ABSTRACT

Objectives: The present protocol deals with zirconocene dichloride (Cp₂ZrCl₂) catalyzed synthesis of pyrano[2,3-d]pyrimidinediones through one-pot multicomponent reactions of aromatic aldehydes with malononitrile and barbituric acid at ambient temperature. All the synthesized compounds were characterized and evaluated for antibacterial, antifungal, and antioxidant activities. Furthermore, a molecular docking was carried out to reveal the atomic insights between synthesized compounds and carotenoid dehydrospalenine synthase (PDB ID: 3ACX).

Methods: All the synthesized compounds were evaluated for their in vitro antimicrobial activity by diffusion method. Antibacterial activities such as 1,1-diphenyl-2-picrylhydrazyl and radical scavenging activity. A mixture of barbituric acid 1 (1 mmol), malononitrile 2 (1 mmol), benzaldehyde 3a (1 mmol), ethanol (5 mL), and Cp₂ZrCl₂ (0.5 mol %) was stirred at ambient temperature for specified time. After completion of reaction as indicated by thin-layer chromatography, the obtained crude product was filtered and purified by column chromatography on silica gel (Merck, 60–120 mesh) using ethyl acetate:pet ether as eluent; 1H NMR, 13C NMR, and mass spectroscopy.

Results: All the synthesized pyrano[2,3-d]pyrimidinediones were characterized by spectroscopic analysis. The results revealed that pyrano[2,3-d]pyrimidinediones (4 a-k) displayed the zone of inhibition in the range of 3–13 mm. The most active compound 4b displayed largest zone of inhibition of 13 mm for Escherichia coli (NCIM-2832) and 9 mm for Bacillus subtilis (NCIM-2635). The antifungal and antioxidant activity of all synthesized pyrano[2,3-d]pyrimidinediones (4a-k) showed moderate to good activity. Molecular docking studies suggest that pyrano[2,3-d]pyrimidinediones might inhibit the carotenoid dehydrospalenine synthase activity.

Conclusion: All the synthesized pyrano[2,3-d]pyrimidinediones display moderate to good antibacterial, antifungal, and antioxidant activity. This molecular docking studies supported that pyrano[2,3-d]pyrimidinediones might inhibit the carotenoid dehydrospalenine synthase (PDB ID: 3ACX).

Keywords: Zirconocene dichloride, Pyrano[2,3-d]pyrimidinediones, Antimicrobial, Antioxidant, Carotenoid dehydrospalenine synthase, Molecular docking.

INTRODUCTION

Zirconocene represents an important class of organometallic compounds in which zirconium is sandwiched between two cyclopentadienyl rings. Due to high reactivity and feeble acidity, zirconocenes have attracted substantial applications in the area of catalysis [1]. Initially, the zirconocene catalyst was limited to the olefin polymerization. However, recent reports concerning to successful applications of zirconocene in synthetic chemistry have been demonstrated their versatility in organic synthesis which has spurred a resurgence of interest in this class of compounds [2]. Zirconocene dichloride (Cp₂ZrCl₂) is an air and moisture stable and non-hazardous, d₄ zirconocene that has been subject of immense interest in catalytic technology due to its Lewis acidic character. It is one of the most efficient and widely employed catalysts in Ziegler–Natta polymerization [3]. Organometallic Lewis acids play an important role in green chemistry and sustainable development [4]. Recently, Cp₂ZrCl₂ has been explored for the synthesis of carboxyl group transformation reactions [5], bis(indole) methanes [6], intramolecular coupling of alkyne, EtMgBr (ethylene or CO) [7], quinoxalin-4(3H)-ones [8], 1-amidoalkyl-2-naphthols [9], and benzimidazoles [10]. In addition, Cp₂ZrCl₂ has also been employed for acetylation of phenols/ alcohols/amines [11], coupling of terminal alkynes, and intramolecular coupling of amines and alkynes. Significant application of zirconium in organic synthesis mainly includes Cp₂Zr(II) species, the so-called zirconocene [12] and Reformatsky and Barbier reactions [13].

