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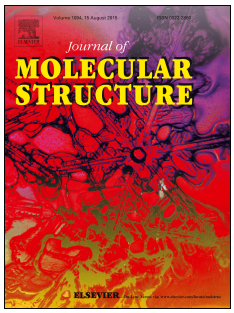

Green synthesis, antioxidant and antibacterial activities of 4-aryl-3,4-dihydropyrimidinones/thiones derivatives of curcumin. Theoretical calculations and mechanism study

Nassima Khaldi-Khellafi, Malika Makhloufi-Chebli, Djamila Oukacha-Hikem, Souhila Terachet Bouaziz, Kamilia Ould Lamara, Taous Idir, Amina Benazzouz-Touami, Françoise Dumas

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Graphical Abstract

Green synthesis, Antioxidant and antibacterial activities of 4-aryl-3,4-dihydropyrimidinones/thiones derivatives of curcumin. Theoretical calculations and mechanism study.

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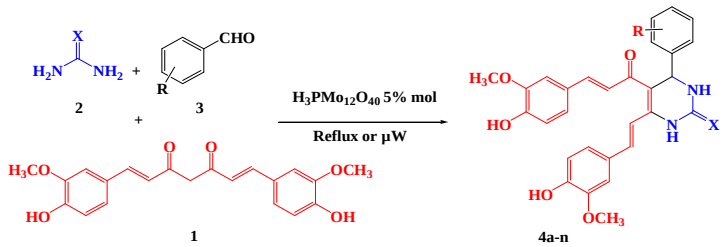

An efficient green synthesis of 3,4-Dihydropyrimidin-2(1*H*)-one/thione analogs of curcumin was developed involving a one-pot multi-component cyclocondensation of curcumin using substituted aromatic aldehydes and urea/thiourea catalysed by commercial heteropolyacid Keggin type $H_3PMo_{12}O_{40}$ catalyst under conventional heating and microwave irradiation. The derivatives were screened for antioxidant and antimicrobial activity.

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ABSTRACT

3,4-Dihydropyrimidin-2(1*H*)-one/thione analogs of curcumin were synthesized in good yield by a one-pot multi-component cyclocondensation using curcumin, substituted aromatic aldehydes, and urea/thiourea in less volume of ethanol catalysed by commercial heteropolyacide Keggin type $H_3PMo_{12}O_{40}$ 5% mol as a recyclable and nontoxic catalyst under conventional heating and microwave irradiation. All the synthesized curcumin derivatives 4a–n were screened for antioxidant and antimicrobial activity. Biological activity data of the synthesized showed that most of the synthesized compounds exhibited greater antioxidant and antibacterial activity than curcumin. Geometries of synthesized compounds were optimized by using B3LYP method with 6-31G* basis set. Then, DFT based reactivity descriptors such as HOMO, LUMO, chemical hardness, electronegativity, chemical potential were calculated and discussed.

Introduction*

Curcumin **1**, which imparts the yellow color to curry, is a natural product of the spice turmeric, *Curcuma longa* L. (Zingiberaceae). Curcumin **1** exhibits a variety of pharmacologic activities including anti-inflammatory, anticancer, antioxidant, wound-healing and antimicrobial effects [1], antiallergic activity [2,3] and inhibits degranulation of the RBL-2H3 tumor mast cell line in culture [4,5]. Also, it prevents biliary disorders, anorexia, coughs, diabetes, hepatic disorders, rheumatism, sinusitis, cancer and Alzheimer's disease [6,7]. The ethyl acetate extract of *Curcuma longa* L. and curcumin were found to decrease histamine release from mast cells by blocking intracellular signalling events in mast cells. The anti-allergy activities of curcumin 1 and curcumin-related compounds are in relation to their antioxidant activities. Most of these compounds were shown to inhibit histamine release from RBL-2H3 cells induced by concanavalin A or a calcium ionophore [8]. Chemically, curcumin **1** or 1,7-bis(4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione consists of two backbones, each with a ketone linked to a central $–CH_2$ group separating the backbones and a terminal meta-methoxy-para hydroxyl phenyl ring on each side. It has been suggested that the antioxidant activity of the curcumin molecule depends upon the presence of a phenolic group [9]. Other studies concluded that the hydrogens of active methylene group are important for antioxidant activity [10], or that the both active methylene group and phenolic groups are responsible as well [11].

Pyrimidinone derivatives are widely distributed in nature and exhibit various biological properties, such as antimalarial [12-14], antibacterial [15], antifungal [l6], anti-HIV [17], antiviral [18], anticancer [19] and anti-inflammatory [20,21] activities. Therefore, the corresponding dihydropyrimidinones (DHPMs) exhibited important therapeutic and pharmacological properties, namely as the integral backbone of several calcium channel blockers [22], antihypertensive agents [23] and α1a-antagonists [24]. A broad range of biological effects including antiviral, antitumor, antibacterial, and anti-inflammatory activities have been described for these compounds [24-26]. Functionalized DHPMs have shown significant antibacterial

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[27], antiviral [28] and antitumor [29] activities. The synthesis of DHPMs has been the focus of great interest for organic and medicinal chemists [24,27].

The development of dihydropyrimidinones/thiones scaffolds as biologically active compounds contributed toward Biginelli cyclocondensation application in drug industry. The biological significance of curcumin **1** and dihydropyrimidinones/thiones inspired us to synthesize these compounds and evaluate them as antioxidant and antibacterial agents. Earlier 3,4-dihydropyrimidin-2(H)-one/thione analogs of curcumin were reported and synthesized by $SnCl_2.2H_2O$ [30], chitosamine hydrochloride [31] and H_2SO_4 [32] as catalysts.

In continuation of our interest on the synthesis of heterocycles, using polyoxometallates as green catalysts [33-36], herein we describe a simple and efficient strategy for the synthesis of a series of 4-aryl-5-(4-Hydroxy-3-methoxyphenyl ethylene carbonyl)-6-(4-hydroxy-3-methoxyphenylethylene)-3,4-dihydropyrimidin-2(1*H*)-ones/thiones 4**a-e** under mild conditions using curcumin as a key synthon. In the present study, commercial heteropolyacide Keggin type $H_3PMo_{12}O_{40}$ was used as catalyst to accomplish the synthesis by conventional heating and under microwave irradiation, and the percentage yields of the compounds were compared with the reported ones. Antioxidant and antibacterial studies were also performed.

Experimental

2.1. Materials and Methods

The chemicals reagents and solvents (Fluka products) used were of analytical grade and were used without further purification. Melting points were determined on a Stuart scientific SPM3 apparatus fitted with a microscope and are uncorrected. The infrared spectra were recorded in the region 4000–400 cm^{-1} on a BRUKER TENSOR 27 IR spectrophotometer without KBr. Electronic spectra were measured on a JENWAY 6800 ultraviolet-visible spectrophotometer; measurements were made from 200 to 800 nm. The elemental microanalysis (C, H, N) was carried out by the Truspec 630-200-200 Elementary Analysis-Equipment, Service of Microanalysis, Department of Chemistry-University of Aveiro, Portugal. The needle voltage was set at 3000 V, with the ion source at 80 °C and desolvation temperature at 150 °C. Cone voltage was 35 V. Screening of the compounds for antimicrobial activity was done at the Pharmaceutics laboratory. The compounds were synthesized using adaptation of previous reports [30,31]. For synthesis under irradiation, a multimode microwave reactor (a modified household microwave oven Candy mga20 m) used as a single magnetron (2450 MHz) with a maximum delivered power of 800 W. It was directly graduated in W (from 100 to 800 W). Experiments were carried out in a Pyrex reactor fitted with a condenser. During experiments, time, temperature and power were monitored. Temperature was monitored with the aid of an external infrared (IR) thermometer (Flashpoint FZ400). The progress of the reactions was monitored throughout by TLC plates (silica gel G) using mobile phase, dichloromethane: methanol (5:1), and the spots were identified by iodine vapors or UV light.

