Research Article

Acefylline Derivatives as a New Class of Anticancer Agents: Synthesis, Molecular Docking, and Anticancer, Hemolytic, and Thrombolytic Activities of Acefylline-Triazole Hybrids

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Received 3 March 2022; Revised 11 May 2022; Accepted 12 May 2022; Published 2 June 2022

1. Introduction

The most common type of liver cancer is hepatocellular carcinoma (HCC) which is the third leading cause of death in humans due to cancer [1]. Only 11% of cancerous cells are cured with chemotherapy, 49% with surgery, and 40% with radiotherapy [2]. Different chemotherapeutic drugs are available but are expensive, have negative side effects, and are not very effective. Therefore, in the search for anticancer drugs, there is a considerable surge in the design and development of novel agents [3, 4].

Recently, various pyrimidine and caffeine derivatives have been successfully synthesized, and their biological activities were evaluated [5–7]. Pyrimidine-containing compounds have many pharmacological applications and have been found to be active against pathogens [8–10]. For example, theophylline or methylxanthine (1; Figure 1) belongs to a class of xanthine alkaloids, which grabs great attention because of its extensive therapeutic use to treat respiratory disorders such as chronic obstructive pulmonary disease (COPD) and asthma [11]. Asthma is a heterogeneous syndrome with airway inflammation that remained under consideration by scientists, and many efforts have been made for its treatment. Among various medications, theophylline derivatives have played a remarkable role. For example, 8-anilide theophylline derivatives were synthesized...
and were found to be effective [12, 13]. It is a bronchodilator drug that relaxes stiffer muscles and open-air passageways [14]. Moreover, it possesses anti-inflammatory properties that suppress the hyperinflation of airways and reduce the chances of dyspnea [15].

The efficiency of theophylline (1) as an anti-inflammatory agent varies with the nuclear factor-KB, phosphodiesterase certification, and apoptosis [16]. To treat COPD, it shows anti-inflammatory activity by inhibition of activated inflammatory genes [17]. Theophylline (1) not only inhibits the mediators of the inflammatory process but also inhibits the production of oxygen-free radicals. Theophylline (1) pharmaceutical activity, as a bronchodilator and anti-inflammatory drug in vivo, affects the glucocorticoid receptors that ultimately reduce THF-A concentration [18]. Moreover, 1 sugar hydrazones were found to be effective and have antimicrobial properties against Aspergillus fumigatus (AF) and Penicillium italicum (PI) [19]. However, 1 is a second-line bronchodilator due to its narrow therapeutic range and index along with side effects such as insomnia, nausea, and vomiting [20].

Acefylline derivatives exhibit important biological activities and belong to the bronchodilators class of drugs. Along with bronchodilation, acefylline derivatives are also reported to exhibit potent activities such as anticancer [21], antibacterial and antiviral properties [22], and antiasthmatic activities [23]. Moreover, they have a cardiac stimulant [24], and adenosine antagonist receptor [25], and therefore, acefylline (2) (Figure 1) has become attractive for researchers.

Recently, we have reported the activity of 1,3,4-oxadiazoles [26] and 1,2,4-triazoles [27] derived from 2 as potential anticancer drug candidates. Considering the importance and anticancer activity of 1,2,4-triazoles, we have considered the synthesis of a new series of acefyllines that have different aryl groups and evaluated their anticancer activity. In addition, to explore what effect the aryl group in compounds 8 could have on the reactivity of the synthesized derivatives 9.

2. Materials and Methods

2.1. Materials and Methods. Analytical grade reagents were purchased from Alfa Aesar (Kandel, Germany) and Merck (Gillingham, UK) and used without further purification. The synthesized compounds were purified using the recrystallization technique or column chromatography. IR spectra were obtained on Bruker FTIR spectrometer (Bruker, Zürich, Switzerland) using KBr discs. The NMR spectra were accessed using Bruker Spectrometer model AV-400 (Bruker, Zürich, Switzerland) at 400 MHz for $^1$H and 100 MHz for $^{13}$C spectra. Deuterated dimethyl sulfoxide (DMSO-d$_6$) was used as a solvent, and chemical shift values were recorded in ppm. The melting points were evaluated using the Gallenkamp apparatus. The glass column filled with grade 60 silica gel was used for column chromatography. The TLC was performed using analytical grade solvents on silica gel coated TLC plates (60 F254). The progress of reactions was monitored using TLC plates, and the spots were checked under UV light.