Zirconocene dichloride (Cp₂ZrCl₂) catalyzed synthesis of pyrano[2,3-d]pyrimidinediones through one-pot multicomponent reaction of aromatic aldehydes with barbituric acid and malononitrile at ambient temperature. Among several approaches developed for this purpose, one-pot multicomponent reaction of aromatic aldehydes with active methylene compounds and barbituric acid represents the most efficient and powerful process for synthesis of pyrano[2,3-d]pyrimidinediones [27]. Several techniques such as ultrasound, microwave irradiation, as well as ionic liquids have been reported to carry out this reaction [28,29]. However, despite impressive progress, there is still scope to develop new protocol for synthesis of...
pyrano[2,3-d]pyrimidinediones, especially using metalloocene-based catalyst related to applications of metalloccenes in organic synthesis [30].

Considering aforementioned discussion, we report herein Cp2ZrCl2 catalyzed synthesis of pyrano[2,3-d]pyrimidinediones and their biological activities including molecular docking studies.

MATERIALS AND METHODS

Material and physical measurements

The chemicals and reagents used for the synthesis were obtained from commercial sources. All other chemicals and solvents were of analytical grade. Brjisor formamid (FT-IR) spectra were recorded with Perkin Elmer FT-IR spectrophotometer (KBr disc; 4000–400 cm\(^{-1}\)). The samples were examined as KBr discs (ca 5% w/w). Nuclear magnetic resonance (\(^1\)H NMR) and \(^{13}\)C NMR spectra were recorded on a Brucker AC200 (400 MHz for \(^1\)H NMR and 100 MHz and \(^{13}\)C NMR) using dimethyl sulfoxide (DMSO)-\(d_6\) and CDCl\(_3\), as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) with TMS as an internal reference and coupling constants \(J\) in Hz.

Spectral data of representative compounds

7-Amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (Table 1, Entry a)

Yellow solid; yield: 95%; MP: 225–227°C (Lit. MP: 224–226°C) IR (KBr cm\(^{-1}\)): 3374 (-NH), 3305, 3215 (-NH), 3117 (C-H) 2151 (-CN). 1698 (-C=O), 1576 (-C=C) cm\(^{-1}\); \(^{1}\)HNMR (400 MHz, DMSO-\(d_6\)): \(\delta = 8.09\) (s, 1H, NH); 10.81 (s, 1H, NH); 7.34 (br, \(J = 7.6\) Hz, 2H, Ar-H); 7.18–7.09 (m, 3H, Ar-H); 6.86 (s, 2H, NH). ppm. \(^{13}\)C NMR \(^{13}\)CNMR (100 MHz, DMSO-\(d_6\)): \(\delta = 161.38, 144.95, 128.69, 128.47, 128.65, 118.25, 50.86,\) ppm; Ms (m/z):283.09 [M+H]+.

7-Amino-S-(3-nitrophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (Table 1, Entry b)

White powder, yield: 85%; MP: 256–257°C (Lit. MP: 253–264°C) IR (KBr cm\(^{-1}\)): 3317 (NH), 3306, 3248 (NH), 2945 (C-H), 2214 (C=N). 1609 (C=O), 1476 (C=C). \(^{1}\)HNMR (400 MHz, DMSO-\(d_6\)): \(\delta = 12.05\) (s, 1H, NH); 10.25 (s, 1H, NH) 8.37 (s, 1H, Ar-H), 8.24 (d, \(J = 6.4\) Hz, 2H, Ar-H). ppm. \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta = 166.12, 160.73, 157.01, 151.56, 150.57, 146.11, 146.11, 129.23, 123.08, 119.45, 104.42, 79.32, 71.10 ppm; Ms (m/z): 328.2 M+H+.

