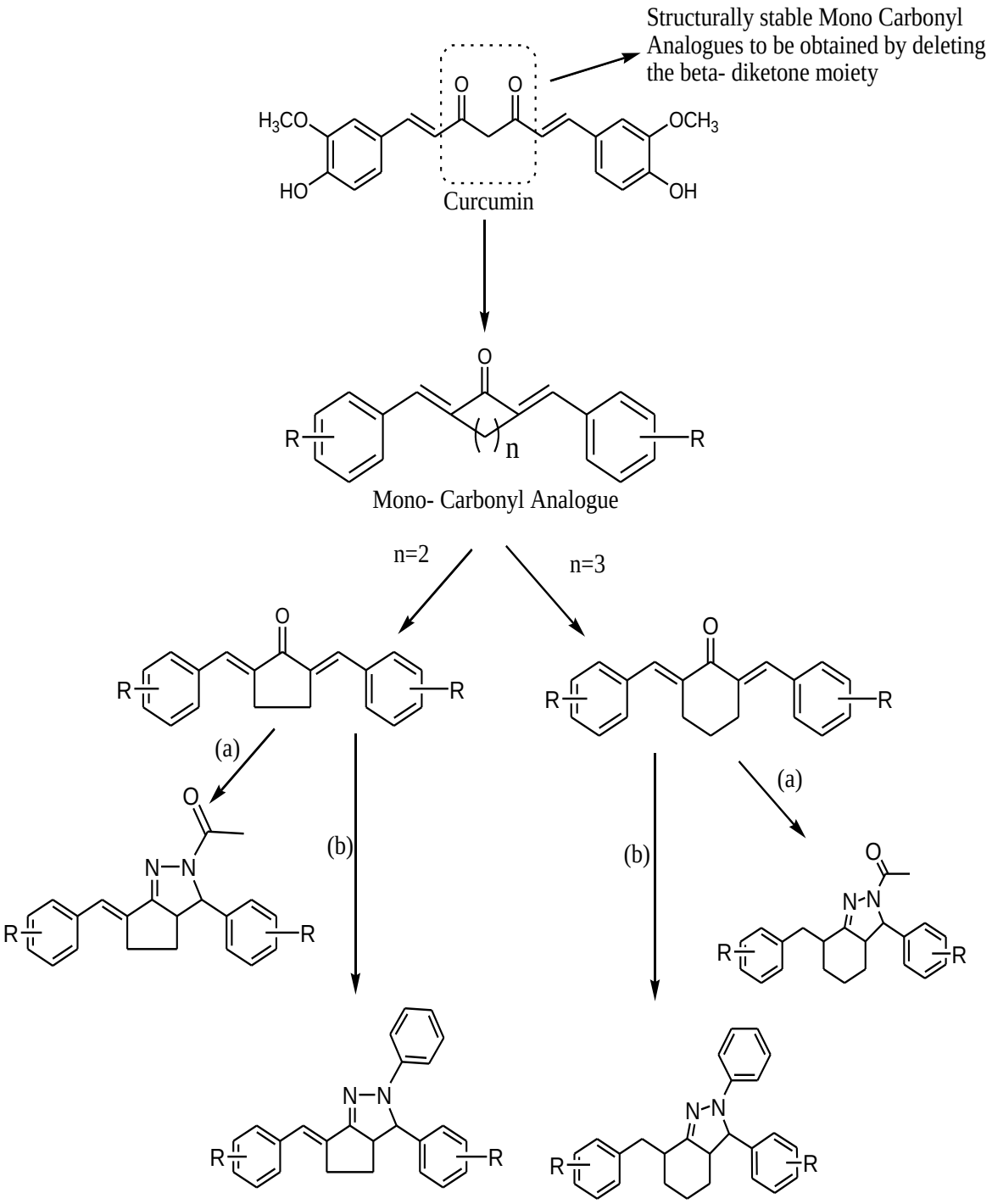
Turmeric, the bright yellow spice extracted from the rhizome of the plant *Curcuma longa* linn (Zingiberaceae), has been used in traditional Indian and Chinese systems of medicine for centuries to treat a variety of ailments, including jaundice and hepatic disorders, rheumatism, anorexia, diabetic wounds, and menstrual difficulties. Most of the medicinal effects of turmeric have been attributed to curcumin, the principal curcumanoid found in turmeric. Recent reports indicate that curcumin exhibits strong anti-inflammatory and antioxidant activities. It modulates the expression of transcription factors, cell cycle proteins, signal transducing kinases and has prompted the mechanism-based studies on the potential of curcumin to primarily prevent and treat cancer and inflammatory diseases. Little efforts has been made to study curcumin on the development of antimicrobial and anti-malarial agents. It won't be rationale unless concealed area is focused in research so I planned to explore the effect of curcumin analogues as antimicrobial and anti-malarial agents.

However, clinical applications of curcumin have been significantly limited because of instability due to the keto-enol tautomerism of β-diketone moiety of curcumin and leading to poor pharmacokinetic profile. In the present study, an effort has been made to address the problem of instability of curcumin by developing novel curcumin analogues.