2.2. General Procedure for the Synthesis of Acefylline Derivatives 9a-9e. Compounds 9a-9e were synthesized according to the reported procedures [26–28]. A mixture of appropriate triazole (0.2 g, 0.45 mmol) and pyridine (0.12 g, 1.5 mmol) in DCM (10 mL) was stirred for 15 minutes. 2-Bromo-N-phenyl/arylacetamide (0.46 g, 2.0 mmol) was added, and the reaction mixture was stirred for 24–48 h at 25°C. After reaction completion, n-hexane (15 mL) was added to the reaction mixture, and the resulting solids were collected by filtration. The solids were purified by recrystallization using EtOH.

2.2.1. 2-(4-(3,4-dichlorophenyl)-5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-4H-1,2,4-triazol-3-yl)(thio)-N-phenylacetamide (9a). Cream powder; yield: 71%; m.p 209°C; IR (KBr): ν 3349 (N–H), 1648 (C=O), 1639 (C=O), 1541 (C=N), 1545 (C=C). $^1$H NMR (δ/ppm): 3.14 (s, 3H, Me), 3.39 (s, 3H, Me), 4.15 (s, 2H, SCH$_2$), 5.66 (s, 2H, NCH$_2$), 7.19–7.80 (m, 8H, Ar), 7.98 (s, 1H, CH), 9.96 (s, 1H, NH). $^{13}$C NMR (δ/ppm): 27.9 (Me), 29.9 (Me), 37.3 (SCH$_2$), 41.2, (NCH$_2$), 106.5, 115.1, 119.6, 121.1, 124.0, 127.5, 129.2, 132.4, 133.1, 138.3, 139.2, 143.3, 143.5, 148.4, 151.6, 151.8, 154.6 (C=O), 165.8 (C=O). MS m/z (ES$^+$) 570.0748 (M$^+$+H$^+$) (100%). Anal. Calcd. For C$_{25}$H$_{20}$Cl$_2$FN$_8$O$_3$S: C, 48.91; H, 3.25; N, 19.01%.

2.2.2. 2-(4-(3,4-dichlorophenyl)-5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-4H-1,2,4-triazol-3-yl)(thio)-N-(2-methoxyphenyl)acetamide (9b). Light brown, amorphous solid; yield: 69%; m.p 180°C; IR (KBr): ν 3349 (N–H), 1648 (C=O), 1639 (C=O), 1541 (C=N), 1545 (C=C). $^1$H NMR (δ/ppm): 3.46 (s, 3H, Me), 3.46 (s, 3H, Me), 4.15 (s, 2H, SCH$_2$), 5.65 (s, 2H, NCH$_2$), 7.15–7.86 (m, 8H, Ar), 7.98 (s, 1H, CH), 9.78 (s, 1H, NH). $^{13}$C NMR (δ/ppm): 27.9 (Me), 29.9 (Me), 37.2 (SCH$_2$), 41.2, (NCH$_2$), 106.5, 115.1, 119.6, 121.1, 124.0, 127.5, 129.2, 132.4, 133.1, 138.3, 139.2, 143.3, 143.5, 148.4, 151.6, 151.8, 154.6 (C=O), 165.8 (C=O). MS m/z (ES$^+$) 570.0748 (M$^+$+H$^+$) (100%). Anal. Calcd. For C$_{25}$H$_{22}$Cl$_2$FN$_8$O$_3$S: C, 48.91; H, 3.25; N, 19.01%; found: C, 50.24; H, 3.64; N, 19.40%.

2.2.3. 2-(4-(3,4-dichlorophenyl)-5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-4H-1,2,4-triazol-3-yl)(thio)-N-(2-methoxyphenyl)acetamide (9c). Light brown, amorphous solid; yield: 64%; m.p 175°C; IR (KBr): ν 3349

![Figure 1: Structures of theophylline (1) and acefylline (2).](image-url)
2.2.4. N-(2-chlorophenyl)-2-(4-(3,4-dichlorophenyl)-5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)acetamide (9d). *Off white, 2H, CH), 9.86 (s, 1H, NH).* 

**13C NMR** (ES+) 604.0366 (M +) (100%). Anal. Calcd. For C24H19Cl3N8O3S: C, 47.58; H, 3.16; N, 18.49%; found: C, 47.99; H, 3.16; N, 19.32%.

