Research Article

Synthesis of Curcumin Analogs

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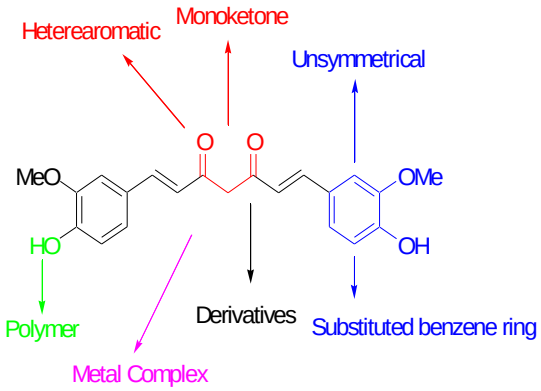
ABSTRACT

Curcumin is one of traditional medicine ingredients. It can be isolated from turmeric. It is still popular until nowadays. Different method of synthesis of curcumin analogs have been published by researchers around the world. Here, we will see some methods that have been summarized.

Keywords: Analog, curcumin, synthesis.

INTRODUCTION

One of very popular traditional medicine is turmeric. Curcumin is one of its active compounds. Its biological activities[1,2,3] have been investigated by researchers around the world. Curcumin has some limitations in making it into drug market like its bioavailability and solubility. To solve this problem, a lot of research findings have been published in order to make better properties of curcumin including in making its analogs. Synthetically, curcumin analogs have been successfully made. Until at the end of year 2014, there are thousands of publications about synthesis of curcumin analogs. Most of them have similar synthetic method and it is summarized in nine types of synthetic modifications.



Graphical Abstract

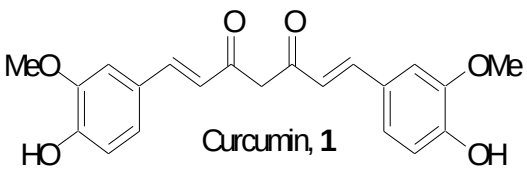


Figure 1: Structure of Curcumin

Synthesis of Curcumin analogs

New structure of curcumin analogs have been designed by putting different substitutions on benzene ring, removing the β-ketone moiety to mono-ketone or changing to heteroaromatic ring, making derivate of curcumins, coupling as co-polymer and metal complex and others.

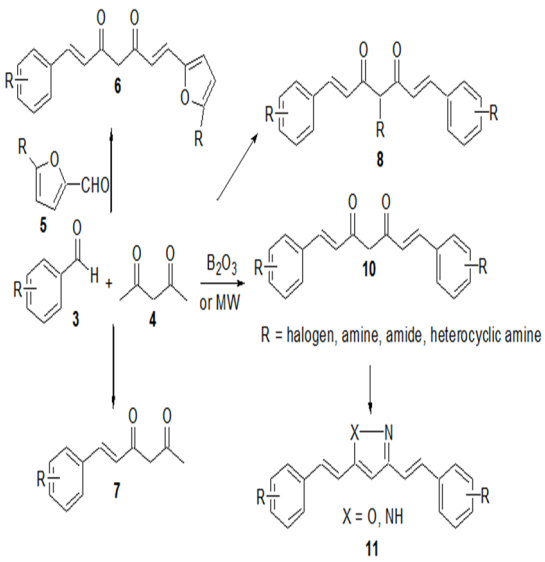
Each of these will be explained like below.

Synthesis of substituted benzene ring of curcumin

Halogenated curcumin analogs **10**[4] have been carried out by using condensation reaction between 2,4-pentadione **4** and appropriate benzaldehyde **3**[5] in solution of boron oxide and tributylborate in EtOAc and solution of butyl amine in EtOAc at -40 °C for 24 h.[6] Amines, amide and heterocyclic amine of benzaldehyde also have been applied to the synthesis of substituted curcumin as cytotoxic agents.

The aliphatic amine was used as catalyst and 2,2-dimethoxypropane or tributylborate as dehydrating agent.[7] Microwave irradiation has also been applied to the synthesis of curcumin analog through one pot system at 160 W for 60-120 second and calcium oxide as catalyst.[8]

Hispolon analog of curcumins **7** have biological acitivities as anti-proliferative and anti-inflammatory agents.[9] In investigating of the important of α,β-unsaturated 1,3-diketone moiety of curcumin, isoxazole[10] and pyrazole curcumin scaffold derivatives **11** have also been synthesized.[11,12] Elaboration of curcumins with enaminones, oximes and isoxazole heterocycle were also been synthesized.[13] Unsymmetrical curcumin analogs **6** also have been successfully synthesized by using two different aldehydes with 2,4-pentadione.[14] And electron rich curcumin analogs as 1,3-diketone analogs **8** as anticancer agent have been synthesized by Amolin through this carbonyl condensation reaction.[15]



