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SYNTHESIS AND CHARACTERIZATION OF NEW 1,2,3-TRIAZOLES FROM SUBSTITUTED SALICYLDEHYDES

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Abstract:

In search of potent antimicrobial agents new 1,2,3-triazoles have been synthesized from 4-(diethylamino)-2-hydroxybenzaldehyde. The newly synthesized 1,2,3-triazoles synthesized starting from 4-(diethylamino)-2-hydroxybenzaldehyde. 4-(Diethylamino)-2-hydroxybenzaldehyde (**1**) was reacted with propargyl bromide (**2**) in N,N-dimethylformamide in the presence of potassium carbonate as a base to obtain a key intermediate, 4-(diethylamino)-2-(prop-2-yn-1-yloxy)benzaldehyde (**3**). This alkyne (**3**) was then condensed with freshly prepared phenyl azides (**4a-j**) in presence of $CuSO_4$ and sodium ascorbate by following click chemistry approach to obtain better to excellent yields of the titled compounds (**5a-j**). All the newly synthesized compounds were thoroughly characterized by using ^{1}H NMR, ^{13}C NMR and HRMS analyses.

Keywords
1,2,3-Triazole, Substituted salicyldehydes, Click Chemistry, Spectral Analyses.

1. Introduction

In search of potent antimicrobial agents, nitrogen containing heterocycles mainly, 1,2,3-triazoles are gaining immense importance due to their broad spectrum applications in different areas such as bioconjugations, surface sciences, biochemical, polymers and pharmaceuticals [1]. Among the various 1,2,3-triazoles, 1,4-disubstituted-1,2,3-triazole derivatives accompanying with various biological activities such as antifungal [2], antibacterial [3] , antitubercular [4], antidiabetic [5], anticancer [6], anti-HIV [7] and antiviral [8]. Literature survey revealed that 1,2,3-Triazole derivatives have also been used as various enzyme inhibitors against histone deacetylase, alkaline phosphatase, cysteine protease and acetylcholinesterase [9]. 1,2,3-Triazole scaffold is an attractive prototype, as it is remarkably stable under oxidative/reductive conditions, enzymatic degradation and is capable to exhibit hydrogen bonding, dipole-dipole moments and π-stacking interactions [10]. These unique features of 1,2,3-triazole have increased its importance in the field of medicinal chemistry. [11].

1,2,3-Triazole is also reported as a core structural moiety in several important antifungal agents viz fluconazole, itraconazole, voriconazole and ketoconazole [12].These aforementioned broad and potent activities of triazole and its derivatives have established them as pharmacologically active scaffolds.

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Following are some of the molecules, possessing antitubercular activity (**Figure 1**).

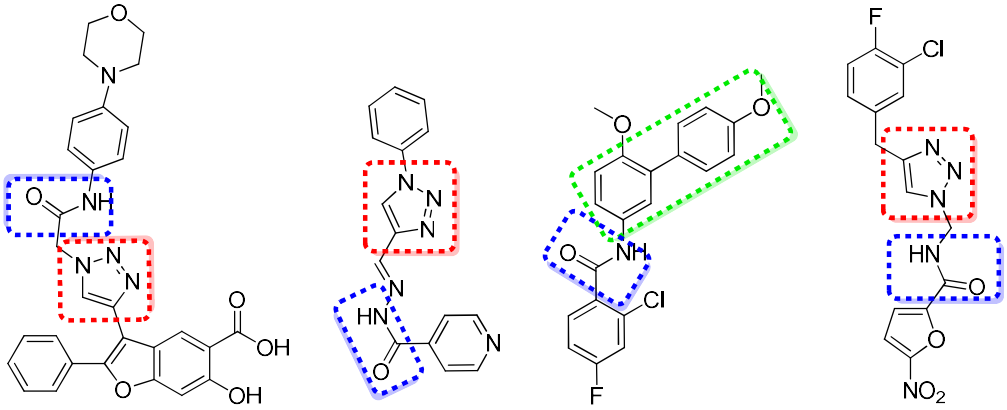

Figure 1. 1,2,3-Triazole containing bioactive molecules

2. Results And Discussion

Final products, new 4-(diethylamino)-2-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)benzaldehydes (**5a-j**) have been synthesized starting from 4-(diethylamino)-2-hydroxybenzaldehyde (**1**). 4-(Diethylamino)-2-hydroxybenzaldehyde (**1**) was allowed to react with propargyl bromide (**2**) in presence of K_2CO_3 in Dimethyl formamide (DMF) for 3h at room temperature to get a key intermediate, 4-(diethylamino)-2-(prop-2-yn-1-yloxy)benzaldehyde (**3**). Then 1,3-dipolar cycloaddition of intermediate, 4-(diethylamino)-2-(prop-2-yn-1-yloxy)benzaldehyde (**3**) was carried with phenyl azides **(4a-j)** in the presence of $CuSO_4$ and sodium ascorbate in PEG-400: H_2O for 4h and obtained the titled products, 4-(diethylamino)-2-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)benzaldehydes (**5a-j**), with excellent yields.

