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SILICASUPPORTED COPPER(II) OXIDE FOR THE SYNTHESIS OF CURCUMIN DERIVATIVES CONTAINING PYRAZOLE AND ISOXAZOLE SCAFFOLDS

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ABSTRACT

Preparation of CuO/SiO_2catalyst has been done via sol-gel method using copper nitrate solution and TEOS as precursors. Several instruments such as FT-IR, SEM, EDAX, XRD and particle sizer were employed to characterize the obtained material. Then, CuO/SiO_2 catalyst was successfullyusedin the synthesis of three curcumin derivatives, 4,4'-((1*E*,1'*E*)-(1*H*-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) (Compound 1), 4,4'-((1*E*,1'*E*)-(1-phenyl-1*H*-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) (Compound 2) and 4,4'-((1*E*,1'*E*)-(isoxazole-3,5-diylbis(ethene-2,1-diyl))bis(2-methoxyphenol) (Compound 3) with good yields.

Keywords: Heterogeneous Catalyst, Curcumin, Pyrazole, Isoxazole.

INTRODUCTION

Curcumin is a polyphenol compound present in *Curcuma longa* L. rhizomes (turmeric).[1] Along with demethoxycurcumin and bisdemethoxycurcumin, they are called curcuminoids. It mainly contributes to pharmacological activities of turmeric, such as antioxidant and antimicrobial.[2-4] Curcumin has been known to demonstrate a wide spectrum of bioactivities like anticancer, antitumor, anti-inflammatory, antidiabetic and analgesic properties.[5-9] However, the potential utility of curcumin as therapeutics molecule is limited due to its poor bioavailability. The presence of 1,3-diketone moiety makes it quickly decomposed in neutral and basic conditions.[10-12] To circumvent the problem of rapid degradation and metabolism, there is a challenge to modify curcumin structure, specifically in active methylene and carbonyl groups.[13]

Pyrazole and isoxazole are aromatic five-membered heterocyclic molecules constituted by three carbons and existence of N-N or N-O bond, respectively. These moieties in secondary metabolites are rare.[14] Even though, they play a prominent role in medicinal chemistry because of pyrazole and isoxazole scaffolds found in many marketed drugs, such as celecoxib (anti-inflammatory), rimonabant (anti-obesity), fezolamine (antidepressant), sulfamethoxazole and cycloserine (antibiotics).[15-17] In this line of continuation to obtain pyrazole and isoxazole derivatives of curcumin, we report the synthesis of three derivative compounds using CuO/SiO_2 catalyst.

EXPERIMENTAL

Materials

Chemicals used were an analytical grade, such as curcumin for synthesis (Merck), hydrazine hydrate (Sigma-Aldrich), hydroxylamine hydrochloride (Sigma-Aldrich), tetraethyl orthosilicate (Merck), glycerol (Merck), HNO_3 (Merck), glacial acetic acid (Merck), ethanol (Merck). Infrared spectra were recorded on Shimadzu Prestige 21 spectrophotometer, whereas UV-Vis spectra on Shimadzu UV Visible spectrophotometer model UV-mini 1240. The size distribution was measured using Beckman Coulter LS 13 320 particle sizing analyzer. Identification of organic compounds was done by UPLC-MS ACQUICITY UPLC H-Class Xevo G2-S QTof. Morphology and elemental composition were analyses using Zeiss MultiSEM505 tandem EDAX instruments.

