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Thiophene and benzodioxole appended thiazolyl-pyrazoline compounds: Microwave assisted synthesis, antimicrobial and molecular docking studies

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ABSTRACT

A novel series of thiophene and benzodioxole appended thiazolyl-pyrazoline derivatives have been designed, synthesized and evaluated against different bacteria and fungi. The antimicrobial activity of the synthesized compounds were screened using MIC method and were proved synthesized compounds **7o**, **7r** and **7t** to show good antimicrobial activity against bacteria and fungi. In silico molecular docking studies revealed that all the synthesized molecules showed good binding energy toward the target receptor DNA topoisomerase IV, ranging from −10.42 to −11.66 kcal/mol.

Thiazole moiety plays a vital role in diverse biological activities and is a key feature of some of the most interesting and important classes of compounds. Many thiazole scaffold containing compounds are pharmacologically active, functioning as potent *pan*-Src kinase inhibitor,[1] thymidylate synthase inhibitor,[2] ABCB1 inhibitor,[3] metastatic cancer cell migration and invasion inhibitor,[4] tubulin polymerization inhibitor,[5] and SIRT1 activator.[6] Some novel thiazolones[7] and thiazole derivatives especially BILS 179 BS[8] were reported to exhibit a high antiviral activity against hepatitis C virus (HCV) and HSV, respectively. Pyrazole derivatives play an important role on designing of new drugs, since they present an interesting pharmacological profile, especially, transforming growth factor β type 1 receptor (ALK5) inhibitors[9] and some novel pyrazoles were reported to exhibit a high antiviral activity against hepatitis A virus.[10] Interestingly, thiazolyl-pyrazoline derivatives were reported to exhibit variety of significant biological importance such as antimicrobial,[11] antiviral,[12] anti-inflammatory,[13] antiamoebic activity,[14] anticancer,[15] β-ketoacyl-acyl carrier protein synthase III (FabH) inhibitors,[16] selective EP_1 receptor antagonists for treatment of overactive bladder,[17] EGFR TK inhibitors,[18] super oxidase inhibitors and free radical scavengers.[19] In addition, thiophene ring containing compounds exhibit different biological activities such as SGLT2 inhibitors,[20] antitumor,[21] antimicrobial,[22] DHODH inhibitors,[23] BACE1 inhibitors,[24] antioxidant,[25] c-Jun-N-terminal kinase inhibitor,[26] 5-HT2A receptor antagonists,[27] anti-inflammatory[28] and vitronectin receptor antagonists.[29] In addition, 1,3-dioxolane ring containing compounds exhibit different biological activities such as antifungal, plant growth regulator,[30] and VLA-4 antagonists.[31]

Our goal in this work was to incorporate these four independently biologically active moieties into one molecule to generate compounds with better biological activities. Thiophene attached thiazolyl-pyrazoline compounds was identified as FabH inhibitors[16] and benzodioxole attached thiazolyl-pyrazoline was identified as potential anticancer agents.[15b] In continuation of our work on synthesis of some pharmacologically important heterocycles, a novel series of thiophene and benzodioxole attached thiazolyl-pyrazolines was designed, synthesized (Scheme 1) and evaluated against different bacteria and fungi.

Synthesis of novel thiazolyl-pyrazoline compounds is followed the general pathway outlined in the given Scheme 2.[32] Firstly, the chalcone derivatives were obtained by direct condensation by the 2-acetyl thiophene **1** and corresponding benzodioxole aldehyde **2a**–**b** using sodium hydroxide in ethanol. Secondly, cyclization of different chalcone derivatives with thiosemicarbazide **4** under basic condition (KOH) using ethanol as solvent leads to the formation of pyrazole derivatives **5a**–**b** containing thiourea

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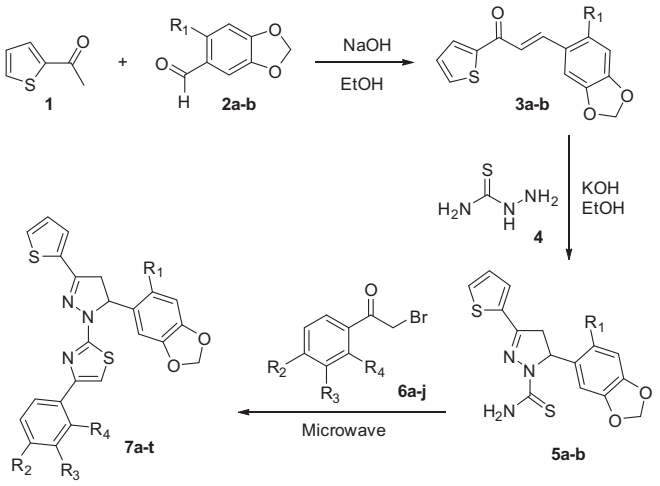


Scheme 1. Synthetic scheme of novel thiazolyl-pyrazoline derivatives.

