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Synthesis and Characterization of Pyrrole-2,5-dione based Heterocyclic Compound

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Abstract: ***A desired pyrrole-2,5-dione based heterocyclic compound i.e. 3,5-bis(3-((E)-2-hydroxy-3-methoxybenzylidene)-2,5-dioxopyrrolidin-1-yl) benzoic acid has been synthesized from 3,5-diaminobenzoic acid in three steps with good yield. All synthesised compounds have been characterised by FT IR, ^{13}C NMR, ^{1}H NMR, and HRMS spectrophotometry.***

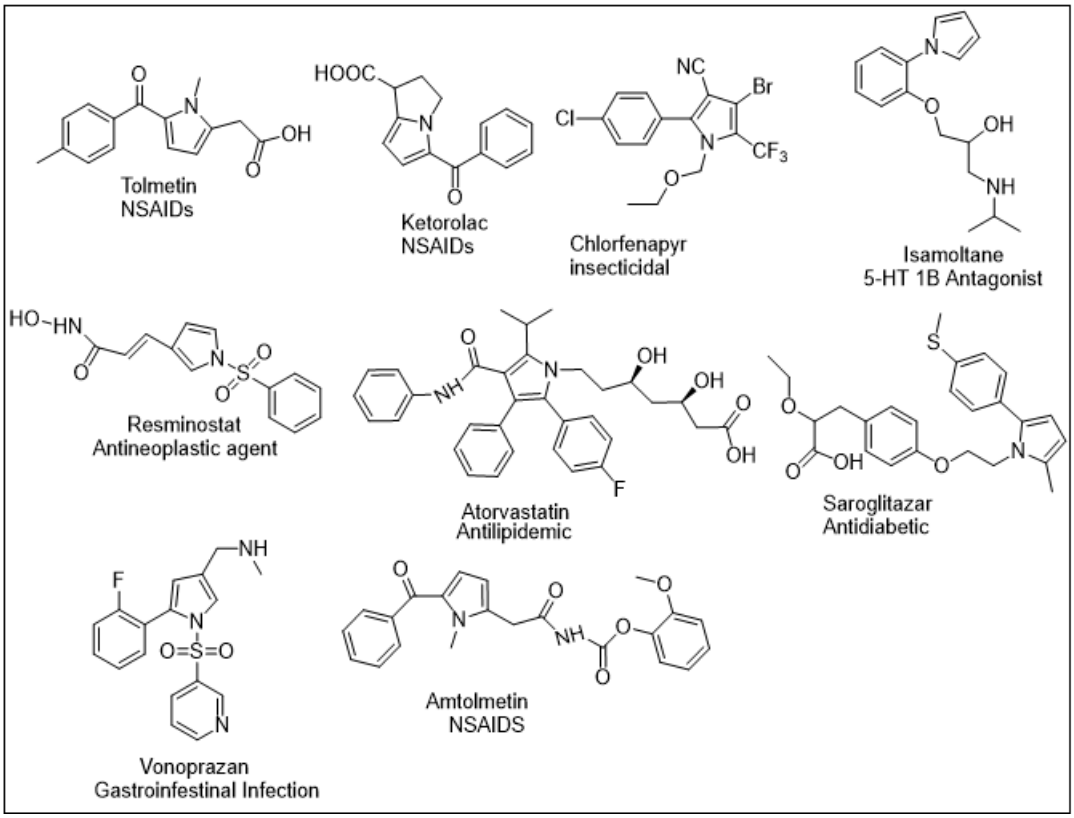
Keywords: Pyrrole, oxo-pyrrolidine, 3,5-diamino benzoic acid