Scheme 1: Synthesis of substituted benzene ring of curcumin

Synthesis of mono-ketone curcumin analogs

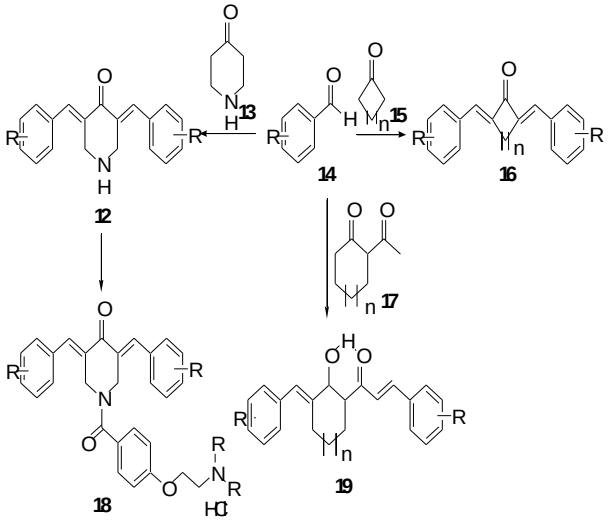
By deleting the 1,3-diketone moiety on curcumin to single ketone curcumin analog **16**, Sardjiman[16] has designed and synthesis three series of curcumin analogs which have good activity as antioxidant[17] and anti-inflammatory agent. Synthesis started by reacting substituted-benzaldehyde and cyclopentanone, cyclohexanone or acetone in basic condition without solvent for 1 – 14 days moderate to good yield. There are 47[18] analog of curcumin were made by this method. Leow[19] improve these reaction condition by reacting the starting materials in methanol at room temperature in NaOH (20 % w/v) for 20 minutes with yield. They successfully synthesized 43 curcumin analogs which are divided into 5 series. These curcumin analogs are screened in HEK293T cells for inhibition of β-catenin transcriptional activity with 6.5 to 60 fold more potent than curcumin. The substituent positions are on meta and para of benzene ring and other appropriate aldehydes[20,21]. The reactions were done at room temperature in methanol for 20 minutes mixing before adding 20 % (w/v) of NaOH. In this reaction, protection is needed when making hydroxylated curcumin analogs. Both syntheses used the same substituents on both side of aromatic rings and still keep the hydroxyl group on that. Some other publication showed only by changing the methoxy group on curcumin with other substituents and these were evaluated to test their inhibitory potencies. The reactions were carried out in NaOEt as a base.[22]

Yuan also made 8 curcumin analogs with similar method as above. They used benzaldehyde without hydroxyl group on para position as starting material with substituents on positions 2 and six as flouro, bromo or trifloromethyl in ethanol at room temperature for 20 minutes then KOH (5 %) at room temperature. These compounds were designed for inhibition of 11β-hydroxysteroid dehydrogenase type 1 with antidiabetic properties.[23] Similar to these, mono-ketone analog **12** with 4-piperidines **13** were made, instead of cyclic ketone for the treatment of lung cancer[24,25], breast cancer[26] and anti-inflammatory agents[27]. The reaction conditions were in AcOH/HCl and K_2CO_3 as a base or in EtOH and NaOH as a base at room temperature.[28] The similar analogs were transformed into other derivates **18** for treatment of skin disease.[29,30]

Hydroxy group on para position, sometimes make reaction difficult for some reactions.[31,32] Like what Liu did, they made 33 novel O-allylated and O-prenylated mono carbonyl analogs of curcumin as antiinflammatory agents in 5 series compounds. The reaction conditions are in EtOH-H_2O (2:1) at room temperature overnight in 30-80 % yield. For open hydroxyl group on para position they used 3,4-dihydro-2H-pyran as protecting group.[33] In the other publication, the hydroxyl group was functionalized to amine groups and these curcumin analogs were screened for their cytotoxicity against different cancer cell lines and anti-malaria activity.[34] And sometimes, functionalized to other functional groups.[35]

Analog of tautomeric curcumin **19** has been also successfully synthesized by Youssef.

There are 15 tautomers synthesized under microwave condition by using morpholine and acetic acid as catalysts for 1 minute reaction. These were screened for *in vitro* cytostatic activity.[36]



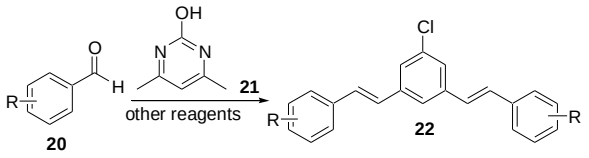
Scheme 2: Synthesis of mono-ketone curcumin analogs

Deleting the reactive β-ketone moiety to heteroaromatic ring

Synthesis of six novel pyrimidine substituted curcumin analogs **22** with or without a hydroxy group like on curcumin were tried by Qiu.

