Molecular modelling, synthesis, and antimalarial potentials of curcumin analogues containing heterocyclic ring

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Abstract The molecular modelling approach was applied to a series of nineteen curcumin analogues to find the possible PfRIO2 kinase inhibitory action. A putative active site in flexible loop (S1) of PfRIO2 kinase was explored computationally to recognize the molecular basis of ligands binding. The ligands (curcumin analogues; 3a–3s) were well accommodated in the selected active site (S1) due to their higher molecular size and length. Further all these synthesized compounds (3a–3s) were evaluated for their in vitro antimalarial activity according to the reported method. The antimalarial data showed that all these compounds to have parasiticidal activity with minimum killing concentrations (MKCs) range between 3.87 and 25.35 μM and schizonticidal activity with IC50 range between 1.48 and 23.09 μM. The compound 3p showed the most significant result with maximum schizonticidal (IC 50; 1.48 ± 0.10 μM) and parasiticidal activities (MKC; 3.87 ± 0.36 μM) could be identified as promising lead for further investigations.

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1. Introduction

Malaria is a life-threatening disease caused by five species of parasites and is transmitted through vector infected mosquito of genus Anopheles. An estimated 3.4 billion people are at risk of malaria and there are 107 countries and territories, where malaria is endemic. As per WHO report nearly 207 million cases of malaria and 627,000 death tolls occurred globally in 2012. Most of the cases and deaths occurred in unhygienic and developing African countries (WHO malaria report, 2013). Artemisinin combination therapy (ACTs) has been of much importance over the last decade however emergence of resistance has been reported in Cambodia’s Pailin province (WHO malaria report, 2013; Phylo et al., 2012; Kumar et al., 2005) provides motivation to discover new potential antimalarial agents. More than 65 protein kinases (PKs) have been reported in the parasite kinome with ambiguous cellular target.
drug discovery. It has been reported for curcumin analogues. These recent developments include antimalarial (Lal et al., 2012; Sahu et al., 2012; Zhichang et al., 2012), anti-HIV (Singh et al., 2010), anti-inflammatory (Saja et al., 2015). Various other biological activities, viz. anticancer (Ahsan et al., 2013; Liang et al., 2009; Jia et al., 2009), antibacterial (Lal et al., 2012; Sahu et al., 2012; Zhichang et al., 2012), anti-HIV (Singh et al., 2010), anti-inflammatory (Saja et al., 2007), antimalarial (Mishra et al., 2008), and many more have been reported for curcumin analogues. These recent developments made curcumin as an ideal lead compound for future drug discovery.

2. Results and discussion

2.1. Molecular modelling

The three dimensional structure of PIRIO2 kinase with four different binding sites namely S1–S4 was reported with several important active site residues. The ligand docking studies by choosing S1 and S2 sites of PIRIO2 have been studied earlier (Nag et al., 2013a,b; http://www.plasmodb.org; Parveen et al., 2013; Nag et al., 2013a). It might be due to closeness of S1 site with DNA binding site and S2 site with ATP. The S1 site was employed for the current ligand docking studies. The selected S1 site is comprised of the active site residues including Trp26, Ser128, Lys131, Asp137, Leu141, His142, Tyr138, Lys135, Glu134, Val132, Arg136, Lys133, Thr137, Leu146, Arg149, Val145 and Ile148, and later it was found that is matching with earlier reported studies (Nag et al., 2013a,b; www.plasmodb.org; Parveen et al., 2013; Nag et al., 2013a) The S1 site is present at loop region which is flexible in nature. However, the present molecular docking studies of the curcumin analogues revealed that the binding mode is slightly different from earlier reported (Parveen et al., 2013). Due to higher molecular size and length of the curcumin analogues they occupied the selected active site (S1) totally. The overall major receptor interactions of all ligands observed were the π–π interactions of His142 with one of the aromatic rings and sometimes along with aniline portion of the ligands. Val132 was the major residues that contributed its backbone with methoxy functional group present on the aromatic ring and Tyr26 exhibited the similar interactions with one or two ligands. π-Cationic interactions with Arg149 and Lys131 were found with aniline part and pyrazole ring of the ligands. The Arg152 was present at another end of the ligands and was responsible for side chain H-bonding with methoxy functional group of aromatic ring repeatedly. The pyrazole bearing aromatic rings were observed to be present near to the DNA binding region of the protein. The docking studies finally suggested that the inhibitory activity of the current compounds may be due to interfering with normal functioning of the PIRIO2 kinase. The docking scores are given in the Table 1. The docking scores of the curcumin analogues reported herein showed more affinity towards PIRIO2 kinase than that of standard antimalarial drug chloroquine. The binding mode of all the ligands with the active site of PIRIO2 kinase is shown in Fig. 1.