2.2. General method for the synthesis of 3,4-dihydropyrimidin-2(H)-one/thione analogs of curcumin

A 50 ml round-bottom flask was charged with equimolar mixture of curcumin (0.002 mol; 0.736 g) and substituted aldehydes (0.002 mol) with urea/thiourea (0.003 mol) dissolved in ethanol (2 mL) and $H_3PMo_{12}O_{40}$ (5 mol%), and was refluxed for 6-9 h by conventional heating or irradiated under microwaves for 150-210 s. The reaction was monitored throughout by TLC plates (silica gel G) using mobile phase, dichloromethane: methanol (5:1). After completion of reaction, 2/3rd of the solvent was removed, and the reaction mixture was poured into crushed ice. The precipitate was filtered, washed with hot water, dried, and purified with diethyl ether. Finally the obtained pure curcumin-3,4-dihydropyrimidin-2(1*H*)-one/thione derivatives **4a-n** were identified by melting point measurement, UV-visible spectroscopic methods, FT-IR and elemental analysis. The known compounds have been identified by comparison of IR spectral data and Mp with those reported [30-32]. The general pattern of the reaction is depicted in Scheme 1.

2.2.1 5-(4-Hydroxy-3-methoxyphenylethylene carbonyl)-6-(4-hydroxy,3-methoxyphenylethylene)-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (**4a**): This compound was obtained as dark red powder, mp 203–205 °C; UV/Vis: λabs (DMSO)/nm 272, 365; IR (cm^{-1}): ν 3506 (OH), 3364 (-NH), 2941 (-CH), 1596 (C=O), 1509 (C=C), 1269 (-C-O); Anal. Calcd. for $C_{29}H_{26}N_2O_6$: C, 69.87; H, 5.26; N, 5.62. Found: C, 69.80; H, 5.30; N, 5.56.

2.2.2 5-(4-Hydroxy-3-methoxyphenylethylene carbonyl)-6-(4-hydroxy,3-methoxyphenylethylene)-4-(4-N,N-dimethylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**4b**): This compound was obtained as dark green crystals, mp 194–196 °C; UV/Vis: λabs (DMSO)/nm 270, 347, 426; IR (cm^{-1}): ν 3494 (OH), 3405 (-N-H), 2934 (-CH), 1587 (C=O), 1507 (C=C), 1261 (-C-O); Anal. Calcd. for $C_{31}H_{31}N_3O_6$: C, 68.75; H, 5.77; N, 7.76. Found: C, 68.81; H, 5.80; N, 7.67.

2.2.3 5-(4-Hydroxy-3-methoxyphenylethylene carbonyl)-6-(4-hydroxy,3-methoxyphenylethylene)-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**4c**): This compound was obtained as dark red powder, mp 198–200 °C; UV/Vis: λabs (DMSO)/nm 270, 369, 428; IR (cm^{-1}): ν 3471 (OH), 3368 (-NH), 2940 (-CH), 1583 (C=O), 1507 (C=C), 1265 (-C-O), Anal. Calcd. for $C_{29}H_{25}ClN_2O_6$: C, 65.35; H, 4.73; N, 5.26. Found: C, 65.31; H, 4.80; N, 5.30.

2.2.4 5-(4-Hydroxy-3-methoxyphenylethylene carbonyl)-6-(4-hydroxy,3-methoxyphenylethylene)-4-(2-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**4d**): This compound was obtained as brick red crystals, mp 149–150 °C; UV/Vis: λabs (DMSO)/nm 271, 363, 427; IR (cm^{-1}): ν 3462 (OH), 3359 (-NH), 2961 (-CH), 1587 (C=O), 1507 (C=C), 1261 (-C-O), Anal. Calcd. for $C_{29}H_{26}N_2O_7$: C, 67.70; H, 5.09; N, 5.44. Found: C, 67.65; H, 5.23; N, 5.36.

2.2.5 5-(4-Hydroxy-3-methoxyphenylethylene carbonyl)-6-(4-hydroxy,3-methoxyphenylethylene)-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**4e**): This compound was obtained as dark green crystals, mp 150–152 °C; UV/Vis: λabs (DMSO) nm 278, 349, 428 ; IR (cm^{-1}): ν 3488 (OH), 3358 (-N-H), 2940 (-CH), 1587 (C=O), 1507 (C=C), 1268 (-C-O), Anal. Calcd. for $C_{29}H_{26}N_2O_7$: C, 67.70; H, 5.09; N, 5.44. Found: C, 67.55; H, 5.19; N, 5.50.

2.2.6 5-(4-Hydroxy-3-methoxyphenylethylene carbonyl)-6-(4-hydroxy,3-methoxyphenylethylene)-4-(3,4-dihydroxyphenyl)-

3,4-dihydropyrimidin-2(*1H*)-one (**4f**): This compound was obtained as dark green crystals, mp 220–222 °C; UV/Vis: λabs (DMSO)/nm 270, 363, 429; IR (cm^{-1}): ν 3465(OH), 3358(-NH), 2934(-CH), 1573 (C=O), 1500 (C=C), 1268 (-C-O); Anal. Calcd. for $C_{29}H_{26}N_2O_8$: C, 65.65; H, 4.94; N, 5.28. Found: C, 65.70; H, 5.03; N, 5.32.

2.2.7 5-(4-Hydroxy-3-methoxyphenylethylene carbonyl)-6-(4-hydroxy,3-methoxyphenylethylene)-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (**4g**): This compound was obtained as brown crystals, mp 157–159 °C; UV/Vis: λabs (DMSO)/nm 272, 368, 436; IR (cm^{-1}): ν 3664 (OH), 3365(-N-H), 2980 (-CH), 1587(C=O), 1513 (C=C), 1255 (-C-O); Anal. Calcd. for $C_{29}H_{25}N_3O_8$: C, 64.08; H, 4.64; N, 7.73. Found: C, 64.14; H, 4.70; N, 7.46.

2.2.8 5-(4-Hydroxy-3-methoxyphenylethylene carbonyl)-6-(4-hydroxy,3-methoxyphenylethylene)-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione (**4h**): This compound was obtained as dark brown crystals, mp 214–216 °C; UV/Vis: λabs (DMSO)/nm 272, 365; IR (cm^{-1}): ν 3517 (OH), 3345 (N-H), 2934 (-CH), 1579 (C=O), 1513 (C=C), 1268 (-C-O); Anal. Calcd. for $C_{29}H_{26}N_2O_5S$: C, 67.69; H, 5.09; N, 5.44. Found: C, 67.45; H, 4.93; N, 5.26.

2.2.9 5-(4-Hydroxy-3-methoxyphenylethylene carbonyl)-6-(4-hydroxy,3-methoxyphenylethylene)-4-(4-N,N-dimethylphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (**4i**): This compound was obtained as dark green crystals, mp 195–197 °C; UV/Vis: λabs (DMSO)/nm 271, 348, 398; IR (cm^{-1}): ν 3611 (OH), 3345 (-N-H), 2940 (-C-H), 1587 (C=O), 1507 (C=C), 1261 (-C-O); Anal. Calcd. for $C_{31}H_{31}N_3O_5S$: C, 66.77; H, 5.60; N, 7.54. Found: C, 66.45; H, 5.93; N, 5.46.

2.2.10 5-(4-Hydroxy-3-methoxyphenylethylene carbonyl)-6-(4-hydroxy,3-methoxyphenylethylene)-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (**4j**): This compound was obtained as dark brown powder, mp 198-200 °C; UV/Vis: λabs (DMSO)/nm 272, 370; IR (cm^{-1}): ν 3504 (OH), 3352 (-N-H), 2927 (-CH), 1579 (C=O), 1507 (C=C), 1261 (-C-O); Anal. Calcd. for $C_{29}H_{25}ClN_2O_5S$: C, 63.44; H, 4.59; N, 5.10. Found: C, 64.05; H, 4.83; N, 5.26.

2.2.11 5-(4-Hydroxy-3-methoxyphenylethylene carbonyl)-6-(4-hydroxy,3-methoxyphenylethylene)-4-(2-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (**4k**): This compound was obtained as dark green crystals, mp 260–262 °C; UV/Vis: λabs (DMSO)/nm 272, 374, 428; IR (cm^{-1}): ν 3604 (OH), 3339 (-NH), 2940 (-CH), 1579 (C=O), 1513 (C=C), 1261 (-C-O); Anal. Calcd. for $C_{29}H_{26}N_2O_6S$: C, 65.65; H, 4.94; N, 5.28. Found: C, 65.49; H, 4.93; N, 5.26.

