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Synthesis of 1,7-diphenylhepta-1,6-diene-3,5-diones curcumin derivatives(s) and their characterization

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ABSTRACT: Curcumin has been used to inhibit skin, liver, lung, colon, stomach, and breast carcinogenesis. It has already been shown to suppress the spread of a wide variety of tumor cells in culture and to facilitate cell death through BID cleavage (a Bcl-2 family member protein), cytochrome c release, bcl-2 regulation and caspase amplification..
It has been shown to decrease blood cholesterol, improve survival, prevents excessive wrinkles, inhibit inflammation, foment rheumatoid arthritis, and prevent the replication of the human immunodeficiency virus. We attempted to synthesize nobelcurcumin derivatives using a multiple component reaction (MCR) with aldehyde and 2,4-pentandione in the presence of boron trifluorideetherate in our project.
Keywords: Curcumin, multiple component reaction (MCR), boron trifluorideetherate, 2,4-pentandione

I. INTRODUCTION

From the literature survey we came to know that past and ongoing clinical trials have demonstrated that curcumin is safe at high doses and it seems to respond in various inflammatory and cancer-related diseases. Curcumin and its derivatives have a variety of bioactivities, including antioxidant, anti-inflammatory, and anti-carcinogenic properties. So we decided to investigate the series by further modification and synthesisze the series of cucumin derivatives[1].

Boric oxide is typically used to prevent the enol group in acetylacetone as well as to discourage the highly acidic methylene protons from forming Knoevenegal condensation at the diketone's terminal methyl groups[2]. As boric oxide is expensive, borontrifluorideetherate was used in place of boric oxide.Borontrifluorideetherate (BF_3-Et_2O) and acetylacetone are both commercially available and the boronite complex is formed easily in the reaction. Hence we planned to synthesizecurcumin and its analogues by one step procedure using aldehyde and 2,4-pentandione in presence of boron trifluorideetherate. The reaction was optimized for no. of moles of reactants, catalyst, temperature, solvent suitability and time to give best yield. The whole reaction process was monitored by TLC[3]. Workup required for this method is easy. Also the complete procedure is time saving, clean and neat.

II. MATERIALS AND METHODS

General procedure to synthesis of 1,7-diphenylhepta-1,6-diene-3,5-diones.

In the present work various aldehydes were reacted with 2,4-pentandione , in presence of BF_3-Et_2O to form substituted curcumin (1,7-diphenylhepta-1,6-diene-3,5-diones.) . The reaction was optimized for no. of moles of reactants, catalyst, temperature, solvent suitability and time to give best yield. The reaction was monitored by TLC[4]. Workup required for this method is easy. Also the complete procedure is time saving, clean and neat (Scheme 1).By using the said procedure we synthesized the series of compounds having following general structure (Figure and Table 1).

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Scheme 1: General scheme for synthesis of curcumin analogues.

Figure 1: General structure of curcumin derivatives

Table 1: Series of synthesized compounds with their experimental characteristics .

Compound	R1	R2	Melting Point	Yield
A			182^0C.	80.56%
B			135^0C.	**57.54%**
C			120^0C.	**53.71%**

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D			110^0C.	**65.95%**
E			127^0C.	**71.57 %**
F			140^oC.	56.72 %
G			68.45 %	124^0 C.
H			73.65 %	146^0C.
I			67.43 %	126^0C

OPTIMIZATION OF REACTION

Aldehyde concentration by using vanillin

In a clean ,dry round bottom flask(RBF),different concentration of aldehyde(vanillin) ranging from 0.5mmole to 4 mmoles ,Boron trifluorideetherate($BF_3.Et_2O$) , (1.23ml) and acetyl acetone(0.10 ml) was taken, and 25 ml of ethanol was added.The mixture was refluxed and monitored on TLC by using Ethyl acetate:n-Hexane(1:4).After 3 hours, the product was collected and extracted with ethyl acetate and washed with10% HCl,followed by washing with water.It was then dried over anhydrous Na_2SO_4[5]. The solvent was removed under reduced pressure .This crude product was recrystallized by using hydroalcoholic solution (Table 2).

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Table 2: Maximum yield was found with 2mmoles of aldehyde.

mmole of aldehyde	%yield.
0.5	70.56
1	72.3
2	80.35
3	78.21
4	62.77

Acetyl acetone Concentrations

In a clean ,dry round bottom flask(RBF), aldehyde(3gm) ,Boron trifluorideetherate (BF_3Et_2O,1.23ml)and different amount of acetyl acetone(0.5mmole-4mmoles) was taken, and 25 ml of ethanol was added.The mixture was refluxed and monitored on TLC by using Ethyl acetate:n-Hexane(1:4).After 3 hours, the product was collected and extracted with ehtyly acetate and washed with10% HCl,followed by washing with water.It was then dried over Na_2SO_4[6]. The solvent was removed under reduced pressure .This crude product was recrystallized by using hydroalcoholic solution(Table 3).

