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Synthesis and Study of Some Newer Analogues of Quinolin-8-ol as Potent Antimicrobial Agents

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Abstract: New series of 4-(substituted phenyl)-5-[(quinolin-8-yloxy) methyl]-4H-1,2,4-triazole-3-thiol (**4a-c**), N³-(4-substituted phenyl)-5-[(quinolin-8-yloxy) methyl]-4H-1,2,4-triazole-3,4-diamine (**5a-c**) and N-(4-substituted phenyl)-5-[(quinolin-8-yloxy) methyl]-1,3,4-thiadiazol-2-amine (**6a-g**) have been synthesized and the structures of the new compounds were established on the basis of IR, ¹H NMR spectral data. *In vitro* antimicrobial activity (MIC activity) was evaluated and compared with standard drugs of loxacin and ketoconazole. Compounds **5a** and **6e** in the series have shown interesting antibacterial activity against both *S. aureus* (gram-positive) and *E. coli* (gram-negative) organisms. In this paper, we also describe studies leading to identification of antifungal agents. In the gratifying result, most of the compounds were found to have moderate antimicrobial activity.

Keywords: 1,2,4-Triazole, 1,3,4-Thiadiazole, Antibacterial, Antifungal.

Introduction

Heterocycles bearing a symmetrical triazole or 1,3,4-thiadiazole moieties represent an interesting class of compounds possessing a wide spectrum of biological activities such as anti-inflammatory¹⁻³, antiviral⁴ and antimicrobial^{5,6} properties. It has also been reported in literature that derivative of 1,2,4-triazole and 1,3,4-thiadiazole condensed nucleus systems found that have diverse pharmacological activities such as anti-inflammatory⁷ antitumor⁸, antifungal and antibacterial⁹. Furthermore, literature survey revealed that modification of the carboxyl function of representative non-steroidal anti-inflammatory drugs (NSAIDs) resulted in an increased anti-inflammatory activity with reduced ulcerogenic effect¹⁰⁻¹². Our former studies^{13,14} have shown that certain compounds bearing 1,2,4-triazole and 1,3,4-thiadiazole nuclei possess significant

anti-inflammatory activity with reduced gastrointestinal (GI) toxicity. we describe herein the synthesis of some triazole, thiadiazole derivatives and evaluation of their antimicrobial activities. The reaction sequence leading to the formation of desired heterocyclic compounds are outlined in Scheme 1. The structures of the compounds were assigned on the basis of IR, ^1H NMR spectral data.

Scheme 1

Experimental

Melting points were determined in open capillary tubes. IR spectra were recorded on a perkin-Elmer 157 spectrometer and ^1H NMR spectra on a Bucker WM-400 (400 MHz FT NMR) spectrophotometer using TMS (Tetramethyl Silane) as internal reference (chemical shift in δ ppm). Purity of the compounds was checked by TLC (Thin Layer Chromatography) on silica gel plates and spot were visualized by exposure to iodine vapours. The physical data of the compounds prepared are presented in Table 1.

Table 1. Characterization data of the compounds.

Compounds	Ar	M.P °C	Yield, %	Mol. formula	N %, found	Calcd
4a		278	65	C ₁₉ H ₁₆ N ₄ OS	16.50	16.08
4b		281	57	C ₁₉ H ₁₆ N ₄ O ₂ S	15.84	15.37
4c		285	61	C ₁₈ H ₁₃ ClN ₄ OS	15.40	15.19
5a		267	59	C ₁₉ H ₁₈ N ₆ O	24.40	24.26
5b		257	51	C ₁₉ H ₁₈ N ₆ O ₂	23.25	23.19
5c		269	56	C ₁₈ H ₁₅ ClN ₆ O	22.97	22.91
6a		278	59	C ₁₉ H ₁₆ N ₄ OS	16.15	16.08
6b		265	57	C ₁₉ H ₁₆ N ₄ O ₂ S	15.45	15.37
6c		261	62	C ₁₈ H ₁₃ ClN ₄ OS	15.35	15.19
6d		272	64	C ₂₀ H ₁₈ N ₄ OS	15.66	15.46
6e		271	67	C ₁₈ H ₁₂ ClFN ₄ OS	14.53	14.48
6f		275	58	C ₁₈ H ₁₃ FN ₄ OS	16.10	15.90
6g		268	63	C ₁₈ H ₁₃ BrN ₄ OS	13.71	13.56