2.2.5. N-(4-chlorophenyl)-2-(4-(3,4-dichlorophenyl)-5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)acetamide (9e). *Off white, amorphous solid; yield: 73%; m.p 176°C; IR (KBr) ν 3349 (N-H), 1648 (C=O), 1639 (C=O), 1541 (C=N), 1545 (C=C).*

**1H NMR** (δ/ppm): 3.14 (s, 3H, Me), 3.39 (s, 3H, Me), 4.15 (s, 2H, SCH2), 5.66 (s, 2H, NCH2), 7.19–7.80 (m, 7H, Ar), 7.98 (s, 1H, CH), 9.86 (s, 1H, NH). 

**13C NMR** (δ/ppm): 27.9 (Me), 29.9 (Me), 37.2 (SCH2), 41.4 (NCH2), 106.5, 110.8, 119.6, 120.8, 127.4, 130.5, 131.2, 132.4, 132.5, 139.3, 143.5, 146.7, 147.3, 148.4, 149.4, 151.3, 151.4, 151.9, 154.6 (C=O), 165.8 (C=O). MS m/z (ES+) 604.0366 (M +) (100%). Anal. Calcd. For C24H19Cl3N8O3S: C, 47.58; H, 3.16; N, 18.49%; found: C, 47.44; H, 3.16; N, 19.30%.

2.3. Biological Evaluation

2.3.1. MTT Assay. The cytotoxic potential of the synthesized compounds was tested according to the MTT assay [29]. The synthesized compounds were tested against the cancer cell line Hep G2. The cell line was developed as a monolayer culture in the Dulbecco’s modified Eagle’s medium having FBS (10%) and streptomycin (1%)/penicillin (100 μg/mL). It was incubated in an humid atmosphere having carbon dioxide (5%) and air (95%) and water at 37°C. The cell line (Hep G2) was treated with a suitable concentration (100 μg/100 mL), a solution of synthesized compounds in DMSO. Cells treated with DMSO were used as a negative control in all experiments. The Hep G2 cells were cultured overnight in 96-well plates and further treated with the synthesized compounds (at different concentrations) and incubated for 48 h. After that added MTT reagent (10 μl, 5 mg/mL) to each plate, followed by incubation for 4 h at 37°C. Finally, DMSO (150 μl) was added to each plate to calculate the percentage cell viability by measuring the absorbance at 490 nm via a microplate reader.

2.3.2. Hemolytic Assay. A sample of human blood (3 mL) was taken and centrifuged (1000 x g) for 5 minutes. Erythrocytes were isolated which was dissolved in a phosphate buffer (pH 7.4). A solution of the synthesized compound (20 μl, 10 mg/mL) was added to the RBC suspension (180 μl) followed by incubation for 30 min at 37°C. The ABTS and DMSO were taken as positive and negative controls, respectively. The age hemolysis (%) was calculated using the following equation [30]:

\[
agehemolysis(%) = \frac{\text{Absorbance of sample} - \text{Absorbance of DMSO}}{\text{Absorbance of ABTS}} \times 100.
\]

2.3.3. Thrombolytic Assay. A sample of human blood (1 mL) was incubated for 45 minutes at 25°C in a preweighed tube. After the formation of the clot, the serum was completely removed, and each tube was weighed again to find out the weight of the clot. A solution (100 μl) of each of the tested compounds was added separately and kept at 37°C for 3 hours, and clot lysis in the sample was observed. DMSO was added in some tubes (as a negative thrombolytic control) while ABTS was used as a positive control. After the clot lysis, the tubes were weighed, and the difference in weights was calculated. The percentage of thrombolysis was calculated using the following equation [31]:

\[
\text{Clot lysis} (\%) = \frac{\text{Initial clot weight} - \text{Final clot weight}}{\text{Initial clot weight}} \times 100.
\]