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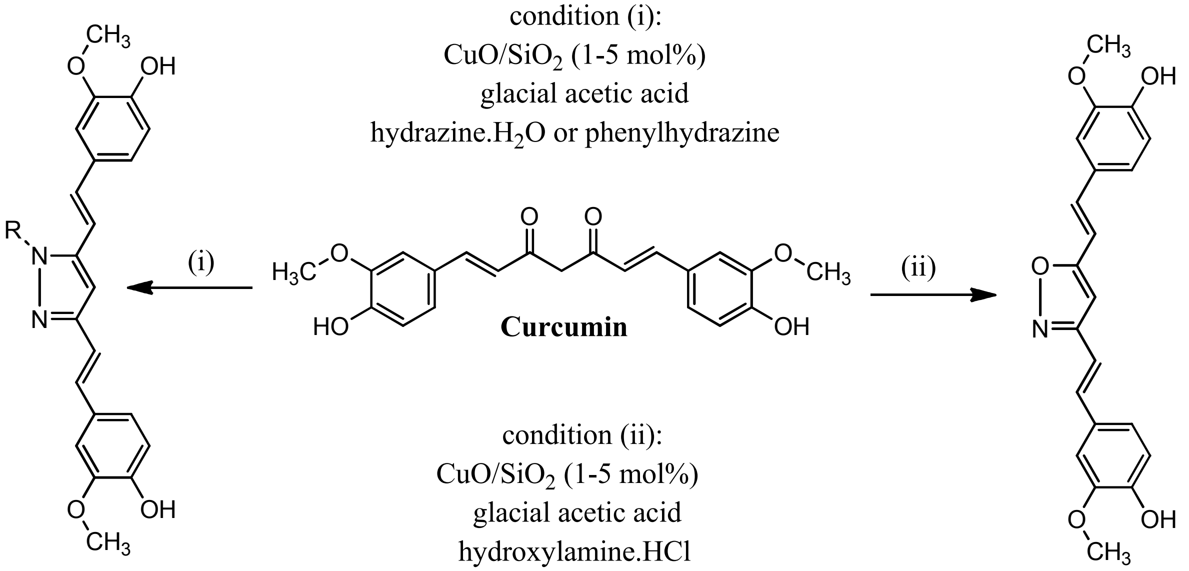
Preparation of CuO/SiO_2 Catalyst

Copper nitrate (1 M), TEOS (10 ml) and glycerol (5 ml) were mixed in a 100 ml Erlenmeyer flask. Then, the pH of the solution was adjusted to 1.5 by adding dilute nitric acid. The mixture was stirred for 3h while ammonia was added dropwise until pH 8-9. The resulting gel was filtered and washed with ethanol. It was stored in water/ ethanol 1:1 solvent for 48-72 h. The mixture was filtered and the residue was dried in an oven at 100ºC for 3h. Subsequently, the residue was calcined at 500ºC for 5h to produce CuO/SiO_2.[18]



Compound 1 (R = H)
Compound 2 (R = Ph)

Compound 3

Fig.-1: Scheme of the Synthesis of Curcumin Derivatives

Synthesis of Curcumin Derivatives

In a 50 ml round-bottom flask equipped with condenser, a mixture containing curcumin (0.6 mmol), hydrazine hydrate (2.25 mmol), and glacial acetic acid (5 ml) was stirred in the presence of different amount of catalyst (0-5 % mol) for various reaction time (6, 7, 8 and 9 h) at specified temperature (60, 70, 80 or 90ºC). After filtration to separate the catalyst, the filtrate was extracted two times with 15 ml of ethyl acetate:water (1:1) for each process. Anhydrous sodium sulfate was added to the combined organic fraction to remove water molecules. The fraction was subjected to vacuum evaporator to yield a crude product. It was then recrystallized from hot ethanol to obtain Compound 1. Meanwhile, the synthesis of Compound 2 and Compound 3 was performed using optimized conditions by changing hydrazine hydrate with phenylhydrazine (2.25 mmol) or with hydroxylamine hydrochloride (1.5 mmol).

RESULT AND DISCUSSION

Catalyst Characterization

Silica and materials containing silica have been widely used in many fields because of its prominent properties.[19-22] Herein, we reported the preparation of silica-supported copper(II) oxide catalyst. FT-IR spectrum of CuO/SiO_2catalyst (Fig.-2a) showed the typical asymmetric stretch of Cu-O at 470 cm^{-1}. Meanwhile, the peaks centered at 1090 and 805 cm^{-1} were observed due to deformation of Si-O bond.[23] The CuO/SiO_2 material also showed a band at 960 cm^{-1}. It is due to the overlapping between the Si-OH bond and Si-O bending vibration.[24] The intense peaks at 3410 and 1620 cm^{-1} correspond to hydroxyl groups and absorbed water to the CuO/SiO_2 surface.

The XRD patterns of the prepared $CuO/SiO_2$was depicted in Fig.-2(b). It can be clearly observed that the few sharp peaks are seen at diffraction angles (2 theta) of 35.4º, 38.6º, 48.8º, 53.5º, 58.3º, 61.5º, 66.2º, 68.0º, and 72.3º. These peaks are fit with the literature No. 48-1548 (JCPDS data Card) of the monoclinic copper oxide.[25,26] There was no presence of peaks for silica because it is an amorphous material.[23] CuO/SiO_2 morphology was observed by SEM, and the micrograph was shown in Fig.-2c. Because of its considerable porosity and structure rigidity, silica is prominent support for various catalysts.[23]