Ferric reducing/antioxidant power (FRAP) assay

The ferric reducing power of synthesized pyrano[2,3-d]pyrimidinediones (4 a-k) was investigated using the method of Benzie and Strain with a slight modification [32]. The working FRAP reagent was prepared by the addition of 300 mM acetate buffer (pH 3.6), 2, 6-tripiryridyl-s-triazine (10 mm) in 40 mm HCl and 20 mm FeCl\(_3\), 6H\(_2\)O in 10:1:1 ratio and heated at 37°C in water bath for 10 min. Respective samples with known concentrations were allowed to react with 2.7 mL of the FRAP reagent. The final volume of the reaction mixture was adjusted to 3 mL with D/W. The reaction mixture was then incubated at room temperature for 30 min in dark condition and absorbance was measured spectrophotometrically at 593 nm, and the results were directly expressed in terms of increase in O. D.

Antifungal activity

The antifungal activity of synthesized pyrano[2,3-d]pyrimidinediones (4 a-k) was assessed using strains such as Candida albicans (NCIM-3466) and Saccharomyces cerevisiae (NCIM-3495). The inoculums of C. albicans (NCIM-3466) and S. cerevisiae were spread on the sterile potato dextrose agar (PDA) plates. The wells in PDA plates were prepared with the hdp of sterile steel borer. The pyrano[2,3-d] pyrimidinediones (4 a-k) were added in each respective wells, and then, these plates incubated at 37°C for 24 h. The results were assessed after completion of incubation time.

Antimicrobial activity

The synthesized pyrano[2,3-d]pyrimidinediones (4 a-k) were assessed for their antimicrobial activity against bacterial strains, namely Bacillus subtilis (NCIM-2635) and Escherichia coli (NCIM-2832), as per earlier methodology [33]. Inoculums of target bacterial cells were prepared using sterile saline water. These inoculums were then spread on a sterile nutrient agar plates using spread plate techniques sterile steel borer was used to prepare wells in the plates. Finally, pyrano[2,3-d] pyrimidinediones (4 a-k) were added in each wells containing B. subtilis (NCIM-2635) and E. coli (NCIM-2832), respectively. All the plates were incubated at 37°C for 24 h.
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Table 1: Cp₂ZrCl₂ catalyzed synthesis of pyrano[2,3-d] pyrimidinediones

| Entry | Aldehyde (3) | Product (4) | Time (min) | Yield* (%) | Melting point observed (°C) | Melting point (Lit.) (°C) |
|-------|--------------|-------------|------------|-------------|----------------------------|--------------------------|
| a     |              |             | 30         | 95          | 223–225                    | 224–226 [31]             |
| b     |              |             | 30         | 85          | 261–263                    | 263–264 [31]             |
| c     |              |             | 40         | 80          | 259–261                    | 261–264 [31]             |
| d     |              |             | 35         | 87          | 160–162                    | 163–164 [27]             |
| e     |              |             | 40         | 85          | 168–170                    | 170–174 [30]             |
| f     |              |             | 30         | 87          | 235–237                    | 235–238 [20]             |
| g     |              |             | 30         | 95          | 235–238                    | 238–239 [26]             |
| h     |              |             | 30         | 88          | 287–288                    | 289–293 [30]             |
| i     |              |             | 40         | 87          | 230–234                    | 230–231 [41]             |

(Contd...)
RESULTS AND DISCUSSION

Our initial studies were directed toward the optimization of reaction conditions. In this context, multicomponent reaction between barbituric acid 1 (1 mmol), malononitrile 2 (1 mmol), and benzaldehyde 3a (1 mmol) was chosen as a model reaction. To obtain the best results, the model reaction was examined in the presence of various quantities of CpZrCl2 in ethanol. In the presence of 5 mol% CpZrCl2, the reaction proceeded smoothly furnishing desired 7-aminomethyl-5-phenyl-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidin-6-carbonitrile (4a) in 85% yield. When the quantity of CpZrCl2 was increased from 5 mol% to 10 mol%, the yield of corresponding product was elevated from 90 to 95% (Table 2, entry 1 and 2). However, further increase in catalyst quantity beyond 10% did not significantly influence yield of the product (Table 2, entries 3, 4).