2.2.12 5-(4-Hydroxy-3-methoxyphenylethylene carbonyl)-6-(4-hydroxy,3-methoxyphenylethylene)-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (**4l**): This compound was obtained as dark brown powder, mp 261–262 °C; UV/Vis: λabs (DMSO)/nm 277, 370; IR (cm^{-1}): ν 3506 (OH), 3372 (-NH), 1579 (C=O), 1507 (C=C), 1261 (-C-O); Anal. Calcd. for $C_{29}H_{26}N_2O_6S$: C, 65.65; H, 4.94; N, 5.28. Found: C, 65.45; H, 4.99; N, 5.42.

2.2.13 5-(4-Hydroxy-3-methoxyphenylethylene carbonyl)-6-(4-hydroxy,3-methoxyphenylethylene)-4-(3,4-dihydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (**4m**): This compound was obtained as dark green crystals, mp 212–214 °C; UV/Vis: λabs (DMSO)/nm 269, 379; IR (cm^{-1}): ν 3505(OH), 3332 (-NH), 1573 (C=O), 1513 (C=C), 1268 (-C-O); Anal. Calcd. for $C_{29}H_{26}N_2O_7S$: C, 63.72; H, 4.79; N, 5.13. Found: C, 63.45; H, 4.93; N, 5.26.

2.2.14 5-(4-Hydroxy-3-methoxyphenylethylene carbonyl)-6-(4-hydroxy,3-methoxyphenylethylene)-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (**4n**): This compound was obtained as dark green crystals, mp 206–208 °C; UV/Vis: λabs (DMSO)/nm 272, 373; IR (cm^{-1}): ν 3664 (OH), 3339 (NH), 2974 (-CH), 1573 (C=O), 1507 (C=C), 1255(-C-O); Anal. Calcd. for $C_{29}H_{25}N_3O_7S$: C, 62.24; H, 4.50; N, 7.51. Found: C, 62.19; H, 4.63; N, 7.36.

2.3. Screening for Antibacterial Activity

The antimicrobial activities of compounds **4a-n** were evaluated for their antibacterial activities against *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853) and *Staphylococcus aureus* (ATCC 25923) bacterial strains by the agar diffusion method [37]. A sterile physiological water solution containing a bacterial colony was prepared at room temperature, with an optical density of 0.08–0.10 corresponding to a concentration of 10^6 cells/mL. The bacterial solution was inoculated in the Muller-Hinton agar medium by swabbing using Petri dishes at room temperature. The tested compounds were dissolved in dimethyl sulfoxide (DMSO) with a 10^{-1} M concentration. Twenty-five microliters of tested sample were poured onto filter paper disks 6 mm in diameter, which were then delicately placed on the surface of the agar plates. These were later maintained at 37 °C for 24 h. Activities were determined by measuring the diameter of the inhibition zone (mm).

2.4. Antioxidant activity

The antioxidant activity (free radical scavenging activity) of the synthesized compounds and curcumin was evaluated by the first time using the 2,2-diphenyl-1-picrylhydrazyl free radical ($DPPH^{\cdot}$) scavenging assay [38,39]. $DPPH^{\cdot}$ solution was prepared by dissolving $DPPH^{\cdot}$ in ethanol to give a concentration of 4 mg/100 mL. Compounds **4a-n** and curcumin **1** were dissolved in DMSO to obtain a 10^{-1} M solution. The solutions of test compounds were diluted with DMSO to get final concentrations of 0.05, 0.025 and 0.0125mol/L for all the compounds. The standards were further diluted to give additional concentration solutions of 0.00625, 0.003125 and 0.0015625 mol/L. Each tested concentration of each compound (40 µL) was added to each well separately in duplicate and then $DPPH^{\cdot}$solution (2 mL) was added. Each negative control wells were loaded with DMSO (40 µL) and $DPPH^{\cdot}$solution (2 mL). After vortexing, the mixtures were incubated at room temperature for 1 h in darkness at 25 °C, and then the absorbance of these compounds at different concentrations was recorded at 517 nm. Ascorbic acid (AA) was used as standard for the antioxidant activity screening. A blank containing only ethanol with DMSO was used as the control. Each measurement was performed in triplicate. The reduction of the DPPH radical was measured by monitoring continuously the decrease of absorption at 517 nm. DPPH scavenging effect was calculated as percentage of DPPH discoloration using equation (1):

$$RSA\ (\%) = [(Ac - As)/Ac] \times 100 \qquad \text{Eq (1)}$$

where Ac is the absorbance of the control (absorbance of DPPH·ethanol solution without sample), and As is the absorbance of the sample compounds tested after 60 min incubation.

2.5. DFT analysis

Synthesized compounds were optimized by density functional theory (DFT) employing Becke's three-parameter hybrid model, Lee–Yang–Parr (B3LYP) correlation functional method with 6-31G* basis set and tight SCF convergence criteria. Geometries optimization was followed by frequency calculations at the same level of theory using ORCA v4 software [40]. In order to study the reactivity of studied compounds, the optimized structures were used to calculate some DFT-based global reactivity descriptors, such as Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital energy (LUMO). The energy associated with HOMO and LUMO were used to calculate the chemical potential (μ) and hardness (η) of system using the equations (2) and (3) below:

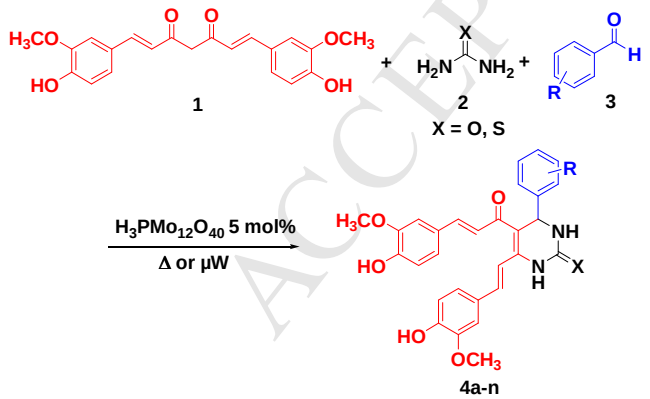
$$\mu = \frac{E_{LUMO} + E_{HOMO}}{2} \qquad \text{Eq (2)}$$

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2} \qquad \text{Eq (3)}$$

3. Results and discussion

3.1. Chemistry

Curcumin **1** was used as the starting material for the preparation of all compounds described in this paper (Scheme 1). A mixture of curcumin **1**, substituted aromatic aldehydes **3** (1eq) and urea/thiourea **2** (1.5eq) in minimum amount of ethanol (2mL) using commercial heteropolyacid Keggin type $H_3PMo_{12}O_{40}$ as a recyclable and nontoxic acid catalyst under conventional reflux and microwave irradiation through an improved procedure to obtain 3,4-dihydropyrimidin-2(1*H*)-one/thione analogs of curcumin **4a-n**.



Scheme 1. Synthesis of 3,4-dihydropyrimidinones/thiones of curcumin **4a-n** under conventional reflux (Δ) or μW irradiation.

The reaction was monitored throughout by TLC plates (silica gel G) using dichloromethane:methanol (5:1) as mobile phase.

In order to evaluate the catalytic efficiency of $H_3PMo_{12}O_{40}$ catalyst in the three component reaction, the mixture of curcumin **1**, benzaldehyde and urea was selected as the model reaction. It was shown that only 5 mol% of catalyst was sufficient to promote the reaction. Lower amounts gave a low yield even after long reaction time, and higher amounts did not improve the efficiency of this transformation. After optimization of the reaction conditions, in order to investigate the scope of this approach, we carried out the three component cyclocondensation reaction of curcumin **1** and urea/thiourea **2** with a series of aromatic aldehydes **3** under similar conditions. Color and physical appearance are given in table 1. Analytical and physicochemical data of synthesized curcumin-DHPMs using $H_3PMo_{12}O_{40}$ are given in Table 2. The reactions were completed after 6–9 h by conventional reflux and 2-3 min under μW irradiation, affording the corresponding curcumin-DHPMs in good to excellent yields. The structure of these compounds was confirmed by elemental analysis and by comparing the melting points and the spectroscopic data of FT-IR and UV-Visible with those reported in the literature.