2.3.4. Molecular Docking. Compound 9e was further in silico modeled to complement its experimental studies to further delineate its potential mechanism of action responsible for its anticancer activity. Compound 9e was screened through the PASS prediction tool that predicts the therapeutic target of the tested molecule (≥95% accuracy) and anticancer target with the probability of activity (Pa) > 50%. It was molecularly docked against the target by using the induced fit docking protocol at the platform of molecular operating environment 2015.10. The chemical structures of compounds were sketched, and energy was minimized under the CHARMM force field utilizing MMFF9x partial charge in Discovery Studio Visualizer 17.2. The three-dimensional (3D) X-ray structure of crystalized STAT3 (PDB ID:5AX3, 2.984 Å) was obtained from RSCB Protein Data Bank (http://www.rcsb.org) and corrected and optimized via
3. Results and Discussion

3.1. Chemistry. The synthesis of thioN-phenylacetamide 3,4-dichlorophenyl-1,2,4-triazoles of acefylline 9a–9e is presented in Scheme 1. Firstly, the esterification of 2 was performed to afford compound 3 in 76% yield followed by reaction with hydrazine hydrate to give 4 in 96% yield. Treatment of 4 with 3,4-dichlorophenyl isothiocyanate (5) gave the intermediate 6 which on treatment aqueous potassium hydroxide (KOH) under reflux condition afforded 7 in 71% yield. Alkylation of 7 with various substituted bromoacetamides 8a–8e in dichloromethane (DCM) containing pyridine at room temperature gave the final products 9a–9e in 64–73% yield.

3.2. Elucidation of Acefylline 9a–9e Structures. The structures of the newly synthesized heterocycles were confirmed using various spectroscopic techniques (see the experimental section for details). The FTIR spectra of compound 9a–9e showed the presence of two different carbonyl groups. The 1H NMR spectra showed the presence of an exchange singlet that appeared within the 9.60–10.09 ppm region due to the amide proton. The CH=N proton appeared as a singlet at 7.98 ppm. The protons of the two methyl groups appeared as two singlets at 3.14 and 3.39–3.46 ppm regions. The 13C NMR spectra of compound 9a–9e showed the presence of two different carbonyl groups that appeared down fielded at 154.6 and 165.8 ppm. In addition, they show the presence of two different methyl groups (27.9 and 29.9 ppm). The NMR spectra of compound 9c showed the presence of the methoxy group that appeared at 3.81 for the protons and at 62.2 ppm for the carbon. Additionally, the structures of 9a–9e were confirmed by the data obtained from the high-resolution mass spectra and elemental analyses. The NMR spectra of 9a–9e are shown in Figures S1–S10.

3.3. Anticancer Activity. The inhibitory potential of compounds 9a–9e against the proliferation of Hep G2 cancer cell line was accessed using the MTT assay and was compared with that obtained for 2. The results showed that compounds 9a–9e were more reactive against cancer cells (cell viability = 22.55 ± 0.95% to 57.63 ± 3.65%) compared with 2 (cell viability = 80 ± 3.87%). Compound 9e showed the most potent antiproliferative activity (cell viability = 22.55 ± 0.95%). Compounds 9a–9d showed moderate activity against the liver cancer cell line Hep G2 (cell viability 53.85 ± 3.30%, 47.66 ± 3.59%, 53.49 ± 1.97%, and 57.63 ± 3.65%, respectively). The anticancer activity of 9e was also tested at different concentrations that ranged from 0.3 μg to 200 μg, and the best activity was observed at the highest concentration (200 μg; Figure 2). For compound 9e, the IC50 was calculated as 5.23 ± 0.95 μM.

3.4. The Structure-Activity Relationship (SAR). The biological activities of compounds 9a–9e along with that for 2 and controls are summarized in Table 1. Compound 9a which contains a phenyl group as a substituent showed a moderate activity (cell viability = 53.85 ± 3.30%) against the liver cancer cell lines Hep G2. Compound 9e which contains an electron-withdrawing group (4-Cl) showed the greatest potential (cell viability = 22.55 ± 0.95%) against the cancer cells compared to the other derivatives. The activity of compounds 9b, 9c, and 9d which contain electron-withdrawing substituents (2-F, 2-OMe, and 2-Cl, respectively) were relatively low. Clearly, the presence of the electron-withdrawing group (e.g., Cl) at the 4-position of the phenyl ring might be responsible for a greater binding activity with the cancer cell.