Next, we investigated the solvent effect on the model reaction by employing an array of solvents. Good yields were obtained in polar protic solvents such as methanol and ethanol (Table 3, entries 1, 2), while comparatively lower yields were obtained in non-polar solvents such as CH3CN, CH2Cl2, 1,4-dioxane, CHCl3, and toluene (Table 3, entries 3-7). The reaction could not be initiated to synthetically useful degree in DMF (Table 3, entry 8). Among all the screened solvents, ethanol was found to furnish excellent yield of the corresponding product in shorter reaction time (Table 3, entry 2).

After optimization of reaction conditions, we investigated the scope of reaction by reacting barbituric acid 1 (1 mmol) and malononitrile 2 (1 mmol), with structurally diverse aldehydes (3a-k). The results are summarized in Table 1. The present methodology is flexible to the presence of different functional groups on aromatic ring in aryl aldehydes and provided the anticipated products in moderate to excellent yields. It is noteworthy to mention that aryl aldehydes possessing electron withdrawing as well as electron-donating substituents did not affect the product yield.

The plausible mechanism for the formation of pyrano[2,3-d] pyrimidinediones (4a-k) using CpZrCl2 is depicted in Scheme 1. Initially, CpZrCl2 activates carbonyl group of aryl aldehyde through coordination of Zr with carbonyl oxygen [8]. This facilitates nucleophilic attack of malononitrile on carbonyl group, leading to the formation of 2-benzylidenemalononitrile, on which there is a conjugate addition of barbituric acid, leading to the formation of a cyclic imine intermediate that undergoes subsequent cyclization to furnish the desired product.

To compare the applicability and efficiency of present protocol with reported methods for the synthesis pyrano[2,3-d] pyrimidinediones, we have summarized the results of CpZrCl2 with reagents (Table 4). The results reveal that CpZrCl2 is better catalyst both in terms of reaction time and yield of the products.

Antimicrobial and antioxidant activity

The antimicrobial activity of pyrano[2,3-d] pyrimidinediones (4a-k) was examined using agar gel diffusion method. The antimicrobial activity

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**Table 1: (Continued)**

| j | ![Chemical Structure] | 40 | 89 | 216–218 | 215–217 [41] |
|---|---------------------|----|----|--------|------------|
| k | ![Chemical Structure] | 35 | 90 | 309–310 | 303–306 [27] |

*Optimal condition: Barbituric acid 1 (1 mmol), malononitrile 2 (1 mmol), and benzaldehyde 3a (1 mmol) in solvent (5 mL) at ambient temperature.

**Table 2: Optimization of catalyst loading in the synthesis of pyrano[2,3-d] pyrimidinediones**

| Entry | CpZrCl2 (mol %) | Time (min) | Yield (%) |
|-------|-----------------|------------|-----------|
| 1     | 5               | 35         | 95        |
| 2     | 10              | 25         | 90        |
| 3     | 15              | 30         | 91        |
| 4     | 20              | 35         | 93        |

*Optimal condition: Barbituric acid 1 (1 mmol), malononitrile 2 (1 mmol), and benzaldehyde 3a (1 mmol) in ethanol (5 mL) at ambient temperature.

**Table 3: Optimization of solvent loading in the synthesis of pyrano[2,3-d] pyrimidinediones**

| Entry | Solvent | Time (min) | Yield (%) |
|-------|---------|------------|-----------|
| 1     | Methanol| 45         | 75        |
| 2     | Ethanol | 30         | 95        |
| 3     | CH3CN   | 45         | 55        |
| 4     | CH2Cl2  | 55         | 65        |
| 5     | 1,4-Diox| 90         | 55        |
| 6     | CHCl3   | 55         | 62        |
| 7     | Toluene | 90         | 45        |
| 8     | DMF     | 70         | 34        |