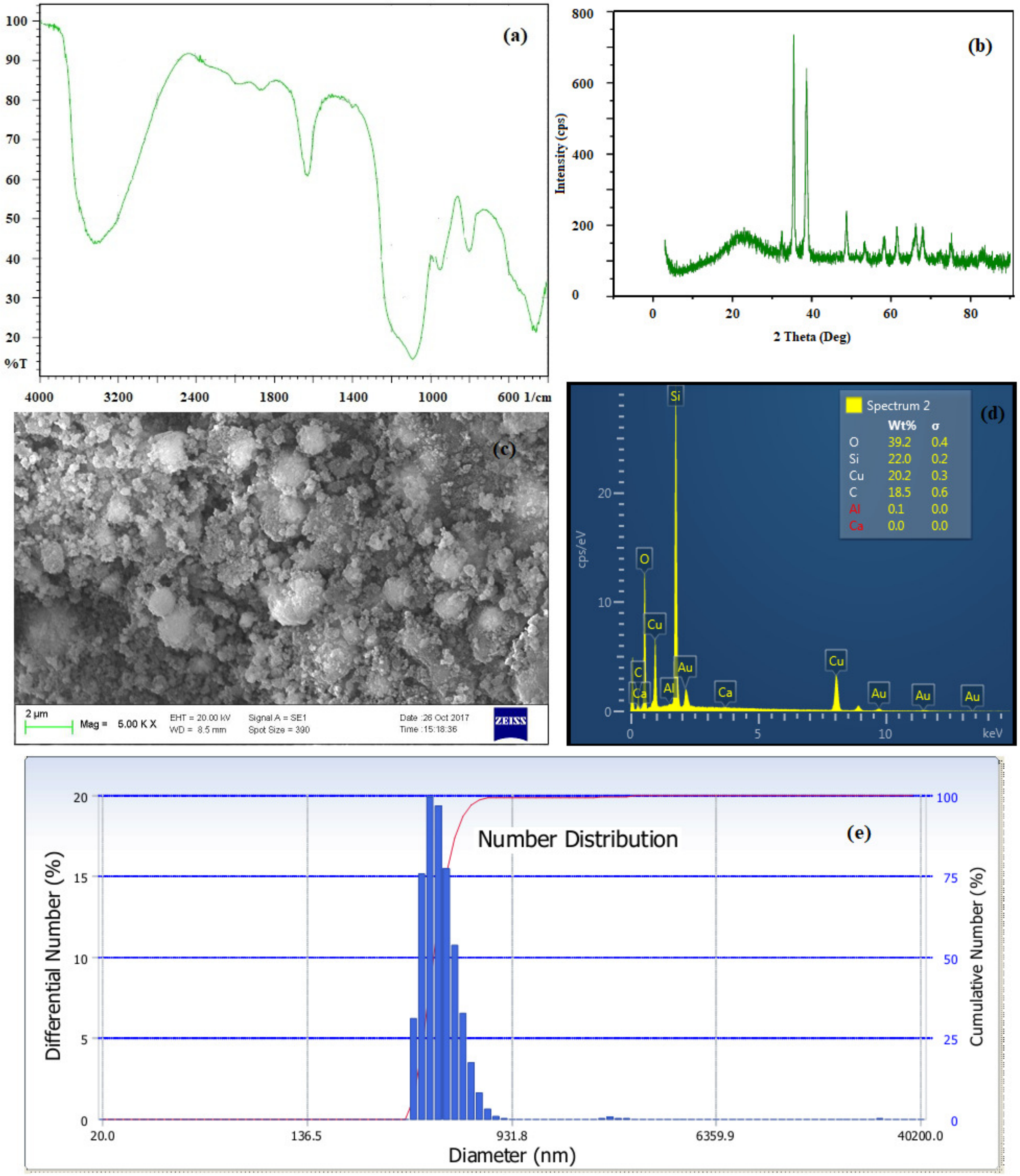


Fig.-2: (a) FT-IR Spectrum, (b) XRD Pattern, (c) SEM Image, (d) EDAX Spectrum and (e) Size Distribution of the Prepared Catalyst

In this case, the SEM image of CuO/SiO_2 showed impregnation of copper oxide on the silica surface. Discontinuity and rough surface of prepared material signified the success of impregnation process. The elemental content of the prepared $CuO/SiO_2$was measured using energy dispersive X-ray (EDAX) analysis

(Fig.-2d). EDAX spectrum of catalyst revealed the intense peaks of silicon (Si) and oxygen (O). Few appeared peaks of copper (Cu) indicated that the obtained material is principally composed by silica with a trace of copper oxide.[27] Analysis using particle sizer (Fig.-2e) was done to obtain the size distribution of CuO/SiO_2. The average size of this material was 525.1 nm.