Table 3: Maximum yield was found with 1 mmole of acetylacetone.

mmole of acetylacetone	%yeild
0.5	72.86
1	79.45
2	78.90
3	78.66

Catalyst

In a clean ,dry round bottom flask(RBF),aldehyde(3g) , different amount of Boron trifluorideetherate (BF_3Et_2O) ranging from 0.5mmole to 3mmoles. and acetyl acetone(0.10 ml) was taken, and 25 ml of ethanol was added.The mixture was refluxed and monitored on TLC by using Ethyl acetate:n-Hexane(1:4).After 3 hours, the product was collected and extracted with ehtyly acetate and washed with10% HCl,followed by washing with water. It was then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure .This crude product was recrystallized by using hydroalcoholic solution[7](table 4).

Table 4: Maximum yield was found with 1mmole of catalyst

mmole of catalyst	%yield
o.5	65.83
1	79.80
2	75.65
3	74.32

Solvent

In a clean ,dry round bottom flask(RBF), aldehyde(3g),Boron trifluorideetherate (BF3Et_2O,1.23ml)and acetyl acetone(0.10 ml) was taken, and 25 ml of different solvent was added. The mixture was refluxed and monitored on TLC by using Ethyl acetate:n-Hexane(1:4).After 3 hours, the product was collected and extracted with ehtyl acetate and washed with10% HCl,followed by washing with water.It was then dried over Na_2SO_4. The solvent was removed under reduced pressure .This crude product was recrystallized by using hydroalcoholic solution[8](Table 5).

Table 5: Maximum yield was found when ethanol was used as solvent. .

Solvents	%yeild
Ethanol	79.56
Methanol	70.83
Chloroform	58.76
Ethlyacetate	56.8

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Temperature

In a clean ,dry round bottom flask(RBF),aldehyde(3g) ,Boron trifluorideetherate(BF_3Et_2O,1.23ml)and acetyl acetone(0.10 ml) was taken, and 25 ml of ethanol was added.The mixture was refluxed at various temperatures and monitored on TLC by using Ethyl acetate:n-Hexane(1:4).After 3 hours, the product was collected and extracted with ehtyly acetate and washed with10% HCl,followed by washing with water.It was then dried over Na_2SO_4. The solvent was removed under reduced pressure .This crude product was recrystallized by using hydroalcoholic solution[9](Table 6).

Table 6: Maximum yield was found at 125°C

Temperature (^OC)	%yield
0	NO REACTION
R.T	10.47
50	30.83
75	56.8
100	72.1
125	80.53
150.	79.2

Optimized parameters in tabular form(table 7)

Table 7: Optimized parameters.

Parameters	**mmoles**	**%yield**
Aldehyde	2 mmoles	**80.56**
Acetylacetone	1mmoles	
Catalyst	1mmoles	
Solvent	ethanol	
Temperature	125°C	

PROCEDURE

Procedure for Synthesis of1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (A): In a clean ,dry round bottom flask(RBF), vanillin (3g),Boron trifluorideetherate (BF_3Et_2O,12.3ml)and acetyl acetone(1.02 ml) was taken, and 25 ml of ethanol was added.The mixture was refluxed at 125^0c and monitored on TLC by using Ethyl acetate:n-Hexane(1:4) for completion of reaction. After 3 hours, the product was collected and extracted with ethyl acetate and washed with10% HCl,followed by washing with water.It was then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure .This crude product was recrystallized by using hydroalcoholic solution.

Procedure for Synthesis of 1,7-diphenylhepta-1,6-diene-3,5-dione (B): In a clean,dry round bottom flask(RBF), Benzaldehyde(2.12g) ,Boron trifluorideetherate (BF_3Et_2O,12.3ml)and acetyl acetone(1.02ml) was taken, and 25 ml of ethanol was added.The mixture was refluxed at various temperatures and monitored on TLC by using Ethyl acetate:n-Hexane(1:4).After 3 hours, the product was collected and extracted with ethyl acetate and washed with10% HCl,followed by washing with water.It was then dried over Na_2SO_4. The solvent was removed under reduced pressure .The product was purified by column chromatography.