*Optimal condition: Barbituric acid 1 (1 mmol), malononitrile 2 (1 mmol), and benzaldehyde 3a (1 mmol) in solvent (5 mL) at ambient temperature.

performed against Gram-negative (*E. coli* NCIM-2832) and Gram-positive (*B. subtilis* NCIM-2635) bacterial strains. The clear zones of inhibition were observed around the wells of *B. subtilis* (NCIM-2635) and *E. coli* (NCIM-2832) plates. The results revealed that pyrano[2,3-d] pyrimidinediones (4a-k) displayed the zone of inhibition in the range of 3–13 mm (Fig. 2 and Table 5). The most active compound 4b displayed having largest zone of inhibition of 13 mm for *E. coli* (NCIM-2832) and 9 mm for *B. subtilis* (NCIM-2635) (Fig. 2 and Table 5). Hence, antibacterial, of all the screened synthesized compounds pyrano[2,3-d] pyrimidinediones, showed moderate to excellent activity against these bacteria. The antioxidant potential of synthesized derivatives of pyrano[2,3-d] pyrimidinedione was...
determined using simple, rapid, and inexpensive assays. The synthesized derivatives show strong DPPH, RSA, and FRAP activity.

The synthesized pyrano[2,3-d]pyrimidinediones (4a-k) were tested for antimicrobial activity against bacterial strains, namely *B. subtilis* (NCIM-2635) and *E. coli* (NCIM-2832) as per earlier methodology [33] and zone of clearance around the wells inoculated with the pyrano[2,3-d]pyrimidinediones. The antifungal potential of pyrano[2,3-d]pyrimidinedione derivatives (4a-k) was examined by the agar gel diffusion method. These results indicate that pyrano[2,3-d]pyrimidinediones derivative (4a-k) also shows decent antibacterial activity against *E. coli* (NCIM-2832) and *B. subtilis* (NCIM-2635) (Table 5).

Molecular docking

Molecular docking studies have been found useful to understand interactions between enzymes and ligands [34-37]. Thus, molecular docking studies were carried out between carotenoid dehydrodrosqualene synthase (PDB ID: 3ACX) and pyrano[2,3-d]pyrimidinediones using Patch dock server [38,39]. The carotenoid dehydrodrosqualene synthase has been used as a target for pyrano[2,3-d]pyrimidinediones due to its important role in bacterial cell for the production of the C30 carotenoid backbone, that is, dehydrodrosqualene [40].

Three-dimensional models of pyrano[2,3-d]pyrimidinediones were constructed using SPARTAN versus 6.01 Software [41]. Then, energy minimization was carried out by Hartree–Fock method [42]. Further,
the minimized structures of pyrano[2,3-d]pyrimidinediones were used to dock with carotenoid dehydrosqualene synthase (PDB ID: 3ACX) [38]. All the docked complexes were analyzed with the help of CHIMERA [43]. The residues of carotenoid dehydrosqualene synthase (PDB ID: 3ACX) forming hydrogen bonding interactions with pyrano[2,3-d]pyrimidinediones were studied by CHIMERA [43]. Similarly, the earlier reports suggested that chemically synthesized molecules can be further used for their activity against several enzymes [44,45]. Docking energy values for all the synthesized compounds along with standard ciprofloxacin are shown in Table 7. The negative docking energy indicates the proper binding mode of compounds within the active site of dehydrosqualene synthase (Table 7). The binding mode of the most potent compounds 4b, 4f, 4i, and 4k is shown in Fig. 3. These compounds are exhibit in hydrogen bonding interactions with the active site residues of carotenoid dehydrosqualene synthase. The H-bond interactions of compound 4b with the active site residues of dehydrosqualene synthase are shown in Fig. 3a. The compound 4b interacts with oxygen atom of TYR 248 and NH2 group of ASN 168 with bond distances 2.397 and 2.183 Å, respectively (Table 8, entry 4a and 4b). The compound 4f has hydrogen bonding interactions with the oxygen atom of ASP 176 (Fig. 3b) with a bond distance 3.083 Å (Table 8, entry 4c and 4d). The compound 4i forms hydrogen bonding interactions with the oxygen atoms of ASP 176 and ASP 48 (Fig. 3c) with the interatomic distances 1.993 and 1.745 Å, respectively (Table 8, entry 4e and 4f). Indicating strong hydrogen bonding interactions with the active site residues of dehydrosqualene synthase. The compound 4i interacts with dehydrosqualene synthase by hydrogen bonding interactions with hydroxyl group of TYR 248 and NH2 group of ARG 265 (Fig. 3d) with the bond distances 2.051 and 2.936 Å (Table 8, entry 4g, 4h, and 4i). The docking studies revealed

