Synthesis of 2-amino-4-(2-ethoxybenzo[d][1,3]dioxol-5-yl)-4*H*-pyran-3-Carbonitrile Derivatives and Their Biological Evaluation

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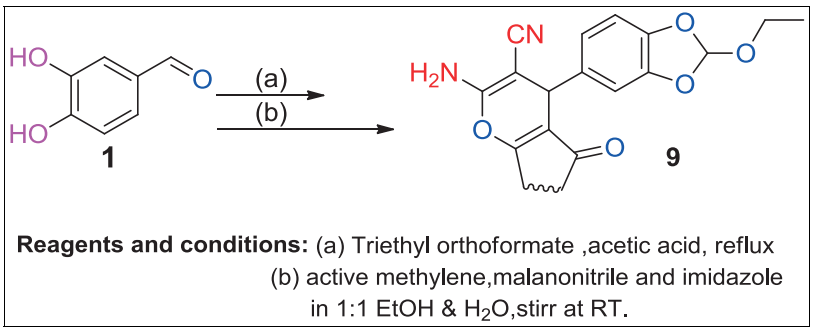

A new class of substituted *2-amino-4-(2-ethoxybenzo[d][1,3]dioxol-5-yl)-4H-pyran-3-carbonitrile* derivatives catalyzed by Imidazole under mild reaction conditions has been developed. A variety of functionalized 2-amino-4-(2-ethoxybenzo[d][1,3]dioxol-5-yl)-4H-pyran-3-carbonitrile scaffolds were assembled in high yields by this catalytic protocol. The newly synthesized compounds have been characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The compounds were then evaluated for antimicrobial activities.

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INTRODUCTION

Over the past decade, antimicrobial resistance has become one of the most serious public health concern across the world. Antimicrobial resistance refers to microorganism that has developed the ability to inactivate, exclude, or block the inhibitory or lethal mechanism of the antimicrobial agents [1]. Structure–activity concept has emerged as a fruitful approach for the new drug discovery and is a rapidly emerging theme in medicinal chemistry. The 2-amino-4*H*-pyran are the model structures, with their inherent affinity for diverse biological receptors, represent an ideal source of core scaffolds and capping fragments for the design and synthesis of targeted molecules on a reasonable time scale [2]. Among them, 2-amino-4*H*-pyran-3-carbonitrile comprise a class of therapeutic compounds that exert a wide range of biological activities such as antitumor, antibacterial, antiviral, spasmolytic, and antianaphylactic [3–6]. Literature survey indicated that many 2-amino-4*H*-pyran derivatives displayed potent for the treatment of Alzheimer, Schizophrenia, Myoclonus diseases [7].

Green chemistry plays an important role in synthetic organic chemistry in recent decades has been multicomponent reactions (MCRs) [8,9]. The MCRs allow combination of more than two reactants in one-pot operations and allow direct access to complex molecules and chemical libraries [10,11]. Herein, we are reporting an Imidazole catalyzed one-pot three-component coupling reaction under nonhazardous solvent, that is, mixture of EtOH and H_2O (1:1) at room temperature and synthesized compounds were evaluated for antimicrobial analysis.

RESULTS AND DISCUSSION

The 2-ethoxybenzo[d][1,3]dioxole-5-carbaldehyde **2** was prepared by the reaction of 3,4-dihydroxybenzaldehyde **1** with triethly orthoformate in presence of acetic acid (Scheme 1)[12]. We first optimized the conditions for the reaction of 2-ethoxybenzo[d][1,3]dioxole-5-carbaldehyde **2** (0.01 mol), malononitrile (0.01 mol), and different active methylene groups (0.01 mol) to produce derivatives of 2-amino-4*H*-pyran-3-carbonitrile (Table 1; **3a–f**). The best results are obtained when both water and ethanol are present in 1:1 equivalent in the presence of imidazole (0.003 mmol) on stirring at room temperature. In the absence of ethanol, a dramatic rate decrease is observed during a reaction and because of the high polarity of the medium, products precipitate in the reaction mixtures. This makes isolation of the products easy by simple filtration and avoids cumbersome chromatographic separations. Further, representative samples were screened for their antibacterial and antifungal activity using disc diffusion method, which shows promising antifungal and antibacterial agents against all the tested fungi and