Table 1
Syntheis of novel thiazolyl-pyrazoline (**7a**–**t**) derivatives

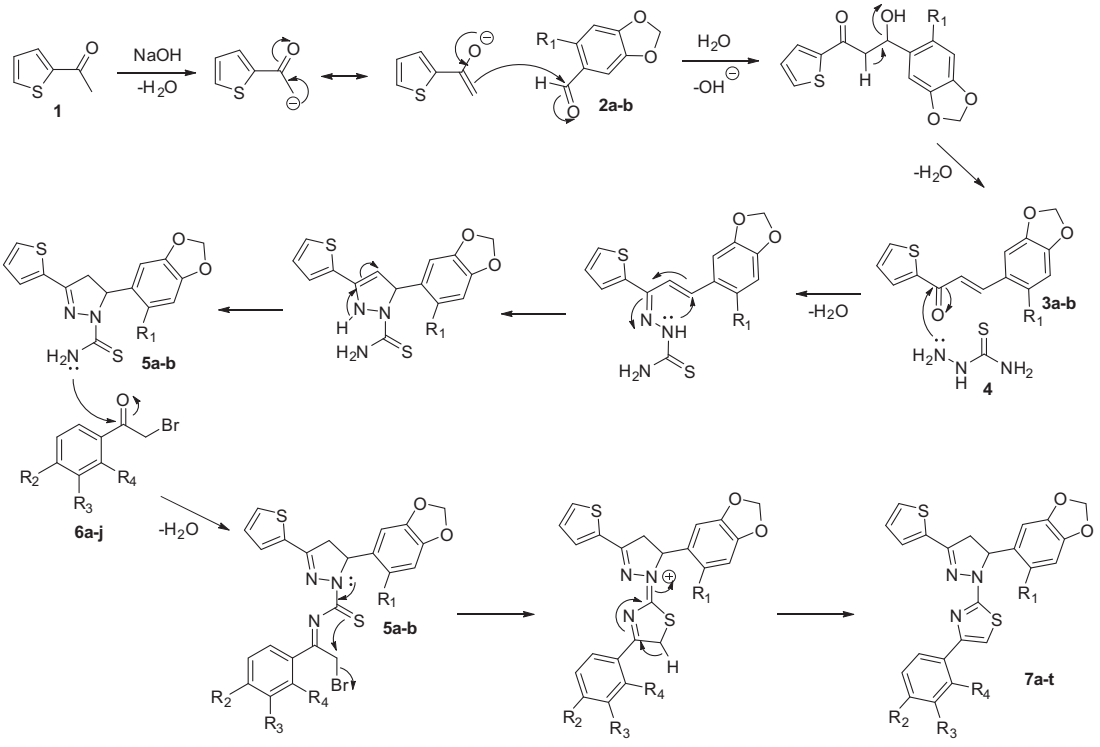
S. No	Compounds	R_1	R_2	R_3	R_4	Yield[a]
1	**7a**	H	H	H	H	90
2	**7b**	H	CH_3	H	H	92
3	**7c**	H	NO_2	H	H	85
4	**7d**	H	CN	H	H	87
5	**7e**	H	H	CN	H	84
6	**7f**	H	F	H	H	86
7	**7g**	H	H	H	F	88
8	**7h**	H	Cl	H	H	89
9	**7i**	H	Cl	F	H	82
10	**7j**	H	Cl	H	F	84
11	**7k**	Br	H	H	H	88
12	**7l**	Br	CH_3	H	H	90
13	**7m**	Br	NO_2	H	H	81
14	**7n**	Br	CN	H	H	85
15	**7o**	Br	H	CN	H	88
16	**7p**	Br	F	H	H	84
17	**7q**	Br	H	H	F	83
18	**7r**	Br	Cl	H	H	87
19	**7s**	Br	Cl	F	H	81
20	**7t**	Br	Cl	H	F	84

[a] Isolated yield in final step

skeleton. Finally, thiazolyl-pyrazoline derivatives **7a**–**t** were obtained by microwave irradiation of compound **5a**–**b** with substituted 2-bromoacetophenone **6a**–**j** (Table 1).

The structure of novel thiazolyl-pyrazoline derivatives was elucidated with the help of ^{1}H NMR, ^{13}C NMR and Mass data as illustrated for **7a**. In the ^{1}H NMR spectrum of compound **7a**, a dd peak at δ: 5.60 ppm with the *J* value 11.8 and 6.5 Hz for a proton corresponds to C-H proton of pyrazoline ring. The two dd peaks at δ: 3.29 and 3.87 with *J* value 17.3: 6.5 Hz and 17.3:11.9 Hz corresponds to two $-CH_2$ protons of pyrazoline ring respectively. And also two doublets at 5.92 and 5.93 ppm with the *J* value 1.4 Hz corresponds to $-CH_2$ protons of benzodioxole ring. The peaks in the range of δ: 6.77–7.71 ppm show the 12 aromatic protons. The ^{13}C and DEPT135 NMR of compound **7a** revealed that, the peak at δ: 64.5 ppm corresponds to the C–H carbon of pyrazoline ring. The peaks at δ: 44.2 and 101.1 ppm confirmed the presence of two $-CH_2$ carbons in pyrazoline and benzodioxole ring respectively. A distinguishing peak observed at *m*/*z*: 432 in the ESI mass spectrum corresponds to $[M+H]^+$ ion of the product **7a**.

In the course of identifying various novel antimicrobial agents, we are particularly interested in the present work with novel thiazolyl-pyrazoline derivatives. In the present study, the antimicrobial activities of 20 newly synthesized compounds were screened against eight bacteria and two fungi using MIC method (Table 2).[33,34] The results revealed that most of the synthesized compounds exhibited antimicrobial activities against bacteria; *Salmonella typhimurium*, *Klebsiella pneumoniae*, *Proteus vulgaris*,



Scheme 2. Mechanism for the formation of novel thiazolyl-pyrazoline derivatives.