Table 1. 3,4-Dihydropyrimidinones of curcumin **4a-n** synthesized under conventional reflux and μW irradiation using $H_3PMo_{12}O_{40}$.

Entry	Compound	R	X	Color and physical appearance
1	**4a**	H	O	Dark red powder
2	**4b**	4-N(CH_3)$_2$	O	Dark green crystals
3	**4c**	4-Cl	O	Dark red powder
4	**4d**	2-OH	O	Brick red crystals
5	**4e**	4-OH	O	Dark green crystals
6	**4f**	3,4-OH	O	Dark green crystals
7	**4g**	3-NO_2	O	Brown crystals
8	**4h**	H	S	Dark brown crystals
9	**4i**	4-N(CH_3)$_2$	S	Dark green crystals
10	**4j**	4-Cl	S	Dark brown powder
11	**4k**	2-OH	S	Dark green crystals
12	**4l**	4-OH	S	Dark brown powder
13	**4m**	3,4-OH	S	Dark green crystals
14	**4n**	3-NO_2	S	Dark green crystals

Excellent yields were obtained with the two heating methods; they are ranging from 80 to 98%. Earlier three different catalysts were used to accomplish the synthesis using conventional method: $SnCl_2.2H_2O$; yield 92-97% [30], microwave assisted synthesis: chitosamine hydrochloride; yield 90-96 % [31] and H_2SO_4, yield 71-86% [32]. When the same reaction carried out with conventional method and under microwave irradiation in the presence of $H_3PMo_{12}O_{40}$, the yield of the compounds was ranging between 80 and 98%. The use of $H_3PMo_{12}O_{40}$ as catalyst in these particular reaction was comparatively more efficient than the use of H_2SO_4 and by the two heating modes, while with the use of $SnCl_2.2H_2O$ catalyst and chitosamine hydrochloride the yields are always high.

Table 2 Analytical and physicochemical data of synthesized curcumin-DHPMs/thiones **4a-n** using $H_3PMo_{12}O_{40}$ as catalyst.

Compound	Time		Yield (%)					Mp (°C)	
			This work		Reported			This work	Reported
	Δ (h)	µW (s)	Δ	µW	H_2SO_4 [32]	$SnCl_2$ [30]	Chitosamine.HCl [31]		
4a	9	150	90	97	79	97	91	203-205	206-207 [31,32]
4b	9	180	80	93	-	-	-	194-196	-
4c	6	150	79	96	82	94	-	198-200	201-203 [31]
4d	9	150	83	97	-	96	93	149-150	150-152 [32]
4e	9	150	84	96	74	95	92	150-152	151-152 [32]
4f	9	150	81	96	-	-	-	220-222	-
4g	9	210	88	98	-	-	-	157-159	-
4h	9	150	85	95	73	95	91	214-216	217-219 [32]
4i	9	150	98	97	-	-	-	195-197	-
4j	6	150	80	96	76	96	-	198-200	202-204 [31]
4k	9	150	98	94	-	-	95	260-262	262-263 [32]
4l	9	150	93	95	71	93	93	261-262	261-263 [32]
4m	9	150	92	98	-	-	-	212-214	-
4n	9	210	95	97	-	-	-	206-208	-

Δ: conventional heating; µW: microwave irradiation.

A plausible reaction mechanism is shown in Scheme 2. In order to explain the formation of the DHPMs/thiones, we have calculated the charges of the electrophilic and nucleophilic sites of the three reagents via theoretical calculations DFT B3LYP/6-31G* using the ORCA software method [40] to identify the entities that react first and deduced the most likely intermediate (Figure 1 reports the charges of each atom in the molecules that participate in the reaction). Calculations show that the carbonyl carbon atoms of curcumin **1** are more positive than the carbon atom of the aldehyde function (see Fig.1 and the Supplementary material section), suggesting that the reactivity of urea **2** with curcumin **1** is the first step of the reaction, then intermediate **5** reacts with aldehydes **1** to give 3,4-dihydropyrimidinones **4a–n** (Scheme 2).

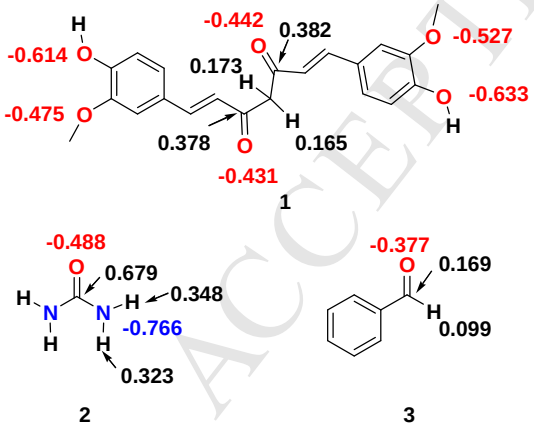
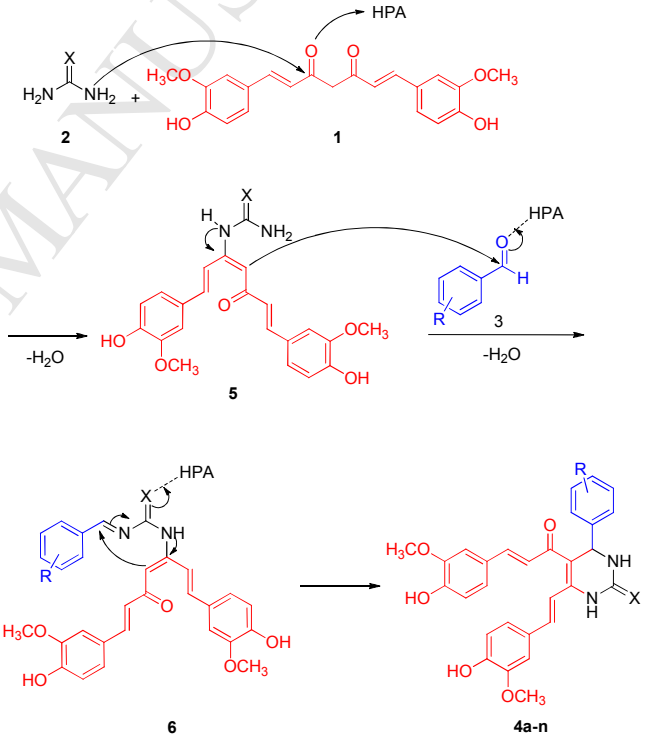


Figure 1. Selected partial charges of curcumin **1**, urea **2** and benzaldehyde **3** in ethanol using the ORCA software method.

3.2. Spectroscopic study, Effect of the substituent on the UV-visible spectrum

The UV-vis absorption spectra of compounds **4** and curcumin **1** at 10^{-5} M concentration were recorded immediately after products' dissolution in DMSO. The absorption spectrum



Scheme 2 Proposed mechanism for the synthesis of 3,4-dihydropyrimidin-2(*H*)-one/thione analogs of curcumin **1** catalysed by $H_3PMo_{12}O_{40}$ (HPA).

for compounds **4** display a weak band at 270-272 nm attributed to the n-π* transition and two other broad bands appearing as shoulders in all cases at 331-373 nm and 398-429 nm respectively [Figure 2], attributed to the π–π* transition related with the carbonyl groups. These bands completely differ from the one of curcumin absorption spectrum which appears at 437 nm. These bands can be attributed to the charge transfer between the aromatic rings and the electron withdrawing pole constituted by the carbonyl groups that reinforce the electron attracting strength on this side of the molecules [Figure 3]. In

addition, the wavelength and the intensity of the absorption spectra were affected when changing the aryl substituent either donor or acceptor in positions 2, 3 and 4 of the aryl ring as well as positional isomerism of the hydroxy group of compounds **4d**, **4e**, **4f** (dihydropyrimidinones) and **4k** (dihydropyrimidin-thione). The nature and position of the substituent affect the absorbance much more than the absorption wavelength. Compounds with hydroxyl substituent show the highest intensity (**4d, 4e** and **4k)** and -OH in position 2 of the aryl ring (**4d** and **4k**) presents highest wavelength due to an extended electron cloud. Compound **4f** with 2 hydroxy substituants substituents shows the lowest intensity.