Table 1 The glide score and E-model scores of the curcumin analogues (3a–s).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Glide score</th>
<th>E-model score</th>
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<tbody>
<tr>
<td>3a</td>
<td>–4.056</td>
<td>–59.44</td>
</tr>
<tr>
<td>3b</td>
<td>–4.043</td>
<td>–66.065</td>
</tr>
<tr>
<td>3c</td>
<td>–4.504</td>
<td>–60.514</td>
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<tr>
<td>3d</td>
<td>–4.765</td>
<td>–61.244</td>
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<tr>
<td>3e</td>
<td>–5.335</td>
<td>–65.602</td>
</tr>
<tr>
<td>3f</td>
<td>–5.289</td>
<td>–66.196</td>
</tr>
<tr>
<td>3g</td>
<td>–5.457</td>
<td>–61.647</td>
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<tr>
<td>3h</td>
<td>–5.861</td>
<td>–60.231</td>
</tr>
<tr>
<td>3i</td>
<td>–6.057</td>
<td>–66.997</td>
</tr>
<tr>
<td>3j</td>
<td>–5.236</td>
<td>–72.968</td>
</tr>
<tr>
<td>3k</td>
<td>–5.618</td>
<td>–76.206</td>
</tr>
<tr>
<td>3l</td>
<td>–5.442</td>
<td>–67.377</td>
</tr>
<tr>
<td>3m</td>
<td>–5.831</td>
<td>–61.797</td>
</tr>
<tr>
<td>3n</td>
<td>–5.486</td>
<td>–63.268</td>
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<tr>
<td>3o</td>
<td>–5.893</td>
<td>–74.414</td>
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<tr>
<td>3p</td>
<td>–5.213</td>
<td>–55.798</td>
</tr>
<tr>
<td>3q</td>
<td>–5.244</td>
<td>–60.119</td>
</tr>
<tr>
<td>3r</td>
<td>–5.719</td>
<td>–63.754</td>
</tr>
<tr>
<td>3s</td>
<td>–5.628</td>
<td>–66.947</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>–4.959</td>
<td>–48.716</td>
</tr>
</tbody>
</table>
in Fig. 1. The docking protocol can be validated using NMR would be an approach for the assessment of molecular recognition (Unione et al., 2014).

2.2. Chemistry

The curcumin analogues (3a–s) described in the study are shown in Table 2 and the reaction sequence for the synthesis is summarized in Scheme 1. The synthesis of curcumin analogues was accomplished in four parts. 1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (curcumin, 1) and substituted phenyl semicarbazide/hydrazide/thiourea/semicarbazide/thiosemicarbazide (2a–s) was refluxed in glacial acetic acid to obtain the 3,5-bis(4-hydroxy-3-methoxystyryl)-N-(substituted phenyl)-1H-pyrazole-1-carboxamide/carboxamide analogues (3a–e, 3r, 3s), 3,5-bis(4-hydroxy-3-methylstyrlyl)-1H-pyrazole-1-yl(substituted phenyl)methanone analogues (3f–o), and pyrimidine analogues (3p–q). We have reported the chemistry of 8 compounds earlier while 5 compounds were reported elsewhere (Ahsan et al., 2013; Lal et al., 2012; Sahu et al., 2012). In the present investigation we report herein 19 compounds including 6 new curcumin analogues.