1. Introduction

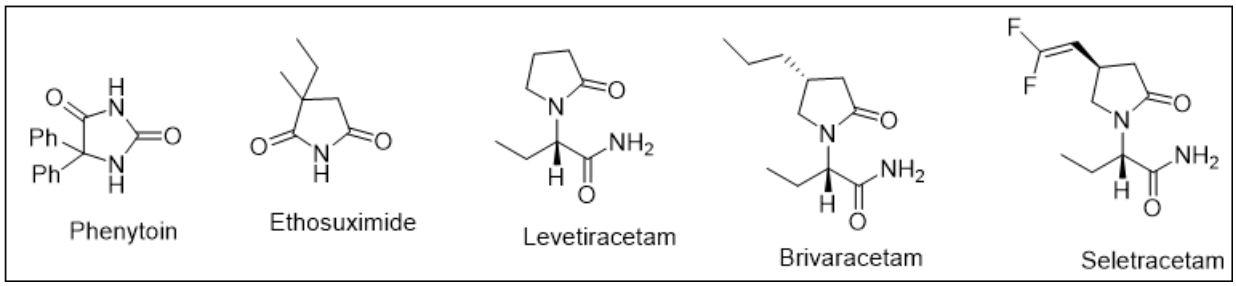
Heterocyclic is the cyclic compound that contains at least one heteroatom such as oxygen, sulfur, nitrogen besides carbon and hydrogen [1]. Nowadays, heterocyclic compounds have gained remarkable attention due to their pharmacological and biological importance [2, 3, 4]. Pyrrole is the N-containing five membered aromatic heterocyclic compound and it is the key component of pigments of life, i.e. vitamin B12, chlorophyll, bile acids, and heme. Among several natural products carrying a pyrrole motif, the popular natural product laminarin has been identified for its bioactivity [5]. Various commercial drugs are available based on pyrrole scaffolds which are known to have diverse biological attributes such as antianxiolytic, antiprotozoal, antiinflammatory, antipsychotic, antimicrobials, antifungal, β-adrenergic antagonist, anticancer, antihyperlipidemic, antimalarial, antibacterial, fungicides, antibiotics, cholesterol-reducing drugs, antitubercular and antitumor activities [6, 7]. Presently, more than twenty-five commercial drugs based on pyrrole scaffolds are available with ketorolac, atorvastatin [8], and tolmetin [9] (**Scheme 1**). Being the top-selling drugs, pyrroles are exploited in various other disciplines of sciences as well. The combination of various pharmacophore in a pyrrole ring structure has led to more active scaffolds [10, 11, 12]. Pyrrole can also be found in diverse forms of polymers, organic dyes, catalyst in various polymerisation process, corrosion inhibitor, additive, or solvent for tars, resin and terpenes and materials, such as BODIPY, conjugated polymers, optoelectronics, as well as semiconductors [13, 14, 15].

Oxo-pyrrolidine heterocyclic exhibited a numerous biological significance such as antifungal [16] growth-stimulating, antiarrhythmic [17], herbicide [18], antibacterial [19]. Antihypertensive [20], Anticonvulsant [21], neuroprotective attributes, especially in the context of Alzheimer's disease [22]. Apart from this, modified 3-pyrroline-2-ones with a 2-pyrrolidinone has a great interest in biological science because numerous derivatives have exhibited historic pharmacological scaffolds, as an anti-inflammatory [23]. Antitumours [24], anti-bacterial [25], anti-microbial [26], HIV-1 integrase inhibitors [27, 28] and anti-cancer agens [29]. A oxo-pyrrolidine based drugs are shown in (**Scheme 2**) [30]. The estimated various synthetic methods of oxo-pyrrolidine have been reported [31, 32].

Owing to broad scope of pyrrole and oxo-pyrrolidine scaffolds in medicinal and other fields, Herein, we synthesised pyrrole-2,5-dione based heterocyclic compound in good yield.



Scheme 1: A pyrrole-based drugs.



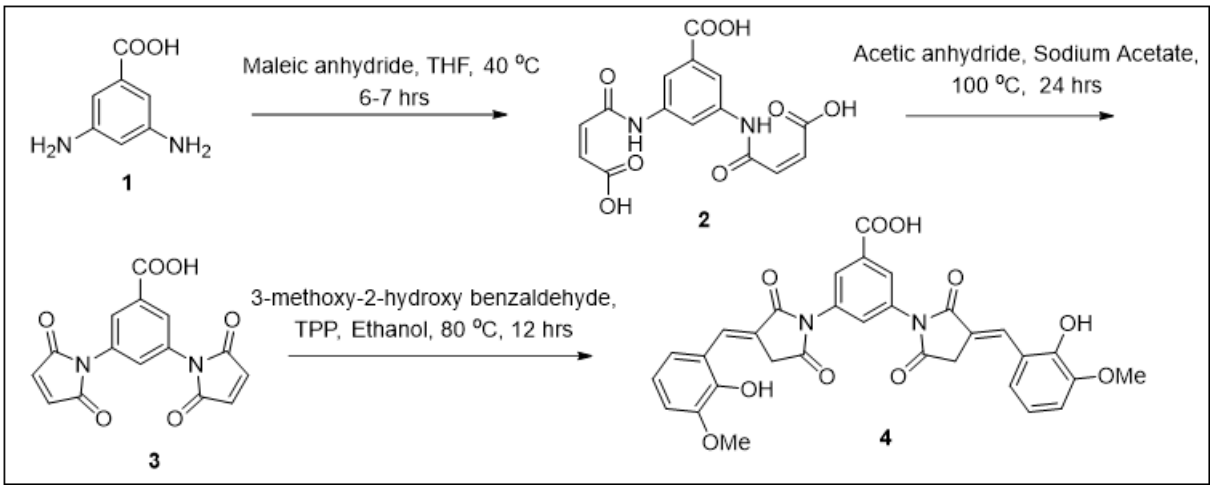
Scheme 2: Heterocyclic oxo-pyrrolidine based drugs.