These compounds were designed for anti-cancer therapy on Epidermal growth factor receptor (EGFR).

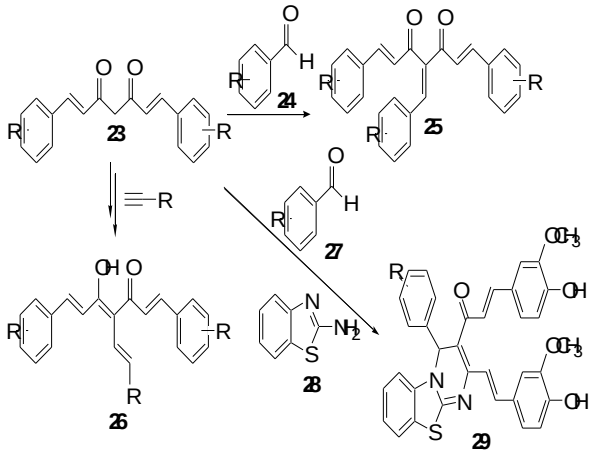
The synthesis was done by reacting 4,6-dimethyl-2-hydroxy-pyrimidine hydrochloride **21** with appropriate substituted benzaldehyde **20** in acid condition.[37]



Scheme 3: Synthesis of reactive β-ketone moiety on curcumin

Derivative of curcumin analog

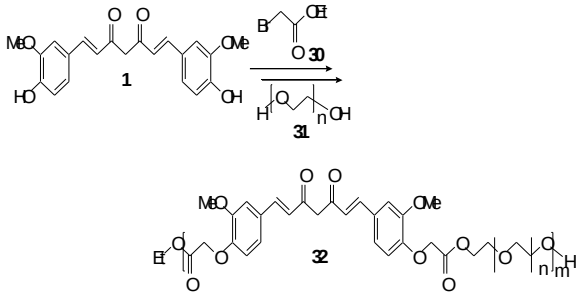
Synthesis of 4-arylidene curcumin analog **25** were done by coupling analog curcumin **23** with various aromatic aldehyde **24**[38,39] through condensation carbonyl catalyzed by AcOH/piperidine. These are potent antiproliferative agents against a panel of cancer cell line.[40] In other publication, 12 conjugate curcumin analog were successfully synthesised as anti-prostate cancer drug candidates[41] and targeting cancer stem cell[42]. Curcumin as anti-tumor agent also have been designed as new 4-ethoxycarbonylethylcurcumin analogs **26**.[43] One pot synthesis of curcumin derivatives have been discovered by Sahu for the synthesis of 4H-pyrimido[2,1-b]benzothiazole, pyrazole and benzylidene derivatives of curcumin **29** under solvent and solvent free conditions in microwave.[44]



Scheme 4: Synthesis of curcumin analog derivatives

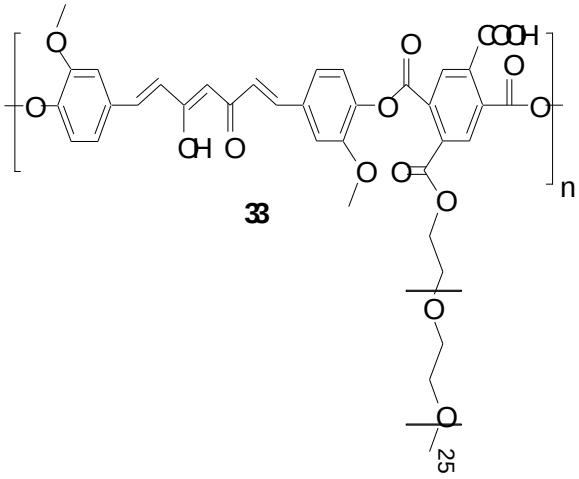
Copolymer curcumin

Synthesis of polymerization of curcumin diester with poly(ethylene glycol) and copolymer curcumin were carried out by Pandey in 2011 in resulting polymer **32**. The enzymatic method was employed by using Novozym 435.