2.3. Antimalarial activity

The schizonticidal and parasiticidal activity of synthetic curcumin analogues were determined as described previously (Parveen et al., 2013). The schizonticidal activity of the curcumin analogues showed IC50 of 1.48–23.09 μM. The compound 3a showed maximum activity (IC50; 9.87 ± 2.21 μM) among carboxamide analogues (3a–e). The compound 3l showed maximum activity (IC50; 4.21 ± 0.62 μM) among the methanone analogues (3f–o). The compound 3p was found to be the most active compound with IC50 of 1.48 ± 0.10 μM, followed by the compound 3l with IC50 of 4.21 ± 0.62 μM. The schizonticidal activity of the compounds (3a–s) is given in Table 2. The minimum killing concentration (MKC) was the concentration of the compounds required to kill the parasite present in the culture and is given in Table 2. The MKC of the compounds range between 3.87
Table 2  Antimalarial activity of curcumin analogues (3a–s).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ar/X</th>
<th>Schizonticidal Activity IC₅₀ (µM ± SD)</th>
<th>Nature of inhibition</th>
<th>MKC (µM ± SD)</th>
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</thead>
<tbody>
<tr>
<td>3a</td>
<td>F</td>
<td>9.87 ± 2.21</td>
<td>parasiticidal</td>
<td>8.17 ± 0.78</td>
</tr>
<tr>
<td>3b</td>
<td>Cl</td>
<td>10.54 ± 0.67</td>
<td>parasiticidal</td>
<td>10.81 ± 1.41</td>
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<tr>
<td>3c</td>
<td>Br</td>
<td>22.47 ± 1.72</td>
<td>parasiticidal</td>
<td>11.18 ± 2.11</td>
</tr>
<tr>
<td>3d</td>
<td>Cl</td>
<td>9.88 ± 0.11</td>
<td>parasiticidal</td>
<td>4.18 ± 0.08</td>
</tr>
<tr>
<td>3e</td>
<td></td>
<td>11.99 ± 1.62</td>
<td>parasiticidal</td>
<td>14.75 ± 0.06</td>
</tr>
<tr>
<td>3f</td>
<td></td>
<td>19.23 ± 0.34</td>
<td>parasiticidal</td>
<td>14.53 ± 2.05</td>
</tr>
<tr>
<td>3g</td>
<td></td>
<td>8.03 ± 0.26</td>
<td>parasiticidal</td>
<td>13.48 ± 0.073</td>
</tr>
<tr>
<td>3h</td>
<td></td>
<td>19.72 ± 2.05</td>
<td>parasiticidal</td>
<td>19.86 ± 0.66</td>
</tr>
<tr>
<td>3i</td>
<td></td>
<td>10.77 ± 2.26</td>
<td>parasiticidal</td>
<td>8.24 ± 0.27</td>
</tr>
<tr>
<td>3j</td>
<td></td>
<td>9.71 ± 0.14</td>
<td>parasiticidal</td>
<td>11.77 ± 0.22</td>
</tr>
<tr>
<td>3k</td>
<td></td>
<td>4.59 ± 0.16</td>
<td>parasiticidal</td>
<td>8.54 ± 0.06</td>
</tr>
<tr>
<td>3l</td>
<td></td>
<td>4.21 ± 0.62</td>
<td>parasiticidal</td>
<td>13.06 ± 0.04</td>
</tr>
<tr>
<td>3m</td>
<td></td>
<td>9.36 ± 0.53</td>
<td>parasiticidal</td>
<td>8.80 ± 1.41</td>
</tr>
<tr>
<td>3n</td>
<td></td>
<td>10.73 ± 1.66</td>
<td>parasiticidal</td>
<td>10.62 ± 0.19</td>
</tr>
<tr>
<td>3o</td>
<td></td>
<td>5.64 ± 0.72</td>
<td>parasiticidal</td>
<td>8.99 ± 0.90</td>
</tr>
<tr>
<td>3p</td>
<td>O</td>
<td>1.48 ± 0.10</td>
<td>parasiticidal</td>
<td>3.87 ± 0.36</td>
</tr>
<tr>
<td>3q</td>
<td>S</td>
<td>13.05 ± 3.03</td>
<td>parasiticidal</td>
<td>6.27 ± 0.09</td>
</tr>
</tbody>
</table>
Table 2 (continued)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ar//X</th>
<th>Schizonticidal Activity IC₅₀ (µM ± SD)</th>
<th>Nature of inhibition</th>
<th>MKC (µM ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3r</td>
<td>O</td>
<td>12.17 ± 0.81</td>
<td>parasiticidal</td>
<td>25.35 ± 1.44</td>
</tr>
<tr>
<td>3s</td>
<td>S</td>
<td>23.09 ± 3.59</td>
<td>parasiticidal</td>
<td>24.70 ± 1.39</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>–</td>
<td>0.078 ± 0.012*</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

A dash (–) indicates activity not done.