Synthesis of Curcumin Derivatives

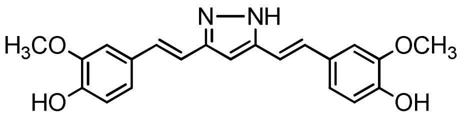
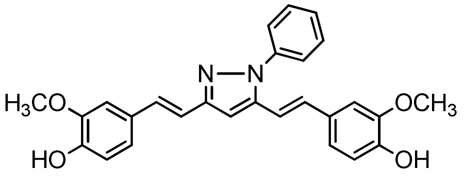
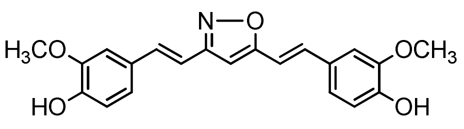
The cyclization reaction between curcumin and hydrazine hydrate was first carried out at 80ºC in the presence of 1 mol% of CuO/SiO_2 catalyst for 6-9 h. The highest yield was obtained after 8 h reaction time in continuous stirring equipped with a condenser (Table-1 Entry 3). The temperature was also varied from 60-90ºC. Moreover, we observed the reaction in the absence of a catalyst. Resultantly, the yield of product was only 59%. Raising the amount of catalyst from 1 to 2.5 or 5 mol% did not increase the yield of Compound 1. Therefore, we presume that Entry 3 with detailed conditions is the best procedure to synthesize this compound. Under the same condition, we have synthesized Compound 2 and 3 with 81 and 80% yield, respectively (Table-2).

Table-1: Optimization in the Synthesis of Compound 1

Entry	Time (h)	T (ºC)	Catalyst (mol%)	Yield (%)
1	6	80	1	60
2	7	80	1	64
3	8	80	1	85
4	9	80	1	78
5	8	60	1	70
6	8	70	1	82
7	8	90	1	81
8	8	80	Free	59
9	8	80	2.5	80
10	8	80	5	82

Reaction conditions: curcumin (0.60 mmol), hydrazine hydrate (2.25 mmol), absence or presence of CuO/SiO_2 catalyst. The reaction was carried out in a round-bottom flask equipped with a condenser.

Table-2: Characterization Data and Yield of Curcumin Derivatives

Compd.	Structure	Characterization Data	Yield (%)
1		Orange solid. IR (1/cm): 3560 (O-H), 3320 (N-H), 3050-3010 (C-H sp^2), 2940-2850 (C-H sp^3), 1602 (C=C), 1563 (C=N), 1480 (phenyl ring), 1140 (C-O). UV-Vis (nm): 326. HRMS (m/z): 365.1499 ($[M+1]^+$).	85
2		Orange solid. IR (1/cm): 3480 (O-H), 3360 (N-H), 3040-3030 (C-H sp^2), 2850 (C-H sp^3), 1598 (C=C), 1565 (C=N), 1480 (phenyl ring), 1100-1040 (C-O). UV-Vis (nm): 326. HRMS (m/z): 441.1824 ($[M+1]^+$).	81
3		Brown solid. IR (1/cm): 3481 (O-H), 3325 (N-H), 3030-3005 (C-H sp^2), 2950-2900 (C-H sp^3), 1597 (C=C), 1524 (C=N), 1440 (phenyl ring), 1070 (C-O). UV-Vis (nm): 421, 334. MS (m/z): 366.1352 ($[M+1]^+$).	80