Scheme 1

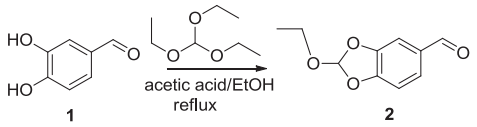
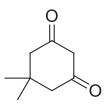
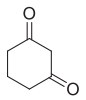
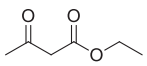
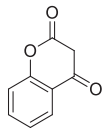
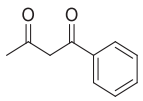


Table 1

2-Amino-4-(2-ethoxybenzo[d][1,3]dioxol-5-yl)-4H–pyran-3-carbonitrile derivatives.

Compd	Substrate	Melting point(°C)	Yield (%)
3a		203–205	92
3b		188–190	94
3c		120–122	89
3d		128–130	90
3e		200–202	88
3f		206–208	86

bacteria as compared with standard miconazole and tetracycline, respectively [13,14].

The structure of compound **2** was established on the basis of analytical and spectral data. Thus, the **^{1}H NMR($CDCl_3$)** spectrum showed δ = 1.25 (t, *J* = 7 Hz, 3H, CH_3), 3.72(q, *J* = 10.5 Hz, 2H, CH_2), 6.82(s, 1H, ─CH), 6.70–6.77 (m, 3H, C_6H_3), 9.61 (s, 1H, ─CHO). The MCR of compound **2** with different active methylene groups and malononitrile gives 2-amino-4H-pyran-3-carbonitrile derivatives **3a–f**, respectively (Scheme 2).

EXPERIMENTAL

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Bruker 500 MHz, 700 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

Synthesis of 2-ethoxybenzo[d][1,3]dioxole-5-carbaldehyde (2). A mixture of 3,4-dihydroxybenzaldehyde **1** (0.1 mol), triethly orthoformate (0.1 mol), and 0.4 g of acetic acid was brought to reflux for 30 min. The progress of the reaction was monitored on TLC. Upon completion, the ethyl alcohol formed in the reaction mixture was removed by distillation. The organic residue was then poured into a 150 mL of 5% NaOH aqueous solution. The organic layer was separated, combined with an extract of the aqueous phase, dried over sodium sulfate, and distilled under vacuum to yield (**2**).

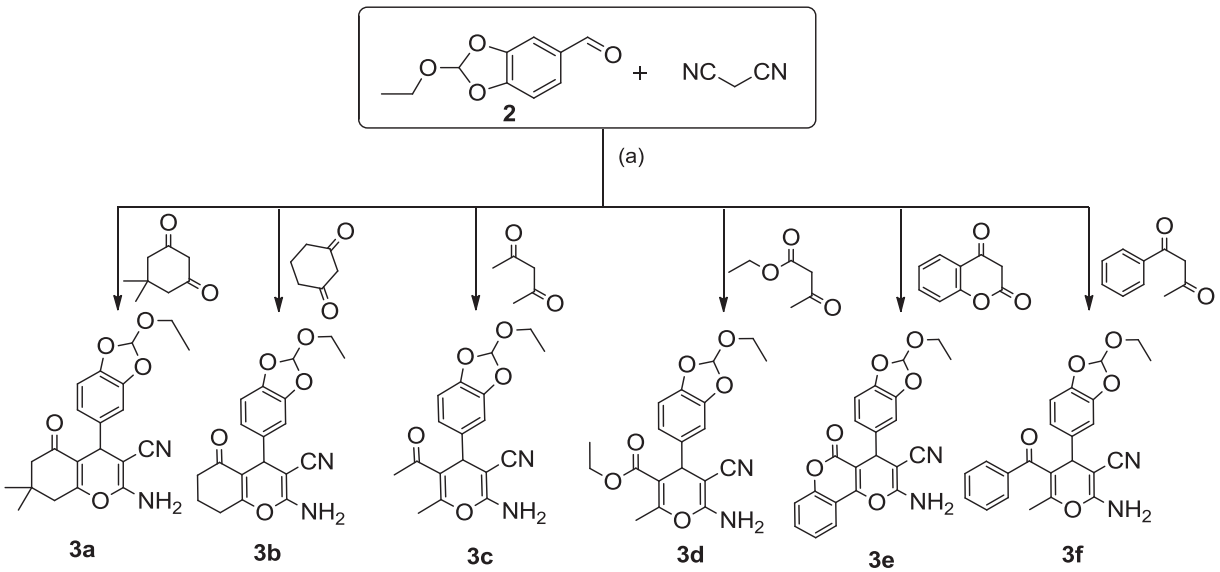
$$\mathbf{b.p.} = 155\text{-}57^{\circ}\mathrm{C}, \mathbf{yield} = 68\%$$