### Table 4: Comparison of catalytic activity of Cp₂ZrCl₂ with reported catalyst

| Entry | Catalyst | Solvent | Quantity | Temp (°C) | Time | Yield (%) | References |
|-------|----------|---------|----------|-----------|------|-----------|------------|
| 1     | L-Proline| EtOH    | 17 mol%  | Reflux    | 30 min | 80        | [18]       |
| 2     | H₂[NaP₅W₁₀O₃₄] | EtOH | 1 mol%  | Reflux    | 30–60 min | 85        | [22]       |
| 3     | SBA-PrSóH | Solvent Free | 0.02 g | 140 | 45 min | 91        | [20]       |
| 4     | [BMIM] BF₄ | [BMIM] BF₄ | 1.5 g | 90 | 5 h | 82        | [21]       |
| 5     | DAHP      | EtOH    | (10 mol%) | R.T.     | 2 h  | 71        | [17]       |
| 6     | Cp₂ZrCl₂  | EtOH    | 5 mol%  | R.T.     | 30 min | 95 | This work |

### Table 5: Zone of clearance around the wells inoculated with the pyrano[2,3-d]pyrimidinediones in the (b) *Escherichia coli* (NCIM-2832) plates and *Bacillus subtilis* (NCIM-2635)

| Entry | Compound | Zone of Clearance in mm | *Escherichia coli* (NCIM-2832) | Zone of clearance in mm | *Bacillus subtilis* (NCIM-2635) |
|-------|----------|-------------------------|---------------------------------|-------------------------|---------------------------------|
| 1     | 4a       | 4                       | 3                               | 9                       |
| 2     | 4b       | 13                      | 9                               | 11                      |
| 3     | 4c       | 9                       | 1                               | 7                       |
| 4     | 4d       | 5                       | 5                               | 5                       |
| 5     | 4e       | 1                       | 1                               | 9                       |
| 6     | 4f       | 8                       | 9                               | 9                       |
| 7     | 4g       | 7                       | 8                               | 8                       |
| 8     | 4h       | 5                       | 9                               | 9                       |
| 9     | 4i       | 7                       | 7                               | 7                       |
| 10    | 4j       | 8                       | 9                               | 9                       |
| 11    | 4k       | 8                       | 8                               | 8                       |
| 12    | Ciprofloxacin | 16            | 1                               | 1                       |

### Table 6: Zone of clearance around the wells inoculated with the pyrano[2,3-d]pyrimidinediones in the *Candida albicans* (NCIM-3466) and *Saccharomyces cerevisiae* (NCIM-3495)

| Entry | Compound | Zone of clearance in mm | *Candida albicans* (NCIM-3466) | Zone of clearance in mm | *Saccharomyces cerevisiae* (NCIM-3495) |
|-------|----------|-------------------------|---------------------------------|-------------------------|---------------------------------|
| 1     | 4a       | 5                       | 7                               | 7                       |
| 2     | 4b       | 14                      | 11                              | 11                      |
| 3     | 4c       | 12                      | 13                              | 13                      |
| 4     | 4d       | 7                       | 9                               | 9                       |
| 5     | 4e       | 8                       | 10                              | 10                      |
| 6     | 4f       | 7                       | 12                              | 12                      |
| 7     | 4g       | 10                      | 9                               | 9                       |
| 8     | 4h       | 13                      | 11                              | 11                      |
| 9     | 4i       | 9                       | 14                              | 14                      |
| 10    | 4j       | 12                      | 8                               | 8                       |
| 11    | 4k       | 7                       | 7                               | 7                       |
| 12    | Ciprofloxacin | 16            | 1                               | 1                       |