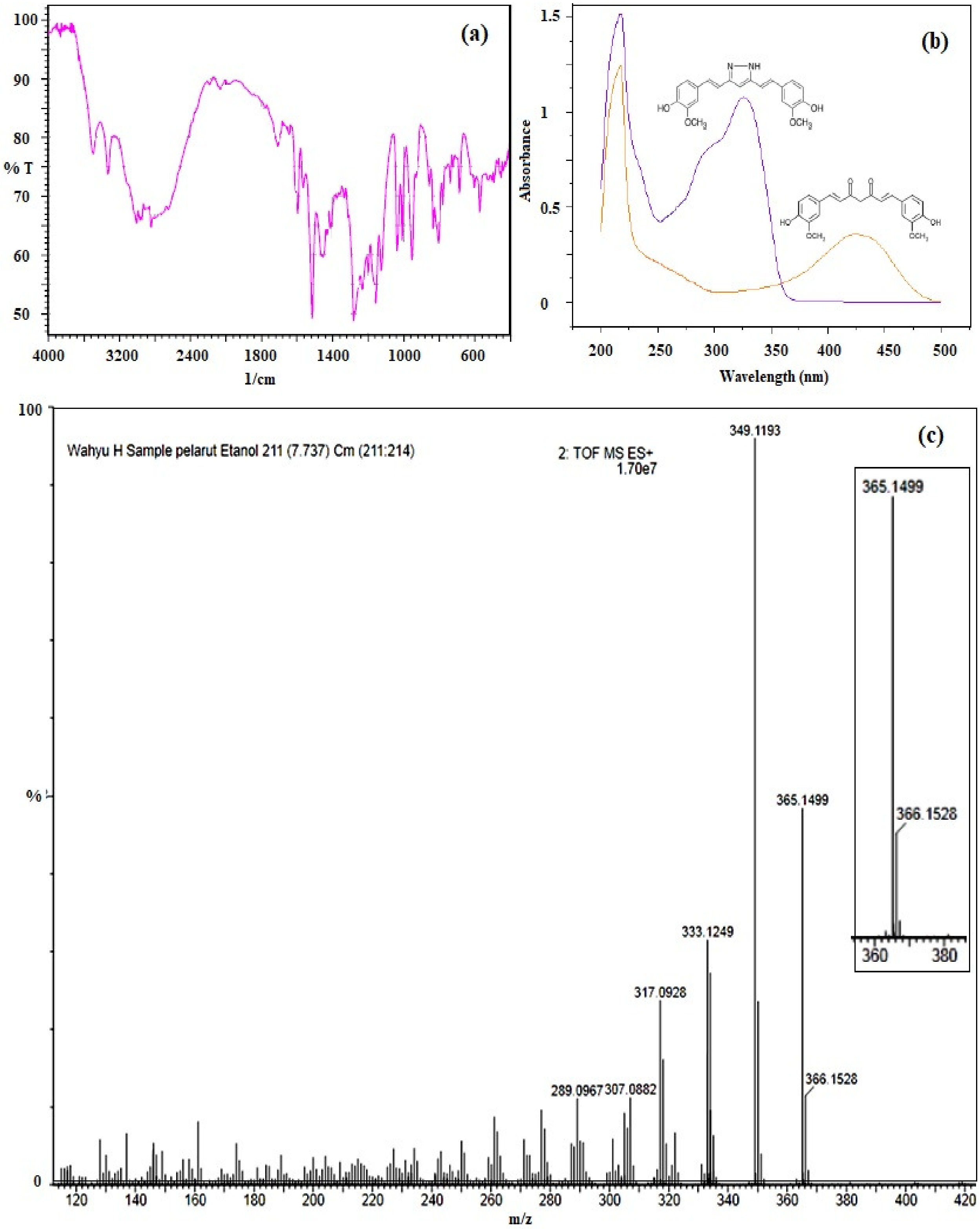


Fig.-3: (a) FT-IR, (b) UV-Vis and (c) MS Spectra of Selected Curcumin Derivatives (Compound 1)

Characterization of Curcumin Derivatives

Figure-3(a) showed the FT-IR spectrum for the synthesized Compound 1, where it is possible to see the presence of characteristic functionalities such as O-H stretching vibration occurs at approximately 3560 cm^{-1}. The peak of C=N in pyrazole skeleton is mainly observed in the spectrum at 1563 cm^{-1}. A band near 1602 $cm^{-1}$is corresponds to C=C bond of olefin exist. Also, bands for stretching vibration of sp^2 and sp^3 C-H are located at 3050-3010 and 2940-2850 cm^{-1}, respectively. At 1480 cm^{-1} the band assigned to the phenyl ring vibration, and at 1140 cm^{-1} the peak band of C-O appears. In UV-Vis analysis (Fig.-3b), the typical bathochromic effect was found due to the decrease of a number of conjugated double bonds in the structure. Compound 1 has a maximum wavelength at 321 nm, whereas curcumin as starting material at 423 nm. Meanwhile, Compound 2 has also 326 nm of maximum wavelength, whereas Compound 3 has two major absorptions at 421 and 334 nm. Confirmation of product structures was done by mass spectrometry (Fig.-3c). These three compounds have $[M+1]^+$peak at MS spectra. All characterization data are in agreement with previously reported works.[1,28,29]

CONCLUSION

We described the preparation and characterization of CuO/SiO_2 catalyst via sol-gel method. The $CuO/SiO_2$was successfully applied as an efficient catalyst in the synthesis of three curcumin derivatives integrated with pyrazole and isoxazole moieties. The organic products were obtained in good yields.

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