Procedure for Synthesis of 1,11-diphenylundeca-1,3,8,10-tetraene-5,7-dione(C): In a clean,dry round bottom flask(RBF), cinnamylaldehyde (4.95 ml, 0.02moles),Borontrifluoridetherate (BF_3Et_2O,12.3ml,0.01moles) and acetyl acetone(1.02 mll,0.01mole) was dissolved in 25 ml of ethanol . The mixture was refluxed at 125^0C and monitored on TLC by using Ethyl acetate:n-Hexane(1:4).After 3 hours, the product was collected and extracted with ehtyl acetate and washed with10% HCl, followed by washing with water.It was then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. This crude product was purified by column chromatography.

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Procedure for Synthesis 1,7-bis(3,4-dimethoxyphenyl)hepta-1,6-diene-3,5-dione(D): In a clean ,dry round bottom flask(RBF),3,4-dimethoxy benzaldehyde(3.3g) ,Boron trifluorideetherate (BF_3Et_2O,12.3ml)and acetyl acetone(1.02 ml) was taken, and 25 ml of ethanol was added.The mixture was refluxed at various temperatures and monitored on TLC by using Ethyl acetate:n-Hexane(1:4).After 3 hours, the product was collected and extracted with ehtyly acetate and washed with10% HCl,followed by washing with water.It was then dried over Na_2SO_4. The solvent was removed under reduced pressure .This crude product was purified by column chromatography.

Procedure for Synthesis 1,7-bis(2-hydroxyphenyl)hepta-1,6-diene-3,5-dione(E): In a clean ,dry round bottom flask(RBF),Salicylaldehyde(2.4 ml), Boron trifluorideetherate (BF_3Et_2O,12.3ml)and acetyl acetone(1.02 ml) was taken, and 25 ml of ethanol was added.The mixture was refluxed at 125^0C.The reaction was monitored on TLC by using Ethyl acetate:n-Hexane(1:4).After 3 hours, the product was collected and extracted with Ehtyl acetate and washed with10% HCl, followed by washing with water.It was then dried over Na_2SO_4. The solvent was removed under reduced pressure .This crude product was purified by column chromatography.

Procedure for Synthesis 1,7-bis(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione(F): In a clean ,dry round bottom flask(RBF),4-hydroxy benzaldehyde(2.44g) ,Boron trifluorideetherate (BF_3Et_2O,12.3ml)and acetyl acetone(1.02 ml) was taken, and 25 ml of ethanol was added.The mixture was refluxed at 125^oC, and monitored on TLC by using Ethyl acetate:n-Hexane(1:4).After 3 hours, the product was collected and extracted with ehtyly acetate and washed with10% HCl, followed by washing with water.It was then dried over Na_2SO_4. The solvent was removed under reduced pressure .This crude product was purified by column chromatography.

Procedure for Synthesis 1,7-bis(4-methoxyphenyl)hepta-1,6-diene-3,5-dione(G): In a clean ,dry round bottom flask(RBF), Anisaldehyde(2.7ml) ,Boron trifluorideetherate (BF_3Et_2O,12.3ml)and acetyl acetone(01.02ml) was taken, and 25 ml of ethanol was added.The mixture was refluxed at 125^0C .and monitored on TLC by using Ethyl acetate:n-Hexane(1:4).After 3 hours, the product was collected and extracted with ehtyly acetate and washed with10% HCl,followed by washing with water.It was then dried over Na_2SO_4. The solvent was removed under reduced pressure .This crude product was purified by column chromatography.

Procedure for Synthesis 1,7-bis(4-(dimethylamino)phenyl)hepta-1,6-diene-3,5-dione (H): In a clean ,dry round bottom flask(RBF),4-Dimethylamino benzaldehyde(5.9g),Boron trifluorideetherate (BF_3Et_2O,12.3ml)and acetyl acetone (1.02 ml) was taken, and 25 ml of ethanol was added.The mixture was refluxed at 125^0C and monitored on TLC by using Ethyl acetate:n-Hexane(1:4).After 3 hours, the product was collected and extracted with ehtyly acetate and washed with10% HCl,followed by washing with water.It was then dried over Na_2SO_4. The solvent was removed under reduced pressure .This crude product was purified by column chromatography.

Procedure for Synthesis 1,7-bis(2-nitrophenyl)hepta-1,6-diene-3,5-dione (I): In a clean ,dry round bottom flask(RBF), 2- Nitro benzaldehyde(3.022g) ,Boron trifluorideetherate (BF_3Et_2O,12.3ml)and acetyl acetone(1.02 ml) was taken, and 25 ml of ethanol was added.The mixture was refluxed at 125^0C monitored on TLC by using Ethyl acetate:n-Hexane(1:4).After 36hours, the product was collected and extracted with Ethyl acetate and washed with10% HCl,followed by washing with water. It was then dried over Na_2SO_4. The solvent was removed under reduced pressure .This crude product was purified by column chromatography.