### Table 7: Molecular docking between pyrano[2,3-d]pyrimidinediones and carotenoid dehydrosqualene synthase

| Entry | Compound | Energy (in kcal/mol) | PATCHDOCK score |
|-------|----------|----------------------|-----------------|
| 1     | 4a       | −1178.6541620        | 470.00          |
| 2     | 4b       | 1178.661029          | 491.70          |
| 3     | 4c       | −1178.6943076        | 471.40          |
| 4     | 4d       | 1049.651871          | 473.80          |
| 5     | 4e       | −1049.6517024        | 437.70          |
| 6     | 4f       | −3534.9100575        | 452.90          |
| 7     | 4g       | −975.2209925         | 458.10          |
| 8     | 4h       | 1088.4677932         | 456.60          |
| 9     | 4i       | 1088.464011          | 491.10          |
| 10    | 4j       | 1432.0428743         | 440.90          |
| 11    | 4k       | 3534.9103618         | 459.60          |
| 12    | Ciprofloxacin | −1135.2195612    | 524.00          |


Table 8: Hydrogen bonding interactions between carotenoid dehydrosqualene synthase with pyrano[2,3-d] pyrimidinedione derivatives

| Entry | Sr. No. | Interaction between active site residues of carotenoid dehydrosqualene synthase with pyrano[2,3-d] pyrimidinedione derivatives (4B, 4F, 4I, and 4K) | Distance in Å |
|-------|--------|-----------------------------------------------------------------|--------------|
| 1     | 4a     | SER 21.A OG ------ 4B.het H:                                    | 0.839        |
| 2     | 4b     | 4B.het H ------ ASN 168.A ND2:                                   | 2.183        |
| 3     | 4c     | 4F.het H ------ ARG 265.A NH2:                                   | 1.592        |
| 4     | 4d     | ASP 48.A OD1 ------ 4F.het Br:                                   | 2.254        |
| 5     | 4e     | 4I.het H ------ ASP 176.A OD1:                                   | 1.993        |
| 6     | 4f     | ASP 48.A OD2 ------ 4I.het C:                                    | 1.177        |
| 7     | 4g     | ASP 48.A OD2 ------ 4I.het C:                                    | 1.745        |
| 8     | 4h     | 4K.het H ------ TYR 248.A OH:                                   | 2.051        |
| 9     | 4i     | ARG 265.A NH1 ------ 4K.het O:                                   | 2.936        |

that the compounds 4b, 4k, 4f, and 4i are likely to inhibit the carotenoid dehydrosqualene synthase enzyme present in the bacteria. The docking results are inconsistent with the observed antimicrobial activities.

CONCLUSION

We have reported one-pot multicomponent synthesis of pyrano[2,3-d] pyrimidinediones from aromatic aldehydes, malononitrile, and barbituric acid at ambient temperature using catalytic amount of Cp₂ZrCl₂. The present protocol grants advantages including high yields, effective simplicity, less reaction time, and smooth reaction conditions. In addition, the biological screening of pyrano[2,3-d]pyrimidinediones suggests good antimicrobial potential. Further, molecular docking studies of pyrano[2,3-d]pyrimidinediones reveal hydrogen bonding interactions of these compounds with the active site residues of carotenoid dehydrosqualene synthase enzyme present in the bacteria.

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D. Sonawane and K. Awate. Dose and spectral data analysis; and docking studies; Chetan B. Aware has done antioxidant studies; Vikas. D. Sonawane and K. Awate have contributed for manuscript preparation.

CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest.

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