* Activity reported (Parveen et al., 2013).

and 25.35 µM, and compound 3p showed maximum activity with MKC of 3.87 ± 0.36 µM, followed by compound 3d with MKC of 4.18 ± 0.08 µM. All the curcumin analogues (3a–s) showed parasiticidal activity. The structure activity relationship (SAR) was established with the antimalarial data showed that among carboxamide analogues (3a–e), 4-fluoro substitution is more favourable than 2-chloro, 4-chloro and 4-bromo, while 2-chloro substitution showed maximum MKC than 4-fluoro, 4-chloro and 4-bromo substitution in the aromatic ring. The antimalarial activity among methanone derivatives (3f–o) showed that substituted aromatic ring showed maximum activity than unsubstituted aromatic ring (3f, 3n). The activity was maximum when 4-pyridyl ring (3l) was present followed by 4-amino (3k) substitution on aromatic ring. The curcumin analogues with pyrimidine/pyrazole with carbonyl function (3p, 3r) showed maximum activity than thione function (3q, 3s). The compound 3p could be considered as promising lead for further optimization. Microscopic observation of infected RBCs exposed to synthetic curcumin compounds is shown in Fig. 2.

3. Experimental

3.1. Computational studies

The X-ray crystal structure of PfRIO-2 does not exist till date, the homology model using the RIO2 of Archaeoglobus fulgidus (PDB: 1TQI) was reported few times (Nag et al., 2013a,b; http://www.plasmodb.org; Parveen et al., 2013; Nag et al., 2013a). The current experimental 3D-homology model was built using the sequences of PDBs 1ZAO (contains the ATP binding site and Mn ion) and A/RIO-2 by employing Prime module (Nag et al., 2013a,b; http://www.plasmodb.org; Parveen et al., 2013; Nag et al., 2013a). The natural bound ligand along with Mn ion placed at functional site of the 3D model by superimposition of model and A/RIO2 co-crystal complex. The final model was then prepared with all necessary parameters using the protein preparation wizard with default parameters. The experimental model contains the metal ions (divalent) and ATP complex. All the chemical structures of the ligands were drawn using the ACD chemsketch and saved as mol. files and imported in Maestro and prepared by using the Ligprep. Further XP protocol implemented in Glide was employed for the ligand docking studies. The homology model developed must be validated for its quality; the current model was validated using the online server RAMPAGE, it gives the quality of the structure. The Ramachandran plot of current model exhibited that, 93.2% of the residues were present in the favoured region, 5.0% were in allowed region and 1.8% in outlier region. The available co-crystal structures of the RIO-2 exhibited the binding site of the ATP along with Mn ions only, we adopted the sitemap analysis tool of the Schrodinger LLC in order identify the possible binding site. The possible four various binding regions were identified.

Scheme 1 Protocol for the synthesis of curcumin analogues (3a–s).

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through it. Among them the flexible loop regions was selected for further processes (Nag et al., 2013a,b; www.plasmodb.org; Parveen et al., 2013; Nag et al., 2013a). The selected site was employed for the receptor grid generation (Fig. 1a and b).

3.2. Chemistry

All chemicals were supplied by E. Merck (Germany), Konark Herbal (India) and S. D. Fine Chemicals (India). Melting
points were determined by open tube capillary method and are uncorrected. Purity of the compounds was checked by elemental analysis and the progress of reactions was monitored by TLC plates (silica gel G) using mobile phase, hexane: ethylacetate (6:4), and the spots were identified by iodine vapours or UV light. IR spectra were obtained on a Schimadzu 8020 PC, FT-IR spectrometer (KBr pellets). \(^1\)H NMR spectra were recorded on a Bruker AC 300/400 MHz spectrometer using TMS as internal standard in DMSO. Mass spectra were recorded on a Bruker Esquire LCMS using ESI and elemental analyses were performed on Perkin–Elmer 2400 Elemental Analyzer.