Ethyl (quinolin-8-yloxy) acetate (I)

To a solution of 8-hydroxy quinoline (0.5 mole) in dry acetone (150 mL), ethyl chloroacetate (0.60 mole) were added followed by anhydrous K₂CO₃ (1.0 mole). After reflux for 20 hour the solvent was removed and the reaction mixture was treated with water, extracted with benzene several times and the collected organic layer was dried on anhydrous Na₂SO₄, filtered and evaporated to give liquid ester. ¹H NMR (CDCl₃): δ 1.42 (t, 3H, CH₃), δ 4.36 (q, 2H, OCH₂), δ 7.42-7.74 (m, 6H, Ar-H).

2-(Quinolin-8-yloxy) acetohydrazide (2)

To a RB flask, compound **1** (0.01 mol), hydrazine hydrate (0.2 mol) and absolute alcohol (50 mL) were taken. A condenser with calcium guard tube was attached to the flask and mixture was refluxed for 24 hours on water bath. The mixture was concentrated, cooled and poured in crushed ice. It was kept for 3-4 hours at room temperature and solid mass separated out was filtered and dried, recrystallised in methanol. ¹HNMR (CDCl₃): δ 7.40-7.78 (complex, m, 6H, Ar-H), δ 7.84-7.98 (m, 3H, CONHNH₂).

N-(4-Methylphenyl)-2-[(quinolin-8-yloxy) acetyl]hydrazide (3a)

A mixture of compound **2** (0.001 mole) and 4-methyl phenyl isothiocyanate (0.001 mole) in ethanol (25.0 mL) was refluxed on a water bath for 2 hour. The solvent was concentrated and the precipitated product was filtered, dried and recrystallised from methanol. **3a** IR (KBr): 3387 (N-H), 1648 (CONH), 1608 (ArH), 1042 (C=S). **3a** ¹H NMR (CDCl₃): δ 7.18-7.62 (m, 6H, Ar-H), δ 7.70-7.86 (m, 3H, CONHNHCSNH). Other compounds **3b-g** were prepared similarly and their characterization data are recorded in Table 1

4-(4-Methylphenyl)-5-[(quinolin-8-yloxy) methyl]-4H-1, 2,4-triazole-3-thiol (4a)

Compound **3a** (0.002 mole) was added to ethanol (20 mL). To this NaOH (4N, 2 mL) was added which resulted in clear solution. It was refluxed for 1 hour and treated with decolorizing charcoal and filtered. The filtrate was cooled and pH was adjusted to 4-6 with dilute glacial acetic acid. The mixture was kept aside for 1 hour and the crystals produced were filtered, dried and recrystallised from methanol. **4a** IR (KBr): 3369 (N-H), 1601 (C=N), 1186 (C=S) 2922 (C-H). **4a** ¹H NMR (CDCl₃): δ 3.89 (s, 2H, OCH₂), δ 7.25-7.88 (complex m, 10 Ar-H), 10.52 (s, 1H, SH). **4c** IR (KBr): 3361 (N-H), 1578 (C=N), 1208 (C=S) 2932 (C-H). **4c** ¹H NMR (CDCl₃): δ 3.84 (s, 2H, OCH₂), δ 7.28-7.78 (complex m, 10 Ar-H), 10.60 (s, 1H, SH). Other compounds **3b**, **3c** were prepared similarly and their characterization data are recorded in Table 1.