III. INSTRUMENTAL ANALYSIS

Uv Spectrophotometer

Uv-vis absorption spectra: methanol (solvent) for Compound A(Figure 2).

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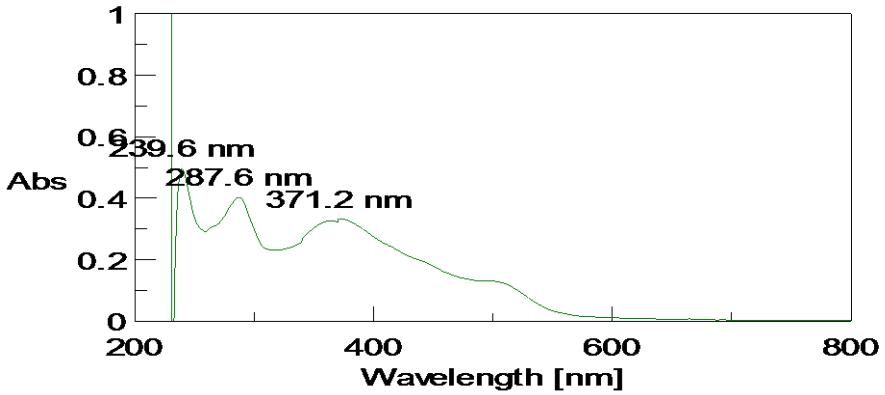

Figure 2: Absorption spectra of compound A

IR Analysis

Compound A: 3398.57 O-H Stretching, 1031.92 C-H bending, 2939.52 C-H stretching, 1514.2 C=C Stretching (aromatic),1624.06 ketone.

CompoundB:3059,3026,2879(C-H STRETCH), 1066.64,752.24,696.30(C-H bending), 1689.64 (C=O ,KETONE), 1539,1494 (C=C STRETCH).

Compound C: 3026.93, 2925.48 (C-H stretch), 1076.05 ,755.5(C-H bending), 1671.98(C=O STRETCH ,KETONE), 1503.08 (C=C Stretch).

CompoundD:2997.38,2833.43(C-Hstretch),1022.27,852.54,806.25,765.85(C-H bending), 1658.32 (C=O stretch ,ketone), 1508.33, 1267.23(C=C stretch), 1139.93 (C-O alkoxy).

Compound E: 3215.34(O-H stretch), 2360.87 (C-H streth), 1157.29,833.25(C-H bending), 1512.19(C=C stretching), 1600.92, 1676.14(C=O stretch , ketone).

Compound F: 3210.54 (N-H stretching, amino compounds), 1348.98 (C-N stretch), 2903.98(C-H stretch), 897.64(C-H bending), 1651.98(C=O stretch ,ketone).

NMR Analysis

Salicylaldehyde&Benzaldehyde: AR- OH- 4.7:4.43 (singlet), R-CHO-9.7:9.12 (singlet), RCHO-9.7:9.12 (singlet)

Vanillin: AR-OH-4.7: 6.60 (singlet), R-CHO- 9.7: 9.53(singlet), R-OCH_3-3.8:3.82(triplet)

3,4-dimethoxy benzaldyehyde: AR-CH_3-2.3:2.6 (triplet), R-CHO-9.7:9.8(singlet)

Anisaldehyde: R-CHO-9.7:9.7(singlet), R-OCH_3-3.8:3.68(triplet)

IV. RESULT AND DISCUSSION

Synthesis of new moiety with newer approach was successfully carried out. Replacement of catalyst was was done and compared. Boric oxide and Boric anhydride was replaced by Boron trifluorideEtherate and reaction was optimized. Parameters like number of moles of reactants, catalyst used ,temperatue of reaction and solvent used were monitored and optimized. We developed the reaction which was time saving ,clean and neat.The synthesized compounds were characterised by their physical constants and spectral studies like UV, IR.

V. CONCLUSION

Curcumin and its analogues can be better candidate in coming future as anticancer and antioxidant . Keeping this in mind we synthesized curumin analogues . The work involves replacement of catalyst to obtain better results so in present work we developed Boron trifluorideetherate as catalyst for synthesis of substitutes 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. The yield of reaction was better and reaction time was also less as compared to other methods.

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