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Synthesis and Characterization of New Biologically Active Pyrrolo[2,3-*b*]Pyridine Scaffolds

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Abstract

The 4-amino-1-(2,4-dichlorophenyl)-3-(3,4-dimethoxyphenyl)-6-phenyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile, 8 and 4-amino-6-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-3-(3,4-dimethoxyphenyl)-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile, 9 were prepared and fully characterized by reaction of the new 2-amino-1-(2,4-dichlorophenyl)-4-(3,4-dimethoxyphenyl)-1H-pyrrole-3-carbonitrile 4 with 2-arylidenemalononitriles 6 and 7 in ethanol and the presence of piperidine (1 mL) to afford 8 and 9 in excellent yield 87% and 91%, respectively.

Keywords: Heterocyclic; Synthesis; Pyrroles; Pyrrolopyridine; Benzylidinemalononitrile

Introduction

Heterocyclic system with pyrrolopyridine nucleus is an important class of organic chemistry that covers several pharmacologically active compounds which can be synthesized in the laboratory as well as obtained from the natural sources [1]. The pyrrolopryridines are present in the molecular structure of various biologically active compounds such as vemurafenib, pexidartinib, Plexxikon, Genentech famitinib, peficitinib, Antalarmin, etc. [2]. They are displaying interesting chemical reactions and important biological actions such as antibacterial [3], antimycobacterial [4], anti-inflammatory [5], antifungal [6], antiparkinson's [7], antitumor [8], antiproliferative [9], antiviral [10], muscarinic antagonist [11], antimicrobial [12], anticancer [13-15]. In light of the above all, it was the target to design and synthesize the expected biologically active structures of pyrrolo[2,3-b]pyridines 8 and 9 by combine the new 2-amino-1-(2,4-dichlorophenyl)-4-(3,4-dimethoxyphenyl)-1H-pyrrole-3-carbonitrile 4 and 2 arylidenemalononitriles 6 and 7.

An essential component of the search for new leads in drug designing program is the synthesis of molecules, which are novel still resembling known biologically active molecules by virtue of the presence of some critical structural features. Moreover, the nature and position of the substituents are important factors toward significantly affect the biological actions [16,17]. Phenolic and poly-phenolic as well as the EDGs such as OCH3 is the key factors to expose the activity of the molecule [18-20].

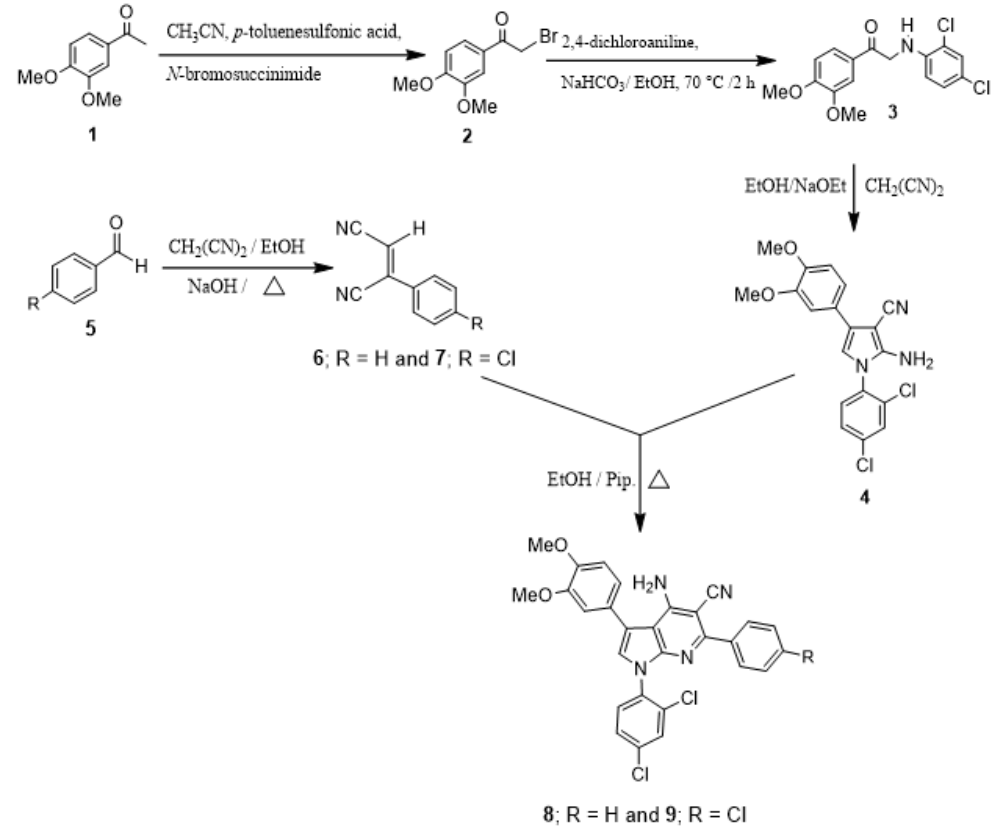
Hence, I synthesized the title compounds with a range of alkoxy substituents such as OCH3 groups at 3,4- positions of the phenyl group on the side of the pyrrole ring; besides, an electron-withdrawing Cl groups were also introduced on the phenyl group which bonded with the pyrrole nitrogen atom at positions 2,4- to improve the activity. Keeping in view the applications of the fused heterocycles like pyrrolopyridine derivatives and in continuation of the previous work [21-25]. I herein report the synthesis and characterization of new 4-amino-1-(2,4-dichlorophenyl)-3-(3,4-dimethoxyphenyl)-6-phenyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile 8 and 4-amino-6-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-3-(3,4-dimethoxyphenyl)-1H-pyrrolo[2,3-b] pyridine-5-carbonitrile 9.