(a)

Tang have made high molecular weight curcumin polymers (polycurcumins) by condensation polymerization of curcumin. These curcumin polymers **33** were tested as anticancer agent.[45]

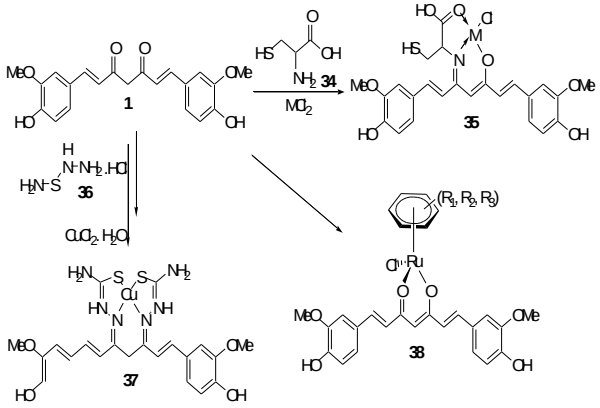


(b)

Figure 2: Copolymer curcumin: (a) the synthesis, (b) polycurcumins

Metal complex of curcumin

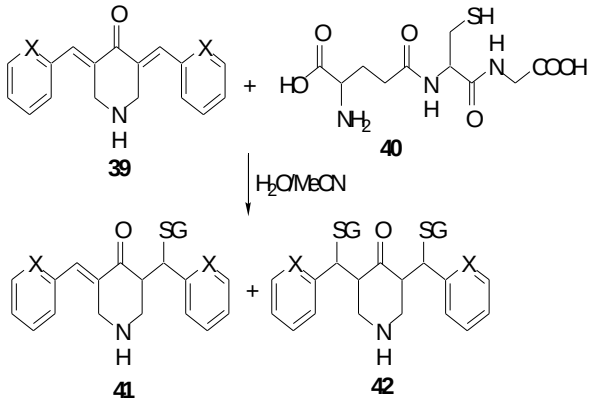
Chandrasekar have successfully synthesized shift base ligan curcumin by reacting between curcumin and amino acid **34** in ethanol at reflux for 6 h which furthermore reacted with transition metal complexes. The complexes were found to have good anti-microbial activities.[46] Non-enolisable curcumin analog and schift bases, as anticancer agent **37**, were synthesized and then conjugated with copper(II).[47] Arene-Ru(II) curcumin complexes **38** were synthesized by reaction between curcumin and [(arene)RuCl2]2 (arene: p-cymene, 1; benzene, 2; hexamethylbenzene, 3) in methanol in the presence of sodium methoxide.[48]



Scheme 5: Metal complex of curcumin

Synthesis of GSH conjugates

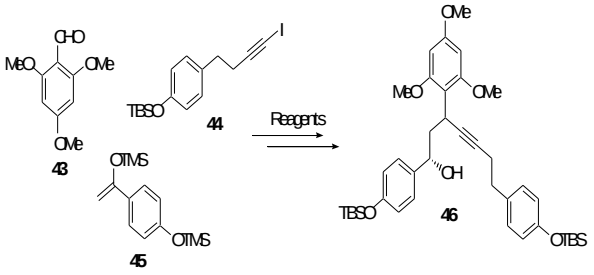
Sun synthesized another series of curcumin analogs as anti-tumor prodrug. They reacted analog curcumin **39** in acetonitrile and Glutathione (GSH) **40** in water at room temperature to produce analog curcumines with one GSH **41** adduct and two GSH adduct **42**.[49]



Scheme 6: GSH conjugates of curcumin

Synthesis of arylated curcumin analogs

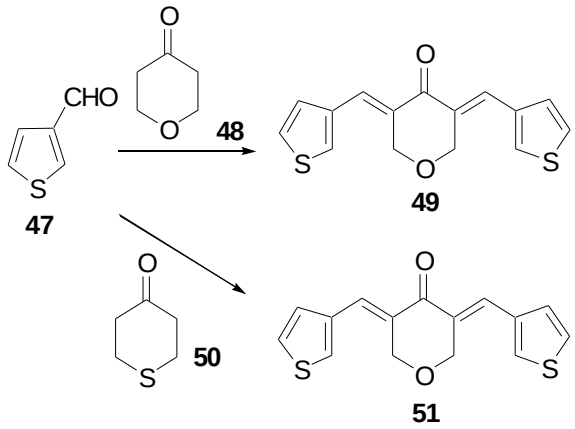
Multicomopnent coupling has been applied to synthesis of arylated curcumin analogs **46** as brain and peripheral nervous system anti-cancer agents. The main reagent used were Cp_2TiCl_2 (2 mol %), $(4\text{-}MeOC_6H_4)_3P$, Zn(0), and Ac_2O and the reaction gave a mixture of β-aryl ketones.[50]



Scheme 7: Synthesis of arylated curcumin analogs

Synthesis of heteroaromatic ring of curcumin

Wei synthesized sixty-one curcumin analogs. Some of them are made by coupling pyridil aldehyde **47** with tetrahydropyran-4-one **48** and tetrahydrothiopyran-4-one **50**. These compounds were evaluated as anticancer agents.[51]



Scheme 8: Synthesis of heteroaromatic ring of curcumin

CONCLUSION

Until 2014, the most modification of curcumin analog structures is on diketone moiety and these have proven many different biological activities.

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