Table 3 UV-Visible spectroscopic characteristics of compounds **4a-n** and curcumin **1** in DMSO

Compound	λ abs (nm)	Compound	λ abs (nm)
Curcumin **1**	437 π-π*	**4g**	272 π -π*
			368 π-π*
			436 π -π*
4a	272 π -π*	**4h**	272 π -π*
	365 π-π*		365 π-π*
4b	270 π -π*	**4i**	271 π -π*
	347 π-π*		348 π-π*
	426 π-π*		398 π-π*
4c	270 π -π*	**4j**	272 π -π*
	369 π-π*		370 π-π*
	428 π-π*	**4k**	272 π -π*
4d	271 π -π*		374 π-π*
	363 π-π*		428 π-π*
	427 π-π*	**4l**	277 π -π*
4e	278 π -π*		370 π-π*
	349 π-π*	**4m**	269 π -π*
	428 π-π*		379 π-π*
4f	270 π -π*	**4n**	272 π -π*
	363 π-π*		331 π-π*
	429 π-π*		373 π-π*

3.2. Antioxidant activity

The antioxidant activity of curcumin **1** and its synthesized curcumin-DHPMs derivatives **4a-n** was measured in terms of their hydrogen donating or radical scavenging ability by UV–Visible spectrophotometry using the stable 2,2-diphenyl-1-picrylhydrazyl radical (DPPH). DPPH radical is a stable free radical and its radical character is neutralized in the presence of molecules capable of donating H atoms. This is visually noticeable as the colour changes from purple to yellow. When a compound is antioxidant, it donates proton to this radical and consequently the initial absorbance of DPPH solution decreases. Figure 4 shows the variation of absorbance versus concentration of the different compounds **4a-n** and curcumin **1** (Fig.4a) and of the standard ascorbic acid (Fig.4b). The lower the absorbance of the reaction mixture indicates the higher free radical scavenging activity (RSA). The capability to scavenge the DPPH (as % of inhibition) was calculated using equation (1).

All the compounds exhibited high scavenging activity. It is very interesting to note that RSA of all the synthesized compounds **4a-n** is greater than the one of curcumin **1** (standard), compounds **4f** and **4m** showing even greater antioxidant activity than ascorbic acid. The results of the antioxidant activity data are in accordance with theoretical expectations, because the number and position of the hydroxyl groups as well as the degree of conjugation of the whole molecule are important. The antioxidant potency of flavonoids of similar conjugation level is roughly proportional to the total number of -OH groups and is positively affected by the presence of *o*-dihydroxy moiety in the benzene ring [41].

The DPPH assay measures the ability of the sample to donate hydrogen to the DPPH radical, resulting in bleaching of the DPPH solution. The greater the bleaching action, the higher the antioxidant activity, and this was reflected in a lower half minimum inhibitory concentrations (IC_{50}) value. Figure 5 shows the values of IC_{50} of the tested compounds, being the most significant those of **4f** and **4m** as the best antioxidant agents.

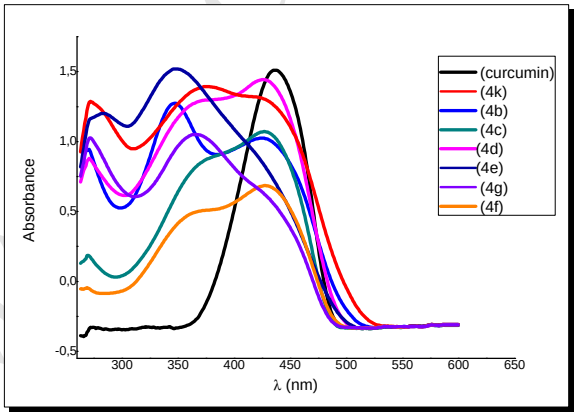


Fig. 2. Absorption spectra of compounds **4** and curcumin **1** in DMSO

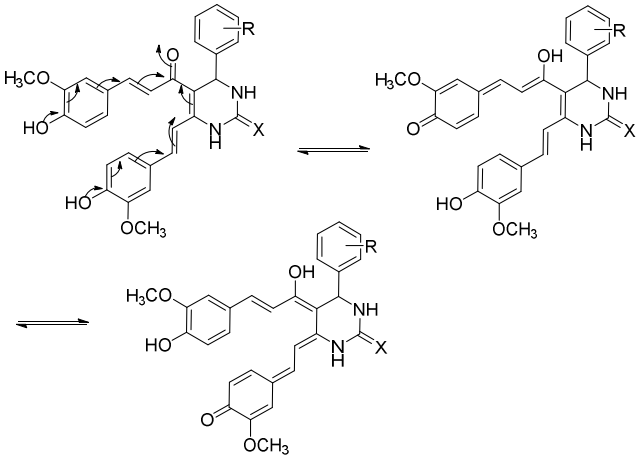
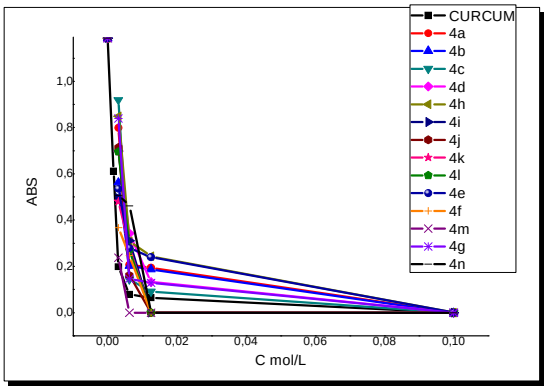


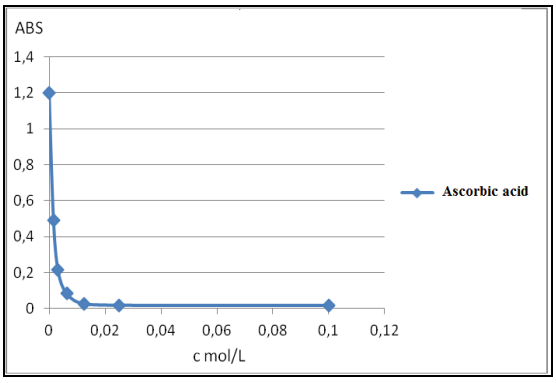
Fig. 3. Possible resonance structures of compounds **4a-n**

3.3. Antibacterial activity

The newly synthesized curcumin derivatives **4a–n** were evaluated for their in vitro antibacterial activity against three bacteria specially causing secondary infections in human being viz. *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeuriginosa*. Zone of inhibition in mm was measured using disk diffusion method (Table 4).



(a)



(b)

Fig. 4. Absorbance at 517 nm vs concentration of **4a-n** and curcumin **1** (a) and of the standard ascorbic acid (b).

The test samples were dissolved in DMSO at a concentration of 10^{-1} M and the antibacterial activity of curcumin-dihydropyrimidinone/thione analogs were compared with the positive control (as standard antibiotic reference drug) chosen according to the nature of the bacterial strain (Table 4). In case of *Staphylococcus aureus* and *Escherichia coli* strains, compounds **4a-n** did not show any zone of inhibition and were completely inactive. In case of *Pseudomonas aeuriginosa*; compounds **4g** and **4n** (bearing electron-withdrawing group on the benzo ring) were totally inactive whereas compounds **4a-f** and **4h-m**, showed much antibacterial activity with better zone of inhibition as comparison to remaining compounds, but were less active than the standards.

The sensitivity to the different products is classified according to the diameter of the zones of inhibition as follows: Not sensitive (-) for diameter less than 8 mm, Sensitive (+) for a diameter between 9 and 14 mm, highly sensitive (+ +) for a diameter between 15 and 19 mm and extremely sensitive (+ + +) for a diameter greater than 20 mm [42]. The results obtained are given in Table 4 and illustrated in Figure 6.