General procedure for the synthesis of 2-amino-4*H*-pyran-3-carbonitrile (3). A mixture of 2-ethoxybenzo[d][1,3] dioxole-5-carbaldehyde **2** (0.01 mol), malononitrile (0.01 mol), different active methylene groups (0.01 mol), and imidazole (0.003 mol) was stirred in 1:1 ethanol and water at room temperature for 4–6 h in each case. The progress of the reaction was monitored by TLC. Upon completion of the reaction, mixture was filtered and recrystallized in ethanol.

Selected spectral data. ***2-Amino-4-(2-methoxybenzo[d][1,3]dioxol-5-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (3a).*** **Yield**: 92%; **m.p**. = 203–205°C: **IR (cm-1):** 3205(NH_2), 1671(CN), 1610(C═O).**^{1}H NMR ($CDCl_3$, δ/ ppm)**: 1.04 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.25 (t, *J* = 7 Hz, 3H, CH_3), 2.25 (q, *J* = 16.8 Hz, 2H, CH_2), 2.47 (q, *J* = 17.5 Hz, 2H, CH_2), 3.72 (q, *J* = 10.5 Hz, 2H, CH_2), 4.34 (s, 1H, pyran H-4), 6.70–6.77 (m, 3H, ArH), 6.82 (s, 1H, CH), 7.26 (s, 2H, NH_2). **^{13}C NMR ($CDCl_3$, δ/ ppm)**: 14.82, 27.84, 28.73, 32.21, 35.27, 40.69, 50.71, 59.34, 107.70, 107.95, 114.12, 118.54, 120.96, 121.05, 137.27, 145.12, 146.28, 157.39, 161.30, 195.85**. LCMS; m/z**: 382.41; ***Anal.*** **Calcd for** $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60% **Found:** C, 64.05; H, 5.23; N, 6.97%.

5-Acetyl-2-amino-4-(2-ethoxybenzo[d][1,3]dioxol-5-yl)-6-methyl-4H-pyran-3-carbonitrile (3c). **Yield:** 89%; **m. p.** = 120–122°C: **IR (cm-1)**: 3192(NH_2), 1671(CN), 1633(C═O) **^{1}H NMR ($CDCl_3$, δ/ ppm)**: 1.27 (t, *J* = 7 Hz, 3H, CH_3), 2.08 (s, 3H, ─CH_3), 2.28 (s, 3H, ─$COCH_3$), 3.73 (q, *J* = 7 Hz, 2H, CH_2), 4.37 (s, 1H, pyran H-4), 6.79 (m, 3H, ArH), 6.84 (s, 1H, CH), 7.26 (s, 2H, NH_2). **^{13}C NMR ($CDCl_3$, δ/ ppm)**: 14.71, 18.54,

Scheme 2



Reagents and conditions: (a) 0.003mol imidazole1:1 EtOH & H_2O,stirr at RT.

29.58, 39.19, 59.50, 59.57, 107.31, 107.36, 108.17, 108.211, 119.16, 120.61, 120.65, 136.93, 146.62, 154.75, 157.06, 198.59. **LCMS; m/z**: 342.35; ***Anal.* Calcd for** $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18%. **Found:** C, 62.95; H, 5.43; N, 8.04%.

