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Ultrasound-assisted, one-pot, three-component synthesis and antibacterial activities of novel indole derivatives containing 1,3,4-oxadiazole and 1,2,4-triazole moieties

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ABSTRACT

Thirteen novel indole derivatives were efficiently synthesized through ultrasound irradiation by using 4-amino-5-(1*H*-indol-3-yl)-4*H*-[1,2,4]triazole-3-thiol (**8**) and 2-mercapto-5-substituted-1,3,4-oxadiazoles (**5a**–**m**). Compared with conventional and microwave methods, yields increased to 82–93%, and reaction times decreased to 15–35 min. The structures of these novel compounds were characterized by spectral data and elemental analysis. Two out of the synthesized compounds (**10f** and **10l**) exhibited excellent activity against *Staphylococcus aureus* and *Escherichia coli*, and thus warrant further research.

1. Introduction

Heterocyclic compounds are well-known pharmaceutically active products, and the development of simple and efficient methods of synthesis of compounds incorporating heterocyclic rings has given a new dimension to drug discovery [1]. 1,2,4-triazole and 1,3,4-oxadiazole are important five-membered heterocyclic compounds, which are of great research interest because of their distinct structures with potential applications in synthetic and medicinal chemistry. Heterocyclic compounds containing 1,2,4-triazole and 1,3,4-oxadiazole nuclei have been tested for a wide spectrum of biological activities, including antimicrobial, antitubercular, antiviral, analgesic, anticancer [2–7], and other biological properties, such as genotoxicity and lipid peroxidation [8,9].

Indoles exhibit relatively low toxicity, high biocompatibility, and several pharmacological activities [10,11]. Several 3-substituted indole derivatives have been used as materials for agrochemicals and pharmaceuticals [12–14]. Furthermore, compounds containing 1,3,4-oxadiazole or 1,2,4-triazole rings have been found in many natural products, and have thus become the focus of intense research in recent years on account of their pharmacological activities [15]. Indole unit modification has been widely reported, with a few studies about indole derivatives containing both 1,3,4-oxadiazole and 1,2,4-triazole moieties. According to the pharmacodynamic principle of superposition, 3-substituted indole derivatives containing both 1,3,4-oxadiazole and 1,2,4-triazole groups potentially exhibit effective antibacterial activity.

Green chemistry has been a major inspiration for organic chemists to develop environment-friendly methods for the synthesis of organic compounds with biological value. In recent years, ultrasound irradiation has been utilized to accelerate a number of synthetically useful reactions [16]. Ultrasonic synthesis is a well-established

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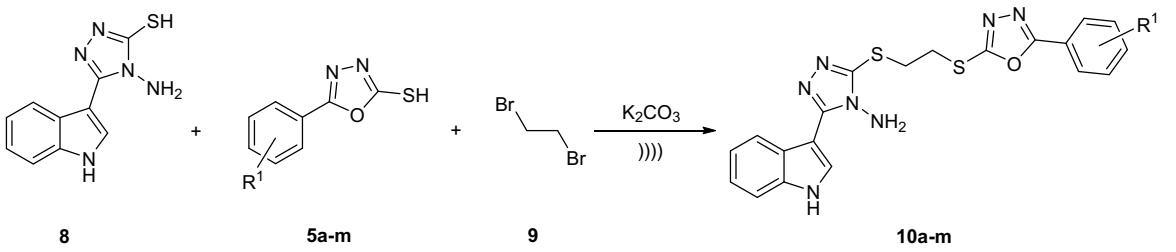

8 **5a-m** **9** **10a-m**

R^1 = **10a** H **10b** 2-CH_3 **10c** 3-CH_3 **10d** 4-CH_3 **10e** 2-OCH_3
10f 4-OCH_3 **10f** 2-OCH_2CH_3 **10h** 4-F **10i** 4-Cl **10j** 4-Br
10k 2,4-CH_3 **10l** 4-NH_2 **10m** NA

Scheme 1. Synthesis protocol of title compounds **10a**–**m**.

technique in green chemistry that has many advantages compared with the conventional methods, such as enhancement of reactions rates and yield as well as modification of the reaction pathway, greater selectivity, simplicity of operation, and energy-saving protocols. This approach led to the development of a simple purification procedure that also fulfils the concept of green chemistry [17,18].

Our research group has previously reported microwave-assisted synthesis of novel Schiff bases derived from 4-amino-3-[3-(1-benzyl)indole]-5-thiomethyl-1,2,4-triazole [19]. A number of these compounds showed strong antibacterial activity. As a further development of our green agenda [20,21], we report an efficient, high yield, and environment-friendly ultrasound synthesis of novel indole derivatives containing 1,3,4-oxadiazole and 1,2,4-triazole moieties (Scheme 1), as well as an evaluation of the antibacterial activities of these compounds against four pathogenic strains, namely, *Escherichia coli* (ATCC 35218), *Bacillus subtilis* (ATCC 6633), *Pseudomonas aeruginosa* (ATCC 27853), and *Staphyloccocus aureus* (ATCC 6538).

2. Results and discussion

We compared the synthesis of **10a**–**m** using ultrasound irradiation, microwave method, and conventional method to study the advantages of the ultrasonic-enhanced reaction. Compared with conventional thermal heating, ultrasonic irradiation decreased the reaction time from 540–900 min to 15–35 min and increased the yields from 40–68% to 82–93% (Table 1). Compared with the microwave method, ultrasonic irradiation increased the yields from 62–86% to 82–93%, and both methods required almost the same reaction time. Thus, ultrasonic irradiation allows a rapid, environment-friendly, and efficient organic synthesis methodology.

Assignment of the selected characteristic infrared (IR) bands of the positions of indole derivatives (**10a**–**m**) revealed valuable information about the structure of the compounds. All the compounds exhibited a characteristic strong absorption in the 3208–3452 cm^{-1} region from the ν(N–H) stretching vibration. The IR spectra showed absorption bands characteristic of C=N stretching in the 1603–1625 cm^{-1} region. Intense absorption bands in the

Table 1
Comparison of synthesis of **10a**–**m** using ultrasound irradiation, microwave method, and conventional method.

Compd.	R^1	Conventional method		Ultrasound method		Microwave method	
		t (min)	Yield (%)	*t* (min)	Yield (%)	*t* (min)	Yield (%)
10a	H	600	56	20	83	15	72
10b	2-CH_3	780	47	25	82	18	69
10c	3-CH_3	720	53	30	87	20	72
10d	4-CH_3	660	62	15	92	12	80
10e	2-OCH_3	720	54	20	86	15	77
10f	4-OCH_3	540	68	15	93	10	86
10g	2-OCH_2CH_3	600	57	20	86	16	75
10h	4-F	840	39	30	82	20	68
10i	4-Cl	840	47	30	88	20	74
10j	4-Br	840	42	30	86	20	62
10k	3,5-CH_3	720	51	20	85	15	79
10l	4-NH_2	900	40	35	86	22	72
10m	NA[a]	780	42	30	82	20	68

[a] Naphthalene.