All the newly synthesized compounds were thoroughly characterized by their ^{1}H NMR, ^{13}C NMR and HRMS analyses. The IR spectrum of compound (**5a**) shows a characteristic absorption peak at 1588 cm^{-1} which correspond to the C=N bond. The ^{1}H NMR spectrum of one of the representative compound (**5a**) displays peaks at δ 5.41, 8.98 and 10.02 ppm, as three singlets due to the OCH_2, triazolyl-H and amido-NH, respectively and a multiplet in the region δ 6.39- 7.92 ppm due to the signals of eight aromatic protons. The presence of two characteristics carbon signals are observed at δ 62.07 and 186.12 ppm in ^{13}C NMR spectrum of compound (**5a**), owing to the signals of OCH_2 and aldehydic carbon group, respectively. The HRMS spectrum further strengthen the structure assigned to (**5a**) as 4-(diethylamino)-2-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde, showing $[M+H]^+$ ion peak at m/z 351.1779 for its molecular formula $C_{20}H_{22}N_4O_2$, confirming the formation of a 1,2,3-triazole ring. The synthetic sequences are depicted in **Scheme 1**.

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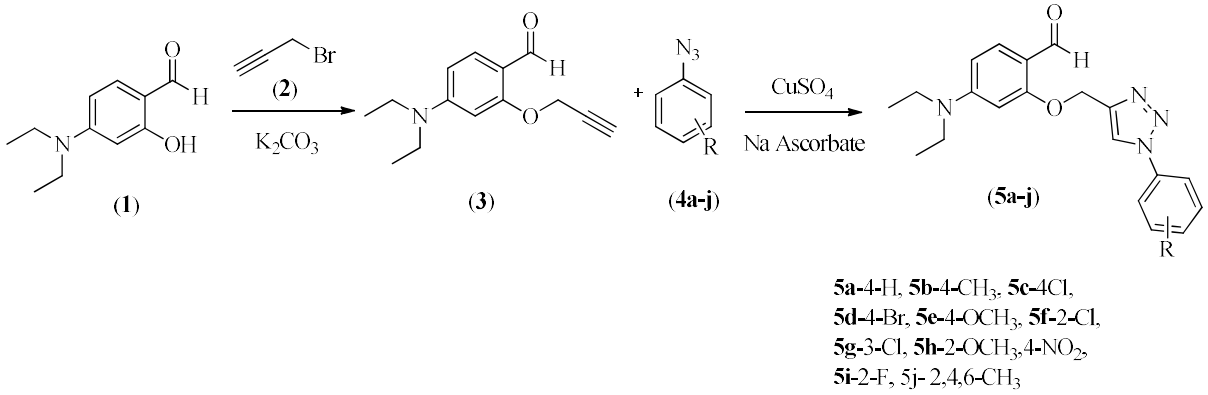

Scheme 1. Synthesis of 4-(diethylamino)-2-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)benzaldehydes (**5a-j**)

3. Experimental Section

3.1. General

All reagents and solvents were obtained from commercial suppliers and used without further purification. All the various azides were synthesized from the reported procedures. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (GF 254) using UV light to visualize the course of the reactions. ^{1}H NMR spectra and ^{13}C NMR spectra were respectively recorded at 300 MHz and 100 MHz spectrometer using $CDCl_3$ and DMSO-d_6 as solvent at room temperature. Chemical shifts (δ) are reported in ppm with TMS as internal standard. Abbreviations for signal couplings are: s, singlet; d, doublet; t, triplet; m, multiplet. Routine monitoring of reaction was performed by TLC using 0.25 mm E. Merck precoated silica gel TLC plates (60 F254).

Synthesis of 4-(Diethylamino)-2-(prop-2-yn-1-yloxy)benzaldehyde (3)

A mixture of 4-(Diethylamino)-2-hydroxybenzaldehyde (**1**) and propargyl bromide (**2**) was dissolved in DMF and to this solution K_2CO_3 was added. The reaction mass was stirred at room temperature for 3h. The progress of the reaction was monitored by thin layer chromatography. After 3h, the reaction mass was poured on ice cold water. The solid obtained was filtered, washed with water and crystallized from ethanol.

Yield: 84 %.

4-(Diethylamino)-2-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (5a)

4-(Diethylamino)-2-(prop-2-yn-1-yloxy)benzaldehyde (**3**) and freshly prepared substituted phenyl azides (**4a-j**) were stirred in presence of copper sulphate (20 mol%) and sodium ascorbate (20 mol%) in PEG-400. The progress of the reaction was monitored by thin layer chromatography using ethyl acetate: hexane (2:8) as solvents. The reaction mass was poured on crushed ice. The synthesized product was filtered, washed with water and crystalized using ethanol:DMF.

Yield: 91 %, M.P.: 148-150 ºC; Brown Solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm = 1.11-1.14 (t, 3H, 6H), 3.44- 3.47 (q, 2H, 4H), 5.41 (s, 2H, OCH_2), 6.39-7.92 (m, 8H, Ar-H), 8.98 (s, 1H, triazolyl-H), 10.02 (s, 1H, aldehydic-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 12.85, 44.63, 62.07, 94.66, 105.21, 113.75, 120.64, 123.25, 129.43, 130.10, 130.43, 136.89, 144.57, 154.12, 162.97, 186.12; HRMS $(ESI)^+$ calcd. for $C_{20}H_{22}N_4O_2$ $[M+H]^+$: 351.1776; found 351.1779.

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4. Conclusion

A series of new 1,2,3-triazoles were synthesized from 4-(diethylamino)-2-hydroxybenzaldehyde. The 1,3-dipolar cycloaddition reaction of alkyne **3** and substituted phenyl azides (**4a-j**) in presence of $CuSO_4$ and sodium ascorbate by following click chemistry approach to obtain better to excellent yields of the titled compounds, 4-(diethylamino)-2-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)benzaldehydes (**5a-j**). The newly synthesized compounds have been thoroughly characterized by using ^{1}H NMR, ^{13}C NMR and HRMS analyses.

Conflict of Interest

The authors declare no conflict of interest.

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