3.5. Hemolytic Activity. The results of the hemolytic activity indicated that compounds 9a–9e were less toxic compared with 2. Moderate activity was observed for compound 9a (4.7%) which contains unsubstituted phenyl ring compared with 2 (43.5%). Compounds 9b–9e had electron-withdrawing substituents on the phenyl ring and appeared to be the least toxic with hemolysis (%) of 1.86, 2.87, 0.23, and 1.20, respectively.

3.6. Thrombolytic Activity. Compounds 9a–9e exhibited low-to-moderate clot lysis activity. Compounds bearing electron-withdrawing substituents at the phenyl ring exhibited a moderate clot lysis activity [9a (39%), 9d (37%), and 9e (26%)] which is much higher than that for acefylline (2; 6.85%). The maximum activity was observed for compounds 9b and 9c that have electron-withdrawing substituents at the ortho-position of the phenyl ring (thrombolysis (%) = 48.0 and 49.4, respectively).

3.7. Molecular Docking Analysis. The in silico studies were carried out for the prediction and elucidation of the potential mechanism for the inhibitory action of compound 9e for its superior anticancer activity in the experimental studies. The PASS predictions resulted in STAT3 as a potential therapeutic anticancer target of compounds 9e with Pa = 0.51. Compound 9e structure-activity relationship was investigated via the induced fit docking protocol using STAT3 hotspot. It has a superior binding affinity (~7.9 ΔG kcal/mol) as compared to 2 binding affinity (~5.32 ΔG kcal/mol). The binding energy and the interaction profile of compounds 2 and 9e are shown in Table 2.
The binding pocket of the STAT3 hotspot comprised the LYS352, TYR306, GLU72, ASP308, TYR122, ARG126, GLN123, and ASP311 (Figure 3). The binding mode analysis revealed that both 2 and 9e efficiently stabilized their conformation within the three-dimensional space of STAT3. The conformational analysis of 2 suggested its stable confirmation at the binding pocket and interacted with vital residues which may destabilize the hotspot. Compound 9e was found to orient its confirmation more towards the STAT3 residues, which may suggest its preferential inhibition of STAT3 complexation.

Acefylline (2) stabilized its confirmation mainly with the H-bonding through the binding with TYR306, ASP311, GLU72, LYS352, GLN123, and ASN73 (Figure 4). In addition, it stabilizes itself through the hydrophobic interaction with the TYR306 and pi-cation and pi-anion interactions with the ASP311 and LYS352 although compound 9e shared the interactions with the majority of residues conserved for 2 interactions, with different bonding interactions that may suggest its superior binding affinity and stabilization at STAT3 hotspot. Compound 9e established H-bond with the TYR122, ASP308, LYS352, GLU72, TYR306, pi-cation, and pi-anion interactions with the ASP311, ARG126, LYS351, and hydrophobic interactions with the LYS351 which led its orientation more towards STAT3 hotspot to inhibit its complexation.

The in silico studies were performed further to elucidate the anticancer activity of 9e and to explore the potential structure-activity relationship complementing the
Table 1: Biological activities of 9a–9e along with that for 2, solvent, and ABTS.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>R</th>
<th>Cell viability*</th>
<th>Hemolysis (%)</th>
<th>Thrombolysis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>pH</td>
<td>53.85 ± 3.30</td>
<td>4.70</td>
<td>39.0</td>
</tr>
<tr>
<td>9b</td>
<td>2-FC₆H₄</td>
<td>47.66 ± 3.59</td>
<td>1.86</td>
<td>48.0</td>
</tr>
<tr>
<td>9c</td>
<td>2-MeOC₆H₄</td>
<td>53.49 ± 1.97</td>
<td>2.87</td>
<td>49.4</td>
</tr>
<tr>
<td>9d</td>
<td>2-ClC₆H₄</td>
<td>57.63 ± 3.65</td>
<td>0.23</td>
<td>37.0</td>
</tr>
<tr>
<td>9e</td>
<td>4-ClC₆H₄</td>
<td>22.55 ± 0.95</td>
<td>1.20</td>
<td>26.0</td>
</tr>
<tr>
<td>Acefylline (2)</td>
<td></td>
<td>79.00 ± 2.54</td>
<td>43.5</td>
<td>6.85</td>
</tr>
<tr>
<td>DMSO</td>
<td></td>
<td>100 ± 0</td>
<td>0.01</td>
<td>0.57</td>
</tr>
<tr>
<td>ABTS</td>
<td></td>
<td>—</td>
<td>95.50</td>
<td>88.0</td>
</tr>
</tbody>
</table>

Note. *Cell viability (Mean ± SD), (triplicate, 100 µg/mL).