2. Result and Discussion

The desired compound pyrrole 2,5-dione substituted heterocyclic compound **4** was synthesised from 3,5-diaminobenzoic acid (**1**) in three steps (**Scheme 3**). Firstly, compound 3,5-diaminobenzoic acid (**1**) was dissolved in tetrahydrofuran solvent then added maleic anhydride and stirred the reaction for 6-7 h at 40 °C to afford compound **2** in 95% yield. The characteristics proton of compound **2** in ^{1}H-NMR spectroscopy appeared at δ 6.27 and 6.38 (unsaturation CH=CH), 7.39 (aromatic ArH), 10.69 (OH) and ^{13}C-NMR appeared at δ 166.5 (C=O), 136.2 and 138.4 (unsaturation CH=CH), 118.4, 130.5 and 136.0 (aromatic ArC). The characteristics frequency in cm^{-1} in Infrared Spectroscopy appeared at 1670 (amide group, C=O), 1720 (carboxylic acid, C=O), 3120 (aromatic, C-H).

In the second step, compound **2** was reacted with acetic anhydride in basic medium at 100 °C for 24 h to accomplish **3** in 92% yield. The characteristics proton of compound **3** in ^{1}H-NMR spectroscopy appeared at δ 7.21 (oxo-pyrrolidine, CH=CH), 7.63 (aromatic proton), 7.96 (aromatic proton), 10.12 (carboxylic acid proton). In ^{13}C-NMR appeared at δ 169.2 (C=O, carboxylic), 161.7 (amide C=O), 135.8 (CH=CH, carbon). 115.4, 130.5, and 132.7 (aromatic carbon). The characteristics frequency in cm^{-1} in Infrared Spectroscopy appeared at 1676 (amide group, C=O), 1725 (carboxylic acid, C=O), 3123 (aromatic, C-H).

The lastly desired heterocyclic compound **4** was accomplished from the reaction between compound **3** and 3-methoxy-2-hydroxy benzaldehyde with TPP in ethanol solvent under refluxing condition for 12 h at 80 °C with 86% yield. The characteristics proton of compound **4** in ^{1}H-NMR spectroscopy appeared at δ 10.24 (OH), 9.46 (CH_2), 8.05-6.89 (aromatic proton). In ^{13}C-NMR appeared at δ 173.8 (amide carbon), 170.3 (carboxylic C=O), The characteristics frequency in cm^{-1} in Infrared Spectroscopy appeared at 1708 (lactam, C=O), 1723 (carboxylic acid, C=O), 3127 (aromatic, C-H), 3380 (OH).



Scheme 3: Synthesis of pyrrole-2,5-dione based heterocyclic compound **4**.

3. Conclusion

In summary, we have synthesised a desired compound pyrrole-2,5-dione substituted heterocyclic compound in three steps from 3,5-diaminobenzoic acid in good yield. The synthesised compound has been characterised by FT IR, ^{13}C-NMR, ^{1}H-NMR, and mass spectrophotometry techniques. This compound may be useful for therapeutic applications.

4. Experimental Section

Analytical grade commercially available chemicals have been bought from commercial suppliers such as sigma-Aldrich, Sd fine and used without purification. The FT IR spectra of synthesised compounds have been documented on a Perkin-Elmer instrument 2000 FT-IR spectrometer by making KBr disc for solid samples. The ^{1}H and ^{13}C-NMR spectra were recorded on a Jeol alpha-400 spectrometer at 400 and 100.6 MHz, respectively, using TMS as internal standard. The chemical shift values are on δ scale and the coupling constants (*J*) are in Hz. Signal patterns were indicated as s for singlet; d for doublet; dd for double doublet; t for triplet; m for multiplet and brs for broad singlet. The high resolution mass spectrophotometry (HRMS) has been done on micro TOF-Q instrument and compound was run in ESI positive mode. Analytical TLC plates were purchased from precoated Merck silica-gel 60F_{254} and spots have been visualized through Ultra Violet light. Silica gel (100-200 mesh) has been used for purification of compounds by column chromatography.