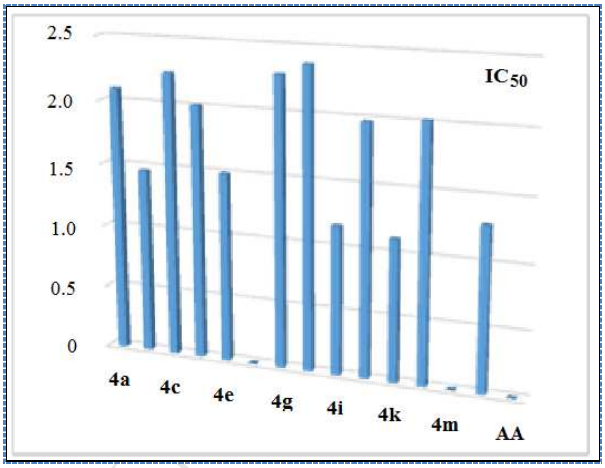


Fig. 5. IC_{50} (mg/mL) values of the antioxidant compounds tested

3.4. DFT analysisaz

The DFT analysis was performed to gain a more insight into the electronic properties of synthesized compounds. According to the frequency calculations results of the optimized geometries, absence of imaginary frequency indicated that the structures were in stationary point. In addition, frontier molecular orbitals HOMO and LUMO play an important role to illustrate the chemical reactivity. The HOMO is considered as electron donor, because it is the outer orbital containing electrons whereas the LUMO can accept electrons [43]. Hence, the LUMO energy is directly related to electron affinity (A = - E_{LUMO}) and ionization potential (I = - E_{HOMO}) is directly related to the energy of the HOMO [44].

Table 4. Diameters of inhibition zones (mm) for compounds **4a-n** and the references antibiotics at 10^{-1} M

Bacterial strain	Diameter of inhibition zones (mm)														
	4a	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	**4i**	**4j**	**4k**	**4l**	**4m**	**4n**	ATB[a]
S. aureus	6	6	6	6	6	6	6	6	6	6	6	6	6	6	20
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+++
E. coli	6	6	6	6	6	6	6	6	6	6	6	6	6	6	25
	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+++
P. aeruginosa	12	12	12	13	10	11	6	11	11	14	13	11	13	6	30
	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+++

a: ATB = Rifampicine (10^{-1} M?) for *S. aureus*; Cotrimoxazole (10^{-1} M?) for *E. coli*; Colistine (10^{-1} M?) for *P. aeruginosa*

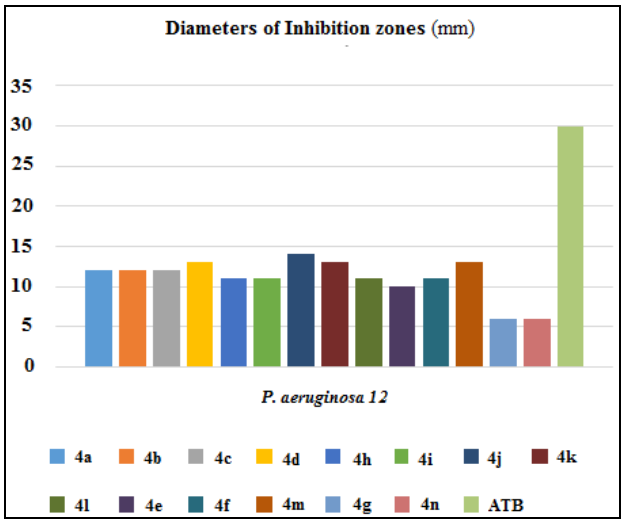


Fig. 6. Antibacterial activity of compounds **4a-n** and the reference antibiotic (ATB) colistine.

The value of HOMO, LUMO, chemical potential (μ) and chemical hardness (η) for various compounds are given in Table 5. It is worth noting that, large HOMO - LUMO gap or when hardness increases the reactivity should decrease and small HOMO - LUMO gap or when hardness decreases the reactivity should increases. According to the calculated chemical hardness (η) of synthesized compounds (equation 3), η (**4m**) = η (**4f**) < η (**4h**) which indicate that **4f** and **4m** are more reactive than **4h**. **Table 5:** Calculated DFT descriptors (eV) for the synthesized compounds

Table 5: Calculated DFT descriptors in (eV) for the synthesized compounds

Compound	HOMO (eV)	LUMO (eV)	μ	η
4a	-5.41	-2.16	-3.79	1.62
4b	-4.99	-2.05	-3.52	1.47
4c	-5.50	-2.25	-3.88	1.62
4d	-5.37	-2.03	-3.70	1.67
4e	-5.35	-2.15	-3.75	1.60
4f	-5.02	-2.19	-3.61	1.42
4g	-5.57	-2.33	-3.95	1.62
4h	-5.46	-2.32	-3.89	1.57
4i	-5.09	-2.20	-3.65	1.44
4j	-5.55	-2.41	-3.98	1.57
4k	-5.33	-2.19	-3.76	1.57
4l	-5.39	-2.30	-3.84	1.55
4m	-5.19	-2.34	-3.76	1.42
4n	-5.64	-2.48	-4.06	1.58

On the other hand, the average values of the HOMO and LUMO energies have been defined as chemical potential (μ), equation 2. The negative of the chemical potential was known as the electronegativity (χ = - μ). The electronegativity represents the power of molecules to attract electrons. According to values reported in table 5, the electronegativity value of **4h** is higher than those of **4f** and **4m**.

The visualization of HOMO and LUMO of the most potent compounds (**4f** and **4m**) and the least active compound (**4h**) are displayed in Figure 7. The positive and negative phases of molecular orbitals are represented in red and green color, respectively. The HOMO of compound **4f** is localized on the substituted phenyl ring at position 4 of the dihydropyrimidinone ring whereas the LUMO is mainly focused on styryl and acryloyl groups.

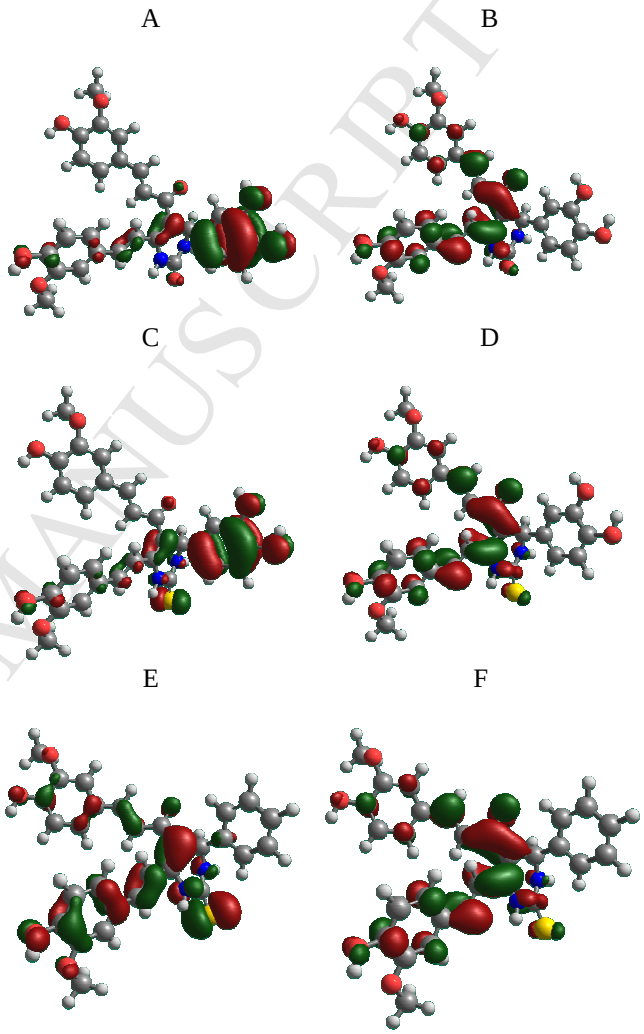


Fig. 7: Plots of frontier molecular orbitals surfaces calculated for the studied compound **4f** (A,B), **4m** (C,D) and **4h** (E,F).

HOMO and LUMO of compound **4m** are localized in the same sites as in compound **4f**. In the case of the least active compound **4h**, the HOMO is mainly localized on sulfur atom and double bond of dihydropyrimidinone ring and along the 4-hydroxystyryl group, whereas LUMO is displayed on the styryl and acryloyl groups. It was interesting to observe that LUMO was never located on the phenyl at position 4 of the dihydropyrimidinone ring which means that this group has a less likely chance to attract electrons.