3.3. General method for the synthesis of 3,5-bis(4-hydroxy-3-methylstyryl)-N-(substituted phenyl)-1H-pyrazole-1-carboxamide analogues (3a–e)

1.7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (I) (0.005 mol) and substituted phenyl semicarbazide (2a–e) (0.005 mol) were refluxed in glacial acetic acid for 12 h (Ahsan et al., 2013). The excess of solvent was removed under reduced pressure and then the reaction mixture was poured into the crushed ice. The solid mass was filtered, washed, dried and recrystallized with ethanol furnished the title 3,5-bis(4-hydroxy-3-methylstyryl)-N-(substituted phenyl)-1H-pyrazole-1-carboxamide analogues (3a–e) (Ahsan et al., 2013).

3.3.1. 3,5-Bis(4-hydroxy-3-methylstyryl)-N-(4-fluorophenyl)-1H-pyrazole-1-carboxamide (3a)
M.p. 70 °C; yield 72% (Ahsan et al., 2013).

3.3.2. 3,5-Bis(4-hydroxy-3-methylstyryl)-N-(4-chlorophenyl)-1H-pyrazole-1-carboxamide (3b)
M.p. 78 °C; yield 66% (Ahsan et al., 2013).

3.3.3. 3,5-Bis(4-hydroxy-3-methylstyryl)-N-(4-bromophenyl)-1H-pyrazole-1-carboxamide (3c)
M.p. 136 °C; yield 74% (Ahsan et al., 2013).

3.3.4. 3,5-Bis(4-hydroxy-3-methylstyryl)-N-(2-chlorophenyl)-1H-pyrazole-1-carboxamide (3d)
M.p. 92 °C; yield 76% (Ahsan et al., 2013).

3.3.5. 3,5-Bis(4-hydroxy-3-methylstyryl)-N-(2-methylphenyl)-1H-pyrazole-1-carboxamide (3e)
M.p. 98 °C; yield 7% (Ahsan et al., 2013).

3.4. General method for the synthesis of 3,5-bis(4-hydroxy-3-methylstyryl)-1H-pyrazole-1-yl(substituted phenyl)methanone analogues (3f–o)

1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (I) (0.005 mol) and substituted phenyl hydrazide (2f–o) (0.005 mol) were refluxed in glacial acetic acid for 12 h. The excess of solvent was removed under reduced pressure and then the reaction mixture was poured into the crushed ice. The solid mass was filtered, washed, dried and recrystallized with ethanol furnished the title 3,5-bis(4-hydroxy-3-methylstyryl)-1H-pyrazole-1-yl(substituted phenyl)methanone analogues (3f–o) (Ahsan et al., 2013).

3.4.1. 3,5-Bis(4-hydroxy-3-methoxystyryl)-1H-pyrazole-1-yl phenyl)methanone (3f)
M.p. 110 °C; yield 84% (Ahsan et al., 2013).

3.4.2. 3,5-Bis(4-hydroxy-3-methoxystyryl)-1H-pyrazole-1-yl(2-chlorophenyl)methanone (3g)
M.p. 168–170 °C; yield 74%; IR (KBr) cm\(^{-1}\): 3412 (OH), 1751 (C=O), 1569 (C=N), 1329 (C=N), 698 (C=Cl). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 3.83 (6H, s, OCH\(_3\)), 6.61 (1H, s, CH=C), 6.76 (2H, d, \(J\) = 12.1 Hz, CH and CH), 6.90 (2H, d, \(J\) = 12.1 Hz, CH and CH), 6.94–8.17 (10H, m, ArH), 9.15 (2H, s, OH); \(m/z\) = 503.0 (M\(^+\)). Cal/Ana: [C (66.85) 66.87 H (4.63) 4.61 N (5.54) 5.57].

3.4.3. 3,5-Bis(4-hydroxy-3-methoxystyryl)-1H-pyrazole-1-yl(4-chlorophenyl)methanone (3h)
M.p. 160–162 °C; yield 78%; IR (KBr) cm\(^{-1}\): 3406 (OH), 1745 (C=O), 1562 (C=N), 1337 (C=N), 698 (C=Cl). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 3.83 (6H, s, OCH\(_3\)), 6.61 (1H, s, CH=C), 6.75 (2H, d, \(J\) = 11.6 Hz, CH and CH), 6.91 (2H, d, \(J\) = 11.6 Hz, CH and CH), 6.93–7.89 (10H, m, ArH), 9.14 (2H, s, OH), 9.89 (1H, s, OH); \(m/z\) = 503.0 (M\(^+\)). Cal/Ana: [C (66.84) 66.87 H (4.63) 4.61 N (5.54) 5.57].