Experimental

As illustrated in Scheme 1, the phenacyl bromide 2 was prepared by reaction of 3,4-dimethoxy acetophenone with N-brmosuccinimide in acetonitrile and the presence of p-toluenesufonic acid as a catalyst as reported in literature [26]. The compound 2 reacted with 2,4-dichloroaniline in ethanol and NaHCO3 at 70 °C to give the new α-aminoketone 3. The 2-aminopyrrolo-3-carbonitrile 4 was synthesized by reaction of 3 with malononitrile in NaOEt/EtOH. The 2-arylidenemalononitriles 6 and 7 were prepared by condensation of benzaldehyde or p-cholorobenzaldehyde with malononitrile in the presence of NaOH/EtOH.

The target compounds 8 and 9 were prepared by cyclocondensation of the 2-aminopyrrolo-3-carbonitrile 4 with the 2-arylidenemalononitriles 6 and 7, respectively, in the presence of drops of piperidine and refluxing ethanol followed by treating

the products with crushed ice/dilute HCl. The compounds 8 and 9 have been crystallized from ethanol in excellent yield 87% and 91%, respectively. The structures of all new compounds prepared in this paper have been confirmed by their spectral data (Scheme 1).



Scheme 1: 4-amino-1-(2,4-dichlorophenyl)-3-(3,4-dimethoxyphenyl)-6-phenyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile 7.

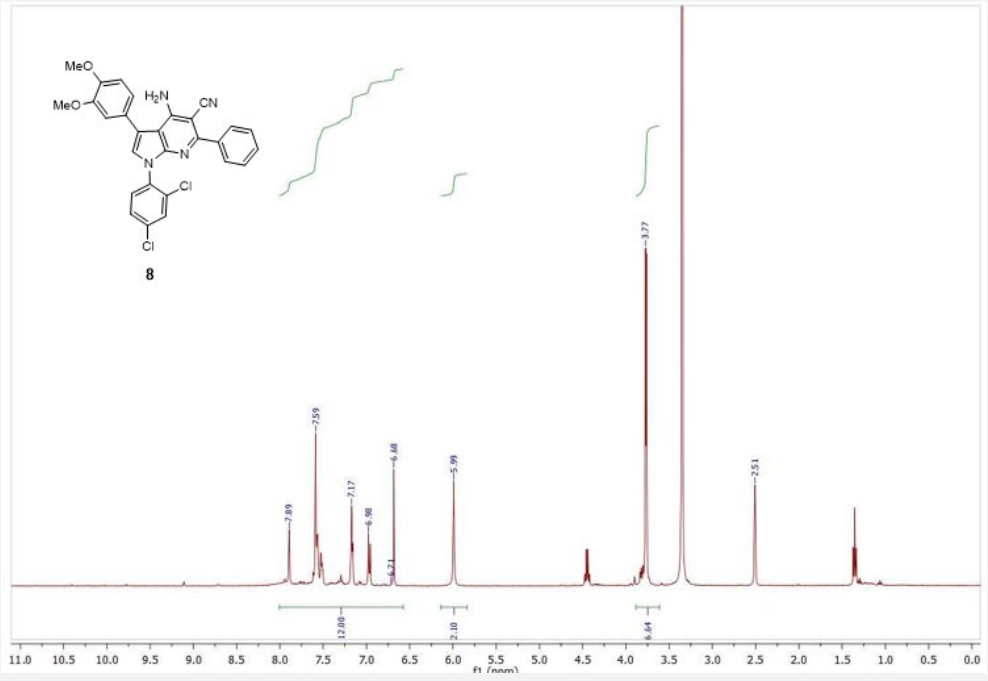


Figure 1: ^{1}H-NMR (DMSO-d_6) of compound 8.

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The IR spectra displayed the presence of NH2, CN, and C=N absorption bands in the 3322–3463, 2172 and 1569 cm-1 regions, respectively, as well as the presence of C=O bands in the 1705 cm-1 for compounds 8 and 9. The 1H-NMR spectrum in DMSO-d6 of compound 8 showed the NH2 protons appears at 5.99 ppm and the expected aromatic signals and the pyrrole CH appears in the rang 6.60 – 7.92 ppm, while the protons of methyl groups appears at 3.77 pm, as shown in figure 1.

Conclusion

Pyrrolopyridine and its derivatives have become important compounds due to their applications in medicinal and natural products chemistry. Pyrrolopyridine synthesis by reacting of 2-amino-pyrrole-3-carbonitrile with 2-arylidenemalononitriles as one of the key components became very demanding since it enables the generation of diverse range of libraries of pyrrolopyridine derivatives. As a part of this initiative, herein there is two of fused pyrrolo[2,3-b]pyridine derivatives have prepared as expected biologically active compounds. The synthesized compounds with alkoxy substituents such as OCH3 groups at 3,4- positions of the phenyl group on the side of the pyrrole ring, besides, an electron-withdrawing Cl groups were also introduced on the phenyl group which bonded with the pyrrole nitrogen atom at positions 2,4- to improve the activity.

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