4. Conclusion

A series of 3,4-dihydropyrimidin-2(1H)-one/thione analogs of curcumin were synthesized in good yield using simple, efficient, and improved Biginelli reaction by a one-pot multicomponent cyclocondensation using curcumin, substituted

aromatic aldehydes, and urea/thiourea in ethanol and $H_3PMo_{12}O_{40}$ Keggin type heteropolyacid as catalyst. These compounds were evaluated for their antioxidant and antibacterial activity and showed excellent antioxidant activity but moderate antibacterial activity.

Curcumin-3,4-dihydropyrimidinones/thiones derived from 2-hydroxybenzaldehyde, 4-hydroxy-benzaldehyde and 3,4-dihydroxybenzaldehyde showed a high intensity in UV-visible absorption spectrophotometry but the wavelengths are less affected by the nature of substituents of the benzaldehyde. The compound derived from 3,4-dihydroxybenzaldehyde and urea showed maximum antioxidant activity, while antioxidant activity decreases in compounds derived from 2-hydroxybenzaldehyde and others.

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References and notes

[1] R.K. Maheshwari, A.K. Singh, J. Gaddipati, R.C. Srimal. Multiple biological activities of curcumin: a short review. *Life Sci.*, 78 (2006) 2081–2087. https://doi.org/10.1016/j.lfs.2005.12.007.

[2] A. Ram, M. Das, B. Ghosh. Curcumin attenuates allergen-induced airway hyper responsiveness in sensitized guinea pigs. *Biol. Pharm. Bull.*, 26 (2003) 1021–1024. https://doi.org/10.1248/bpb.26.1021

[3] V.P. Kurup, C.S. Barrios, R. Raju, B.D. Johnson, M.B. Levy, J.N. Fink. Immune response modulation by curcumin in a latex allergy model. *Clin. Mol. Allergy*, 5 (2007) 1–12. https://doi.org/10.1186/1476-7961-5-1

[4] H. Matsuda, S. Tewtrakul, T. Morikawa, A. Nakamura, M. Yoshikawa. Anti-allergic principles from thai zedoary: structural requirements of curcuminoids for inhibition of degranulation and effect on the release of TNF-alpha and IL-4 in RBL-2H3 cells. *Bioorg. Med. Chem.*, 12 (2004) 5891–5898. https://doi.org/10.1016/j.bmc.2004.08.027.

[5] M. Suzuki, T. Nakamura, S. Iyoki, A. Fujiwara, Y. Watanabe, K. Mohri, K. Isobe, K. Ono, S. Yano. Elucidation of anti-allergic activities of curcumin-related compounds with a special reference to their antioxidative activities. *Biol. Pharm. Bull.*, 28 (2005) 1438–1443. https://doi.org/

[6] C.A.C. Araujo, L.L. Leon. Biological activities of *Curcuma longa* L. *Mem. Inst. Oswaldo Cruz*, 96 (2001) 723–728. http://dx.doi.org/10.1590/S0074-02762001000500026

[7] B. Aggarwal, A. Kumar, A. Bharti. Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res.*, 23 (1A) (2003) 363–398.

[8] A.E. Nugroho, N. Yuniarti, E.P. Istyastono, M.K. Supardjan, L. Hakim. Anti-allergic effects of 1,5-bis(4'-hydroxy-3'-methoxyphenyl)-1,4-pentadiene-3-one on mast cell-mediated allergy model. *Malaysian J. Pharm. Sci.*, 7 (2009) 51–71.

[9] L.R.C. Barclay, R. Melinda, M.R. Vinqvist, On the Antioxidant mechanism of curcumin: classical methods are needed to determine antioxidant mechanism and activity, Org. Lett. 18 (2000) 2841–2843. https://doi.org/10.1021/ol000173t.

[10] S.V. Jovanovic, C.W. Boone, S. Steenken, M. Trinoga, R.B. Kaskey, How curcumin works preferentially with water soluble antioxidants, J. Am. Chem. Soc. 123 (2001) 3064–3068. https://doi.org/10.1021/ja003823x.

[11] G. Litwinienko, K.U. Ingold, Abnormal solvent effects on hydrogen atom abstraction. 2. Resolution of the curcumin antioxidant controversy. The role of sequential proton loss electron transfer, J. Org. Chem. 69 (2004) 5888–5896. https://doi.org/10.1021/jo049254j

[12] C. Santelli-Rouvier, B. Pradines, M. Berthelot, Arylsulfonyl acridinyl derivatives acting on *Plasmodium falciparum*. Eur. J. Med. Chem. 39 (2004) 735–744. https://doi.org/10.1016/j.ejmech.2004.05.007

[13] A.K. Bhattacharjee, M.G. Hartell, D.A. Nichols. R.P. Hicks, B. Stanton, J.E. van Hamont, W.K. Milhous. Structure-activity relationship study of antimalarial indolo [2,1-b]quinazoline-6,12-diones (tryptanthrins). Three dimensional pharmacophore modeling and identification of new antimalarial candidates. Eur. J. Med. Chem. 39 (2004) 59–67. https://doi.org/10.1016/j.ejmech.2003.10.004.

[14] P. Verhaeghe, N. Azas, S. Hutter, Christophe Ducros, M. Laget, S. Rault, P. Rathelot, P. Vanelle. Synthesis and Antiplasmodial Activity of New 4-Aryl-2-trichloromethyl quinazolines. Bioorg. Med. Chem. Lett. 18 (2008) 396–401. https://doi.org/10.1016/j.bmcl.2007.10.027.

[15] A.S. Hossan, H.M.A. Abu-Melha, M.A. Al-Omar, A.-G.E. Amr, Synthesis and Antimicrobial Activity of Some New Pyrimidinone and Oxazinone Derivatives Fused with Thiophene Rings Using 2-Chloro-6-ethoxy-4-acetylpyridine as Starting Material. Molecules 17 (2012) 13642–13655. https://doi.org/10.3390/molecules171113642.

[16] M. Ashok, B.S. Holla, N.S. Kumari, Convenient one pot synthesis of some novel derivatives of thiazolo[2,3-b]dihydropyrimidinone possessing 4-methylthiophenyl moiety and evaluation of their antibacterial and antifungal activities. Eur. J. Med. Chem. 42 (2007) 380–385. https://doi.org/10.1016/j.ejmech.2006.09.003

[17] F. Hamy, V. Brondani, A. Flörsheimer, W. Stark, M.J.J. Blommers, T. Klimkait. A New Class of HIV-1 Tat Antagonist Acting through Tat−TAR Inhibition. Biochemistry 37 (1998) 5086–5095. https://doi.org/10.1021/bi972947s

[18] A.S. Galabov, E. Velichkova, A. Karparov, D. Shizdakova, D. Danchev, N. Chakova. Antiviral activity of tetrahydro-2/1H/-pyrimidinones and related compounds. Arzneim.-Forsch./Drug Res, 34 (1984) 9–14.

[19] S. Karkola, A. Lilienkampf, K. Wähälä, A 3D QSAR Model of 17β-HSD1 Inhibitors Based on a Thieno[2,3-*d*]pyrimidin-4(3*H*)-one Core Applying Molecular Dynamics Simulations and Ligand–Protein Docking. ChemMedChem. 3 (2008) 461–472. https://doi.org/10.1002/cmdc.200700271.

[20] E.S. Lee, J.G. Park, Y. Jahng, A facile synthesis of simple alkaloids synthesis of 2,3-polymethylene-4(3H)-quinazolinones and related alkaloids. Tetrahedron Lett. 44 (2003) 1883–1886. https://doi.org/10.1016/S0040-4039(03)00080-7.

[21] G. Romeo, F. Russo, A. Caruso, V. Cutuli, M. Amico-Roxas. Synthesis of new thieno[2,3-d]pyrimidine-2,4-[1H,3H] diones with analgesic and anti-inflammatory activities. Arzneim.-Forsch./Drug Res. 48 (1998) 167-172.

[22] (a) G.C. Rovnyak, S.D. Kimball, B. Beyer, G. Cucinotta, J.D. DiMarco, J. Gougoutas, A. Hedberg, M. Malley, J.P. McCarthy. Calcium Entry Blockers and Activators: Conformational and Structural Determinants of Dihydropyrimidine Calcium Channel Modulators. J. Med.Chem. 38 (1995) 119-129. https://doi.org/10.1021/jm00001a017; (b) C.O. Kappe, Biologically active dihydropyrimidones of the Biginelli-type — a literature survey. Eur. J. Med. Chem. 35 (2000) 1043-1052. https://doi.org/10.1016/S0223-5234(00)01189-2.