Synthesis of compound 2.
compound 3,5-diaminobenzoic acid (**1**) was dissolved in tetrahydrofuran solvent then added maleic anhydride and stirred the reaction for 6-7 h at 40 °C. Progress of reaction was monitored by TLC in UV light and after accomplishment of reaction mixture, solvent was removed by rotatory evaporator, then extracted the crude product **2** with chloroform and water. Organic layer came in chloroform solvent and again removed chloroform solvent by rotatory evaporator and purified the crude product **2** by column chromatography with methanol and chloroform solvent using silica gel to afford yellow solid in 95% yield.

^{1}H NMR spectrum (400 MHz, DMSO-*d*$_6$), δ, ppm: 6.25 d (2H, *J* = 12.1 Hz, H-2), 6.38 d (2H, *J* = 12.1 Hz, H-3), 7.39 d (2H, *J* = 2.2 Hz, H-2' & H-6'), 8.24 s (1H, H-6') 10.65 brs (OH). **^{13}C NMR** spectrum (**100.6 MHz, DMSO-*d*$_6$**), δC, ppm: 116.5, 118.4, 130.5, 136.0, 136.2, 138.4, 166.0, 166.6, 169.2, **IR (KBr) ν_{max}**, cm^{-1}: 1670 1720, 3120 (Ar$_{C-H}$). In MS: Mass spectrum (HRMS-ESI), *m/z*: 349.04 [*M* + H]$^+$ (calcd for $C_{15}H_{13}N_2O_8$: 349.06).

Synthesis of compound 3.
Compound **3** was achieved from compound **2** by intramolecular cyclization reaction. Compound **2** was treated with acetic anhydride in basic medium using sodium acetate at 100 °C for 24 h. After completion of reaction mixture, crude product **3** was extracted with chloroform and water. Organic layer came in chloroform solvent and removed the chloroform by rotatory evaporator and purified the crude product **3** through column chromatography using silica gel and eluent solvent $CHCl_3$ and CH_3OH to afford as a yellow solid in 92% yield.

^{1}H NMR spectrum (400 MHz, DMSO-*d*$_6$) δ, ppm: δ 7.21 s(4H, H-4' & H-3'), 7.63 d (1H, *J* = 2.2 Hz, H-4), 7.96 d (2H, *J* = 2.2 Hz, H-6 & H-2), 10.12 brs (OH), **^{13}C NMR spectrum (100.5 MHz, DMSO-*d*$_6$)**, δC, ppm: 115.4, 118.4, 130.5, 132.7, 135.8, 161.7, 169.2, **IR (KBr) ν_{max}**, cm^{-1}: 1676, 1725, 3123 (Ar $_{C-H}$), In MS: Mass spectrum (HRMS-ESI), *m/z*: 313.03 [*M* + H]$^+$ (calcd for $C_{15}H_9N_2O_6$: 313.05).

Synthesis of compound 4.
The desired compound **4** was accomplished from the reaction between compound **3** and 3-methoxy-2-hydroxy benzaldehyde with TPP in ethanol solvent. Compound **3** was dissolved in ethanol then added 3-methoxy-2-hydroxy benzaldehyde and TPP and refluxed the reaction at 80 °C for 12 h. On accomplished of reaction mixture, removed the solvent using rotatory evaporator and extracted the crude compound **4** by chloroform and water solvent. Organic layer came in chloroform solvent and again evaporate the chloroform by rotatory evaporator and purified the crude product **4** by column chromatography using silica gel and eluent solvent $CHCl_3$ and CH_3OH in 86% yield as a solid.

^{1}H NMR spectrum (400 MHz, DMSO-*d*$_6$), δ, ppm: 3.78 s (2H), 3.85 s (6H, 2OMe), 6.89 t (2H, *J* = 8.0 Hz), 7.07 d (2H, *J* = 8.1 Hz), 7.18 d (2H, *J* = 8.1 Hz), 7.70 s (1H), 7.96 s (1H),

8.05 s (1H), 9.46 s (4H), 10.24 brs (OH), **^{13}C NMR** spectrum (**100.6 MHz**, **DMSO-*d*$_6$**), δC, ppm: 34.5, 56.3, 113.8, 119.8, 121.2, 121.8, 124.0, 128.0, 129.9, 132.3, 133.7, 147.0, 148.5, 166.4, 170.3, 173.8, **IR (KBr) ν_{max}**, cm^{-1}: 1708, 1723, 3127 (Ar_{C-H}), 3380 (OH), In MS: Mass spectrum (HRMS-ESI), *m/z*: 585.13 $[M + H]^+$ (calcd for $C_{31}H_{25}N_2O_{10}$: 585.15).

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