Table 2: The docking parameters of 2 and 9e using the STAT3 hotspot.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Binding energy $\Delta G$ (kcal/mol)</th>
<th>Interacting residues</th>
<th>Interaction type</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>−5.32</td>
<td>ASP311, GLU72, TYR306, LYS352, GLN123, and ASN73</td>
<td>H-bond, (\pi)-anion, (\pi)-cation, (\pi)-alkyl, and (\pi)-(\sigma)</td>
</tr>
<tr>
<td>9e</td>
<td>−7.9</td>
<td>ASP308, TYR122, ASP311, ARG126, LYS352, GLU72, TRY306, and LYS351</td>
<td>H-bond, (\pi)-anion, (\pi)-cation, and (\pi)-alkyl</td>
</tr>
</tbody>
</table>

Figure 3: Conformational analysis of compounds docked using STAT3 hotspot; simulated best binding mode of (a) 2 and (b) 9e at binding pocket.

Figure 4: Interaction within the binding pocket of STAT3 hotspot of (a) 2 and (b) 9e. Two-dimensional (2D) perspective on docked compounds’ interaction with STAT3 key residues illustrated as balls and sticks colored by type of interaction.
experimental studies. The STAT3 was identified as the potential target of 9e for anticancer activity by the PASS prediction. The binding affinity of 9e to STAT3 was evaluated using the induced fit docking protocol to simulate its complexation, binding mode, and the interactions that reliably simulate the flexibility of the binding pocket upon ligand binding. Compound 9e was found to bind and disrupt the STAT3 hotspot with superior binding affinity as compared to 2. Interestingly, 9e exhibited an improved binding affinity well aligned with the experimental studies as compared to its previous analog [26]. Moreover, the stable orientation of 9e allowed it to establish diverse interactions with key residues of the STAT3 hotspot and orient it more towards the STAT3 to inhibit its complexation. Clearly, 9e has a more potent anticancer activity compared with 2.

4. Conclusions

Nine novel acefyllines containing 3,4-dichlorophenyl-1,2,4-triazole hybrids were synthesized in high yields, and their structures were confirmed. The synthesized acefyllines were tested in vitro for their anticancer activity for the human liver cancer cell line (Hep G2) using the MTT assay. The synthesized acefyllines exhibited moderate activity against the Hep G2. N-(4-chlorophenyl)-2-(4-(3,4-dichlorophenyl)-5-((1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl) methyl)-4H-1,2,4-triazol-3-thio)acetamide (9e) was found to be the most active derivative among the synthesized ones with a cell viability of 22.55 ± 0.95%. The cytotoxic potential of acefyllines was confirmed by evaluating their hemolysis and thrombolysis potentials and was found to exhibit low toxicity and excellent thrombolytic activity.

Data Availability

Data are contained in the article and the supplementary material.

Conflicts of Interest

The authors have no conflicts of interest.

Acknowledgments

El-Hiti is grateful to the Deanship of Scientific Research, King Saud University, for funding through the Vice Deanship of Scientific Research Chairs. The authors acknowledge Government College University Faisalabad for support and facilities to carry out the work.

Supplementary Materials

Figure S1: 1H NMR spectrum of 9a, Figure S2: 13C NMR spectrum of 9a, Figure S3: 1H NMR spectrum of 9b, Figure S4: 13C NMR spectrum of 9b, Figure S5: 1H NMR spectrum of 9c, Figure S6: 13C NMR spectrum of 9c, Figure S7: 1H NMR spectrum of 9d, Figure S8: 13C NMR spectrum of 9d, Figure S9: 1H NMR spectrum of 9e, and Figure S10: 13C NMR spectrum of 9e. (Supplementary Materials)

References