[23] K.S. Atwal, B.N. Swanson, S.E. Unger, D.M. Floyd, S. Moreland, A. Hedberg, B.C. O'Reilly. Dihydropyrimidine calcium channel blockers. 3. 3-Carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarboxylic acid esters as orally effective antihypertensive agents. J. Med. Chem. 34 (1991) 806–811. https://doi.org/10.1021/jm00106a048.

[24] C.O. Kappe, W.M.F. Fabian, M.A. Semones, Conformational analysis of 4-aryl-dihydropyrimidine calcium channel modulators. A comparison of ab initio, semiempirical and X-ray crystallographic studies. Tetrahedron 53 (1997) 2803–2816. https://doi.org/10.1016/S0040-4020(97)00022-7.

[25] B.C. Ranu, A. Hajra, U. Jana. Indium(III) Chloride-Catalyzed One-Pot Synthesis of Dihydropyrimidinones by a Three-Component Coupling of 1,3-Dicarbonyl Compounds, Aldehydes, and Urea: An Improved Procedure for the Biginelli Reaction. J. Org. Chem. 65 (2000) 6270–6272. https://doi.org/10.1021/jo000711f.

[26] K.S. Atwal, G.C. Rovnyak, J. Schwartz, S. Moreland, A. Hedberg, J.Z. Gougoutas, M.F. Malley, D.F. Floyd. Dihydropyrimidine calcium channel blockers: 2-heterosubstituted 4-aryl-1,4-dihydro-6-methyl-5-pyrimidine carboxylic acid esters as potent mimics of dihydropyridines. J. Med. Chem. 33 (1990) 1510–1515. https://doi.org/10.1021/jm00167a035.

[27] Z.D. Aron, L.E. Overman. The tethered Biginelli condensation in natural product synthesis. Chem. Commun. (2004) 253–265. https://doi.org/10.1039/B309910E

[28] G. Byk, H. E. Gettlieb, J. Herscovici, F. Mirkin, New regioselective multicomponent reaction: One pot synthesis of spiro heterobicyclic aliphatic rings, J. Comb. Chem. 2 (2000) 732-735. https://doi.org/10.1021/cc000056p

[29] S.J. Haggarty, T.U. Mayer, D.T. Miyamoto, R. Fathi, R.W. King, T.J. Mitchison, S.L. Schreiber, Dissecting cellular processes using small molecules : identification of colchicine-like, taxol-like and other small molecules that perturb mitosis. Chem. Biol. **7** (2000) 275–286. https://doi.org/10.1016/S1074-5521(00)00101-0.

[30] Jaggi Lal, S.K. Gupta, D. Thavaselvam, D.D. Agarwal. Design, synthesis, synergistic antimicrobial activity and cytotoxicity of 4-aryl substituted 3,4-dihydropyrimidinones of curcumin. Bioorg. Med. Chem. Lett. 22 (2012) 2872–2876. https://doi.org/10.1016/j.bmcl.2012.02.056.

[31] Jaggi Lal, S.K. Gupta, D. Thavaselvam, D.D. Agarwal. Synthesis and pharmacological activity evaluation of curcumin derivatives. Chin. Chem. Lett. 27 (2016) 1067–1072. https://doi. org/10.1016/j.cclet.2016.03.032

[32] R. Sharma, S.S. Jadav, S. Yasmin, S. Bhatia, H. Khalilullah, M.J. Ahsan. Simple, efficient, and improved synthesis of Biginelli-type compounds of curcumin as anticancer agents. Med. Chem. Res., 24 (2015) 636–644. https://doi.org/10.1007/s00044-014-1146-2.

[33] K. Ighilahriz, B. Boutmeur, F. Chami, C. Rabia, M. Hamdi, S.M. Hamdi, A Microwave-Assisted and Heteropolyacids-Catalysed Cyclocondensation Reaction for the Synthesis of 4(3H)-Quinazolinones. Molecules 13 (2008) 779–789. https://doi.org/10.3390/molecules13040779.

[34] L. Saher, M. Makhloufi-Chebli, L. Dermeche, B. Boutemeur-Khedis, C. Rabia, A.M.S. Silva, M. Hamdi. Keggin and Dawson-type polyoxometalates as efficient catalysts for the synthesis of 3,4-dihydropyrimidinones: experimental and theoretical studies. Tetrahedron Lett. 57 (2016) 1492–1496. https://doi.org/10.1016/j.tetlet.2016.02.077

[35] L. Saher, M. Makhloufi-Chebli, L. Dermeche, S. Dermeche, B. Boutemeur-Khedis, C. Rabia, M. Hamdi, A.M.S. Silva. 10-(4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-3-methyl-1*H*,10*H*-pyrano[4,3-*b*] chromen-1-ones from a pseudo-multicomponent reaction and evaluation of their antioxidant activity.Tetrahedron, 74 (2018) 872–879. https://doi.org/10.1016/j.tet.2018.01.009

[36] K. Ighilahriz-Boubchir, B. Boutemeur-Kheddis, C. Rabia, M. Makhloufi-Chebli, M. Hamdi, A.M.S. Silva. Recyclable Keggin Heteropolyacids as an Environmentally Benign Catalyst for the Synthesis of New 2-Benzoylamino-N-phenyl-benzamide Derivatives under Microwave Irradiations at Solvent-Free Conditions and the Evaluation of Biological Activity. Molecules, 23 (2018) 8; https://doi.org/10.3390/molecules23010008.

[37] G.G.F. Nascimento, J. Locatelli, P.C. Freitas, G.L. Silva, Antibacterial Activity of Plant Extracts and Phytochemicals on Antibiotic-Resistant Bacteria. Braz. J. Microbiol., 31 (2000) 247–256. http://dx.doi.org/10.1590/S1517-3822000000400003.

[38] J.S. Lee, H.J. Kim, H. Park, Y.S. Lee. New diarylheptanoids from the stems of Carpinus cordata J. Nat. Prod. 65 (2002) 1367-1370. https://doi.org/10.1021/np020048l.

[39] L.L. Mensor, F.S. Menezes, G.G. Leitão, A.S. Reis, T.C. dos Santos, C.S. Coube, S.G. Leitão, Screening of Brazilian plant extracts for antioxidant activity by the use of DPPH free radical method. Phytother. Res., 15 (2001) 127–130.

[40] (a) F. Neese. "The ORCA program system" Wiley interdisciplinary Reviews - Computational Molecular Science, 2 (2012) 73–78; (b) F. Neese, Calculation of the zero-field splitting tensor on the basis of hybrid density functional and Hartree-Fock theory, J. Chem. Phys. 127(16) (2007) 164112-164119. https://doi.org/10.1063/1.2772857.

[41] R. Apak, K. Guclu, M. Ozyurek, S.E. Karademir. Novel total antioxidant capacity index for dietary polyphenols and vitamins C and E, using their cupric ion reducing capability in

the presence of neocuproine: CUPRAC method. J. Agric. Food Chem. 52 (2004) 7970–7981. https://doi.org/10.1021/jf048741x.

[42] J.L. Avril, H. Dabernat, F. Denis, H. Monteil, Bactériologie clinique. Ellipses ED. 2ème édition. Mars 1992. 9.

[43] J. Fleming, Frontier Orbitals and Organic Chemical Reactions. John Wiley & Sons LTD. London/New York/Syndney/Toronto 1976.

[44] K. Fukui. Role of frontier orbitals in chemical reactions. Science, 218 (1982) 747–754. https://doi.org/10.1126/science.218.4574.747.

Highlights

- $H_3PMo_{12}O_{40}$ as green catalyst in the synthesis of 4-aryl-3,4-dihydropyrimidinones/thiones of curcumin
- Conventional heating and microwave irradiation
- Theoretical calculations and mechanism studies
- Antioxidant and antibacterial activity are greater than curcumin
- Geometries of synthesized compounds were optimized by using B3LYP method with 6-31G* basis set.