3.4.4. 3,5-Bis(4-hydroxy-3-methoxystyryl)-1H-pyrazole-1-yl(2-bromophenyl)methanone (3i)
M.p. 288 °C; yield 76% (Ahsan et al., 2013).

3.4.5. 3,5-Bis(4-hydroxy-3-methoxystyryl)-1H-pyrazole-1-yl(4-methoxyphenyl)methanone (3j)
M.p. 128–130 °C; yield 74%; IR (KBr) cm\(^{-1}\): 3407 (OH), 1745 (C=O), 1561 (C=N), 1334 (C=N), 745 (C=Cl). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 3.83 (9H, s, OCH\(_3\)), 6.61 (1H, s, CH=C), 6.76 (2H, d, \(J\) = 12.2 Hz, CH and CH), 6.92 (2H, d, \(J\) = 12.2 Hz, CH and CH), 6.92–7.92 (10H, m, ArH), 9.15 (1H, s, OH), 10.28 (1H, s, OH). \(^1\)C NMR (100 MHz, DMSO-d\(_6\)): \(\delta\) 55.9, 56.2, 107.7, 112.0, 114.8, 116.8, 120.1, 122.9, 123.6, 128.8, 130.9, 133.4, 133.9, 144.9, 147.3, 151.3, 165.1, 166.5; \(m/z\) = 499.1 (M\(^+\)). Cal/Ana: [C (69.85) 69.87 H (5.24) 5.26 N (5.65) 5.62].

3.4.6. 3,5-Bis(4-hydroxy-3-methoxystyryl)-1H-pyrazole-1-yl(4-a minophenyl)methanone (3k)
M.p. 215–217 °C (reported), 212–214 °C (found); yield 71% (Sahu et al., 2012).

3.4.7. 3,5-Bis(4-hydroxy-3-methoxystyryl)-1H-pyrazole-1-yl(pyrid-4-yl)methanone (3l)
M.p. 105–106 °C (reported), 104–106 °C (found); yield 71% (Sahu et al., 2012).

3.4.8. 3,5-Bis(4-hydroxy-3-methoxystyryl)-1H-pyrazole-1-yl(2 thiophenyl)methanone (3m)
M.p. 120–122 °C; yield 65%; IR (KBr) cm\(^{-1}\): 3396 (OH), 1735 (C=O), 1563 (C=N), 1337 (C=N). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 3.83 (6H, s, OCH\(_3\)), 6.61 (1H, s, CH=C), 6.76 (2H, d, \(J\) = 12.8 Hz, CH and CH), 6.89 (2H, d, \(J\) = 12.8 Hz, CH and CH), 6.92–7.88 (9H, m, ArH), 10.53 (2H, s, OH);
m/z = 475.1 (M⁺). Cal/Ana: [C (65.84) 65.81 H (4.65) 4.67 N (5.94) 5.90].

3.4.9. 3,5-Bis(4-hydroxy-3-methylstyryl)-1H-pyrazole-1-yl-(phenyl)ethanone (3n)

M.p. 138–140 °C; yield 82%; IR (KBr) cm⁻¹: 3401 (OH), 1755 (C=O), 1569 (C=N), 1338 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ 3.66 (2H, s, CH₂), 3.83 (6H, s, OCH₃), 6.61 (1H, s, CH=–C), 6.76 (2H, d, J = 11.8 Hz, CH and CH), 6.89 (2H, d, J = 11.8 Hz, CH and CH), 6.94–7.81 (11H, m, ArH), 9.15 (2H, s, OH); m/z = 482.6 (M⁺). Cal/Ana: [C (72.14) 72.18 H (5.47) 5.43 N (5.79) 5.81].