2-Amino-4-(2-ethoxybenzo[d][1,3]dioxol-5-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (3e). **Yield**: 88%; **m.p**. = 200–202°C: **IR (cm-1):** 3315(NH_2), 1695 (CN), 1669(C═O). **^{1}H NMR (DMSO-d6, δ/ ppm)**: 1.25 (t, J = 7 Hz, 3H, CH_3), 3.72(q, J = 10.5 Hz, 2H, CH_2), 4.25(s, 1H, pyran H-4), 6.50–6.65 (m, 3H, ArH), 7.31(s, 1H, CH), 7.46–7.90 (m, 4H, ArH), 8.86 (s, 2H, NH_2), **^{13}C NMR (DMSO-d6, δ/ ppm)**: 36.61, 58.89, 105.04, 113.38, 115.16, 115.84, 116.95, 117.62, 118.79, 119.73, 122.72, 125.06, 133.19, 134.65, 144.88, 145.49, 152.41, 153.24, 158.27, 159.89. **LCMS; m/z:** 404.37; ***Anal.* Calcd for** $C_{22}H_{16}N_2O_6$: C, 65.34; H, 3.99; N, 6.93% **Found:** C, 65.22; H, 3.82, N, 6.65%.

Antimicrobial activities. The antibacterial and antifungal activity data of the 2-amino-4*H*-pyran **(**Table 1; **3a–f)** are represented in Table 2, respectively. A large number of compounds were found to be the promising antibacterial and antifungal agents against all the tested bacteria and fungi as compared with standard miconazole

Table 2

Antimicrobial activity of the synthesized compounds.

		Zone of inhibition in mm[a]						
		Antibacterial activity				Antifungal activity		
Compd	Conc (μg/mL) in DMSO	*E. coli*	*P. aeruginosa*	*S. aureus*	*C. diphtheria*	*A. niger*	*Penicillium Sp*	*Candida albicans*
3a	100	**21**	**19**	**20**	**18**	**21**	**12**	**10**
3b	100	**20**	**18**	**22**	**22**	16	10	08
3c	100	15	14	18	19	**19**	06	**12**
3d	100	18	19	15	21	18	09	10
3e	100	**22**	**18**	**21**	**20**	**22**	**13**	**11**
3f	100	18	16	14	16	19	11	09
Tetracycline (10 μg/ml)	10	22	25	24	24	-	-	-
Miconazole (10 μg/ml)	10	-	-	-	-	24	14	14
Control (DMSO)	-	-	-	-	-	-	-	-

Maximum inhibition are shown in bold text. -, no inhibition.
[a]Diameter of disc size –6 mm.

and tetracycline, respectively. Thus, as shown in Table 2, the compounds **3a**, **3b**, and **3e** were found to be potent antibacterial agent at the MIC of (100 μg/mL) against all tested bacteria. Compounds **3c**, **3d**, and **3f** from this series were found to be moderately active at the MIC of 100 μg/mL. The compounds **3a**, **3c**, and **3e** in Table 2 exhibited one to twofold more antifungal activity almost against all the tested fungi as compared with the standard miconazole at the same level of concentration (MIC of 10 μg/mL). Compounds **3b**, **3d** and **3f** also showing moderately active at the MIC of 100ppm; 100mg/L.

The sensitivity of microorganisms to the tested compounds is identified in the following manner:

- Highly Sensitive = Inhibition zone: 15–20 mm
- Moderately Sensitive = Inhibition zone: 10–15 mm
- Slightly Sensitive = Inhibition zone: 5–10 mm
- Not Sensitive = Inhibition zone: 0 mm.
- MIC selected was 100 μg/mL and DMSO was used as the solvent.
- Each result represents the average of triplicate readings

CONCLUSION

In summary, a series of novel heterocyclic compounds with the 2-amino-4*H*-pyran nucleus were synthesized via Imidazole catalyzed from the one-pot, three-component reaction, which is very convenient, rapid, and gives good yields. It was also found that the title compounds displayed good to moderate antimicrobial activity against wide range of microorganisms.

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