Earlier **Liang *et al.* (2008)** synthesized three series of mono-carbonyl curcumin analogues by purging the methylene group and one carbonyl group from curcumin. They observed that these newer analogues displayed significant biological activity in comparison to curcumin. This report gave me an impetus to design curcumin analogues that might enhance stability by deleting methylene group and one carbonyl group.

Further**, Bugaev *et al.* (2005)** & **Gokhan-Kelekci *et al.* (2009),** reported that compounds containing hexahydroindazole are active as potent antimicrobial agent.

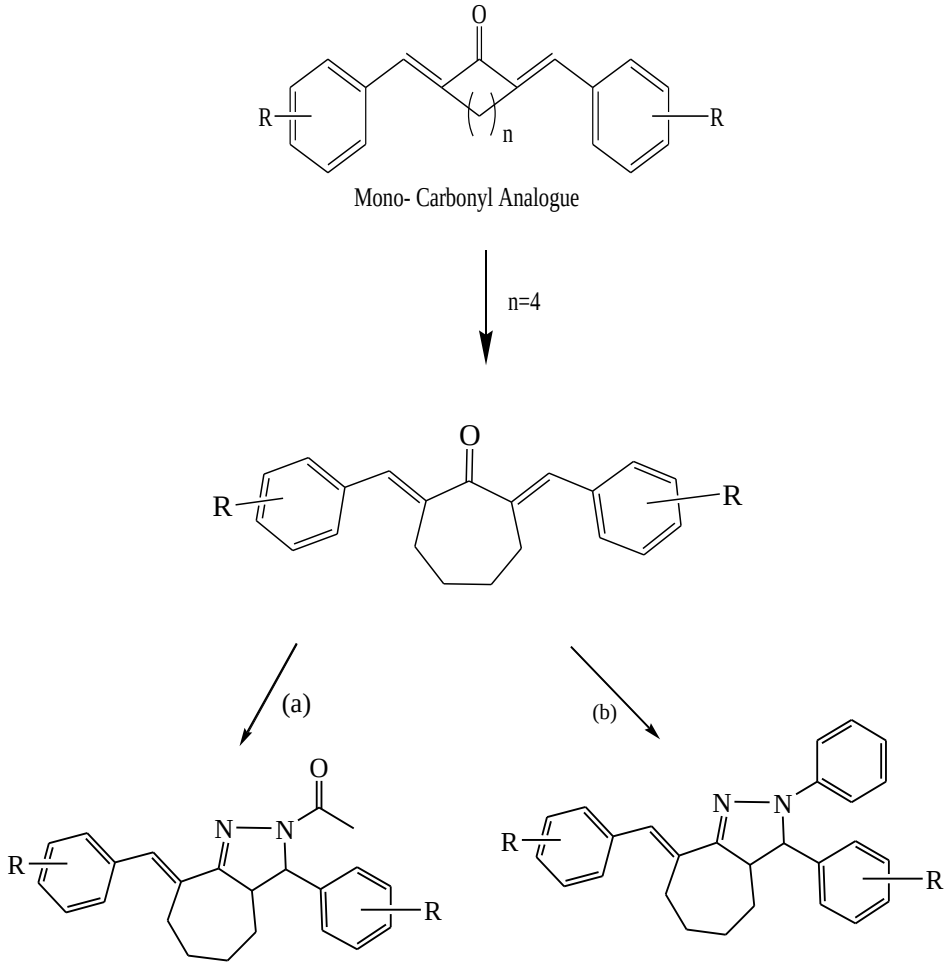
The anti-malarial activity of curcumin analogues of pyrazole was reported by **Mishra *et al.* (2008)**. Recent studies have revealed that hexahyroindazole and pyrazole derivatives could be promising scaffold for developing novel lead candidates as antimicrobial and antimalarial agents.



where, a= $H_2N-NH_2 .H_2O$

b= $H_2N-\overset{H}{N}-Ph$

R= Cl,diCl, OH, OCH_3, NO_2, $N(CH_3)_2$, etc.



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Based on this rationale, I designed three series of curcumin analogues; by incorporating hexahydroindazole, cyclopentanone and cycloheptanone in it and evaluated the effect of substituents on antimicrobial and anti-malarial activities. The *in vitro* antimicrobial activity was performed by agar dilution method and anti-malarial activity by [^{3}H] hypoxanthine incorporation assay. .

Glucosamine-6-phosphate synthase, catalyzes the formation of D-glucosamine 6-phosphate from D-fructose 6-phosphate using L-glutamine as the ammonia source. Since N-acetylglucosamine is an essential buildings block of both bacterial cell wall and fungal cell wall chitin, and are a potential target for antibacterial and antifungal agents. Therefore, it was selected as target of interest to simulate their binding preference with

synthesized molecules using Autodock 4.0/4.2 molecular modeling software package and to predict *in-silico* pharmacokinetic properties and to check the drug-likeness of synthesized compounds.

Finally QSAR model will be developed to compare the predicted and experimental results on basis of structural descriptors.