3.4.10. 3,5-Bis(4-hydroxy-3-methylstyryl)-1H-pyrazole-1-yl-(phenoxy)ethanone (3o)

M.p. 130–132 °C; yield 76%; IR (KBr) cm⁻¹: 3402 (OH), 1755 (C=O), 1569 (C=N), 1334 (C=N), 745 (C=Cl). ¹H NMR (400 MHz, DMSO-d₆): δ 3.79 (2H, s, OCH₂), 3.83 (6H, s, OCH₃), 6.61 (1H, s, CH=–C), 6.76 (2H, d, J = 11.8 Hz, CH and CH), 6.90 (2H, d, J = 11.8 Hz, CH and CH), 6.94–7.38 (10H, m, ArH), 9.15 (2H, s, OH); m/z = 499.1 (M⁺). Cal/Ana: [C (69.84) 69.87 H (4.65) 4.67 N (5.64) 5.62].

3.5. General method for the synthesis of dihydropryrimidine analogues (3p and 3q)

1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (I) (0.005 mol) and urea/thiourea (2p–q) (0.005 mol) were refluxed in glacial acetic acid for 12 h. The excess of solvent was removed under reduced pressure and then the reaction mixture was poured into the crushed ice. The solid mass was filtered, washed, dried and recrystallized with ethanol furnished the title of 3,5-bis(4-hydroxy-3-methylstyryl)-1H-pyrazole-1-carboxamide analogues (3p–q) (Ahsan et al., 2013).

3.5.1. 4,6-Bis(4-hydroxy-3-methoxystyryl)pyrimidine-2(1H)-one (3p)

M.p. 104 °C; yield 72% (Ahsan et al., 2013).

3.5.2. 4,6-Bis(4-hydroxy-3-methoxystyryl)pyrimidine-2(1H)-thione (3q)

M.p. 102–104 °C; yield 75% (Ahsan et al., 2013).

3.6. General method for the synthesis of 3,5-bis(4-hydroxy-3-methylstyryl)-1H-pyrazole-1-carboxamide/carbothioamide analogues (3r and 3s)

1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione (I) (0.005 mol) and semicarbazide/thiosemicarbazide (2r–s) (0.005 mol) were refluxed in glacial acetic acid (AcOH) for 12 h. The progress of reaction was monitored throughout by TLC plates (silica gel G) using mobile phase, hexane: ethylacetate (6:4), and the spots were identified by iodine vapours or UV light. The excess of solvent was removed under reduced pressure and then the reaction mixture was then poured into the crushed ice. The solid mass was filtered, washed, dried and recrystallized with ethanol furnished the title of 3, 5-bis(4-hydroxy-3-methylstyryl)-1H-pyrazole-1-carboxamide/carbothioamide analogues (3r and 3s).

3.6.1. 3,5-Bis(4-hydroxy-3-methylstyryl)-1H-pyrazole-1-carboxamide (3r)

M.p. 204–206 °C (reported), 200–202 °C (found); yield 84% (Lal et al., 2012).

3.6.2. 3,5-Bis(4-hydroxy-3-methylstyryl)-1H-pyrazole-1-carboxamide (3s)

M.p. 100–101 °C (reported), 102 °C (found); yield 79% (Lal et al., 2012).

3.7. Antimalarial activity

The schizonticidal and parasiticidal activity of synthetic curcumin analogues were determined as described previously (Parveen et al., 2013). In brief, parasite culture was treated with D-sorbitol and then ring stage parasite incubated with different concentration of test compounds. After 42 h incubation, smear was prepared and stained with Giemsa stain to monitor the maturation of ring stage parasites into schizonts. To determine the nature of parasite growth inhibition (parasitostatic/parasitidal), the compounds were removed and the cultures were washed three times with albumax II free RPMI-1640 and incubated in complete media with fresh haematoctrit for another 72 h. A thin smear was prepared, and number of RBCs containing viable parasite was counted. The minimum concentration of compounds giving no viable parasite was used to calculate minimum killing concentration (MKC) of compounds with parasiticidal activity.

4. Conclusion

All the compounds were synthesized in satisfactory yield. The molecular modelling studies revealed that the curcumin analogues completely occupied the S1 site of PRIO-2 kinase with different binding modes. All the synthesized compounds showed significant antimalarial activity with parasiticidal nature. One of the synthesized compounds (3p) with significant results was identified as promising lead for further studies and drug discovery in the field of malaria therapeutics. The detailed studies to acquire more information are in progress in our laboratories.

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References

Molecular modelling, synthesis, and antimalarial potentials of curcumin analogues


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