SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 14, pp. 2655–2658, 2004

New Route to Synthesis and QSAR Study of 1,2,4-Aryl Substituted Triazoles

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ABSTRACT

Several substituted 1,2,4-triazoles have been synthesized by a new route and characterized by IR, NMR, mass spectral, and x-ray diffraction studies. The computer programme PASS for the prediction of biological activities established that these compounds are potential candidates for the screening.

INTRODUCTION

Triazole derivatives are known for their antibacterial, fungicidal, pesticidal, hypnotic, analgesic, amoeboidic, anthelmintic, insulin promoter, acute neurological disorder treating, nucleotide metabolism regulating, and antiasthmatic activities. The 1,2,4-substituted triazole derivatives are

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DOI: 10.1080/SCC-200025630 0039-7911 (Print); 1532-2432 (Online)

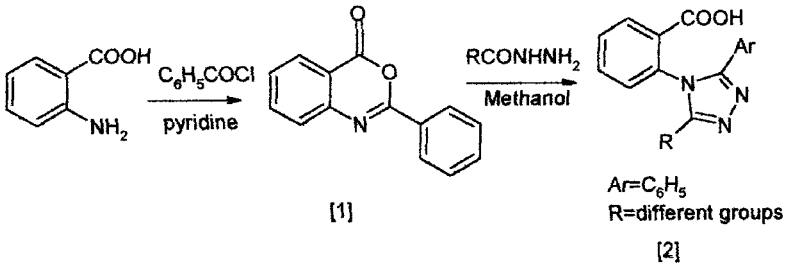
anti-convulsant, hypnotic, analgesic, amoeboidic, and anthelmintic.[1–8] We report a new route to the synthesis of 1,2,4-triaryl triazoles using accessible starting materials.

METHODOLOGY

The basic strategy in the present investigation involved the preparation of 1,3-benzoxazine (**1**), followed by reaction with hydrazides. Large number of triazole derivatives (**2**) were prepared and their structure was confirmed by IR, PMR, mass spectral, x-ray, and elemental analyses. These compounds when tested for their microbial activity showed moderate to good activity.

EXPERIMENTAL SECTION

The melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked on TLC plates coated with silica gel-G. The IR spectra were recorded on a Beckman Acculab-10 spectrophotometer (ν_{max} in cm^{-1}), and the ^1H NMR spectra were recorded in DMSO on a Jeol-JMS D-300 spectrometer. All the chemicals used for the syntheses were from Merck and used without purification. The final products were purified by column chromatography. Reactions including hazardous medium of pyridine were carried out in well-ventilated fume-cupboard.



Scheme 1.

Synthesis of 2-Phenyl-benzo[*d*][1,3]oxazin-4-one (1)

To the solution of anthranilic acid (10 g, 0.07 mol) in pyridine, the benzoyl chloride (20.5 g, 0.15 mol) in pyridine (25 mL) was added dropwise at room temperature with constant stirring for 0.5 hr followed by the addition of 5% $NaHCO_3$ solution. The separated solid was filtered and crystallized from ethanol to get **1**. Yield 12.5 g (80%), M.P. 120°C. Anal. Found: C, 75.20; H, 4.00; N, 6.20 ($C_{14}H_9NO_2$) required: C, 75.33; H, 4.06; N, 6.27%. IR (KBr): ν_{max} 1690 (C═O), 1620 cm^{-1} (–C═N) PMR (DMSO-d_6): δ, 6.8–7.6 (9H, m, Ar-H) ppm.

Synthesis of 2-3-2-Chloro-phenyl-5-phenyl-(1,2,4-triazole-4-yl)-benzoic Acid (2a)

A mixture of **1** (2.23 g, 10 mmol) and 2-chloro benzoic acid hydrazide (1.70 g, 10 mmol) in methanol (10 mL) was refluxed in an oil bath for 1 hr and the reaction mixture was poured into ice-cold water to form desired crystalline solid product. Then the separated solid was filtered and recrystallized from methanol and purified by column chromatography using solvent system (acetone and ethanol) to get **2a**. Yield 2.25 g, (60%). M.P. 197°C. Anal. Found: C, 67.2; H, 3.70; N, 11.2 ($C_{21}H_{14}ClN_3O_2$) required: C, 67.12; H, 3.75; N, 11.18%. IR (KBr): ν_{max} 3520–3300 (OH), 1705 cm^{-1} (CO). PMR (DMSO-d_6): 10.8 (–COOH), 6.2–7.2 (13H, m, Ar-H) ppm.

Synthesis of 2-3-Phenyl-5-*o*-tolyloxymethyl-(1,2,4-triazole-4-yl)-benzoic Acid (2b)

A mixture of **1** (3.75 g, 10 mmol) and *o*-tolyloxy-acetic acid hydrazide (1.80 g, 10 mmol) in methanol (10 mL) was refluxed in an oil bath for 1 hr and the reaction mixture was poured into ice-cold water to get the desired product. The separated solid was filtered and recrystallized from methanol and purified by column chromatographic method to get **2b**. Yield 2.44 g (63.50%). M.P. 198°C. Anal. Found: C, 71.70; H, 5.00; N, 11.00 ($C_{21}H_{14}ClN_3O_2$) required: C, 71.68; H, 4.97; N, 10.90%. IR (KBr): ν_{max} 3520–3330 (OH), 1705 cm^{-1} (C═O). PMR (DMSO-d_6): 2.1 (3H, s, Ar-CH_3), 6.2–7.2 (13H, m, Ar-H), 10.8 (1H, s, br, D_2O exchangeable, COOH) ppm.

Similarly, other derivatives were synthesized; characterized, and their structures were confirmed on the basis of their IR, PMR, and mass spectral and elemental analyses.

The structures of the synthesized compounds were subjected to computer programme PASS to get the predictions about the probable biological activities of the compounds. The relationship between structure and very common activities, such as GABA-A receptor antagonist activity and lipid metabolism regulator activity has been established.

Antimicrobial Screening

The compounds synthesized were screened for antimicrobial activity against some Gram +ve and Gram −ve pathogenic bacterial and fungal species like *E. coli*, *P. valgarism B. subtilis*, *S. aurius*, *A. niger*, and *Phytophora* species. The screening was carried out by paper disc method, and gentamycin sulphate and diethane M-45 were used as standards for comparison.

RESULT AND DISCUSSION

The results indicated that some compounds exhibit good antimicrobial activity against the above mentioned bacterial and fungal species, while some compounds have moderate antimicrobial activity against both Gram +ve and Gram −ve bacterial and fungal species.

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Received March 3, 2004