N3-(4-Methoxyphenyl)-5-[(quinolin-8-yloxy)methyl]-4H-1,2,4-triazole-3,4-diamine (5b)

Compound **3b** (0.025 mole) and hydrazine hydrate (0.025 mole) were refluxed in methanol for 2 hour at a temperature between 50-60°C, reaction mixture was cooled and poured over crushed ice. Solid was filtered and recrystallised from methanol. **5b** IR (KBr): 3292 (N-H), 1618 (C=N), 2928 (C-H). **5b** ¹H NMR (CDCl₃): δ 2.48 (s, 3H, OCH₃), δ 8.26 (bs, 1H, NH), δ 7.08-7.96 (complex m, 10 Ar-H). **5a** IR (KBr): 3296 (N-H), 1623 (C=N), 2938 (C-H). **5a** ¹H NMR (CDCl₃): δ 2.28 (s, 3H, CH₃), 8.24 (bs, 1H, NH), δ 7.05-7.98 (complex m, 10 Ar-H). Other compounds **5a**, **5c** in the series were prepared similarly and their characterization data are recorded in Table 1

N-(4-Methylphenyl)-5-[(quinolin-8-yloxy) methyl]-1,3,4-thiadiazol-2-amine (6a)

Compound **3a** (0.002 mole) was added portion wise in 5.0 mL conc. H₂SO₄ and stirred with cooling for 2 h. The mixture was poured over crushed ice and the precipitated solid was filtered, washed with water, dried and recrystallised from methanol. **6a** IR (KBr): 3218 (N-H), 1626 (C=N), 3039 (C-H). **6a** ¹H NMR (CDCl₃): δ 5.44 (s, 2H, OCH₂), δ 7.23-7.67 (complex m, 10 Ar-H), δ 7.98 (s, 1H, NH). **6f** IR (KBr): 3412 (N-H), 1611 (C=N), 2934 (C-H). **6f** ¹H NMR (CDCl₃): δ 5.46 (s, 2H, OCH₂), δ 7.28-7.74 (complex m, 10 Ar-H), δ 7.96 (s, 1H, NH). Other compounds **6b-g** were prepared similarly and their characterization data are recorded in Table 1

Results and Discussion

Spectral characterization of the compounds

The IR spectrum of the compounds (**4a-c**) showed peaks at 3361-3370 cm^{-1} , N—H stretching; 2922-2935 cm^{-1} , CH stretching; 1577-1601 cm^{-1} , C=N stretching and 1186-1216 cm^{-1} , C=S stretching. The NMR spectrum of the compound **4a** showed a singlet at δ 3.89 indicating the presence of OCH_2 protons. In the aromatic region complex multiplet at δ 7.25-7.88 was observed indicating the presence of ten aromatic protons. A singlet at δ 10.52 was observed for one SH protons. The NMR spectrum of the compound **4c** showed a singlet at δ 3.84 indicating the presence of OCH_2 protons. In the aromatic region complex multiplet at δ 7.28-7.78 was observed indicating the presence of ten aromatic protons. Furthermore a singlet at δ 10.60 was observed for one SH protons. The IR spectrum of the compounds (**5a-c**) showed peaks at 3245-3296 cm^{-1} , N—H stretching; 2928-2938 cm^{-1} , CH stretching; 1618-1624 cm^{-1} , C=N stretching. The NMR spectrum of the compound **5a** showed a singlet at δ 2.28 indicating the presence of CH_3 protons. In the aromatic region complex multiplet at δ 7.05-7.98 was observed indicating the presence of ten aromatic protons. A broad singlet at δ 8.24 was observed for one NH protons. The NMR spectrum of the compound **5b** showed a singlet at δ 2.48 indicating the presence of OCH_3 protons. In the aromatic region complex multiplet at δ 7.08-7.96 was observed indicating the presence of ten aromatic protons. A broad singlet at δ 8.26 was observed for one NH protons. The IR spectrum of the compounds (**6a-g**) showed peaks at 3418-3436 cm^{-1} , N—H stretching; 2928-3039 cm^{-1} , CH stretching; 1610-1660 cm^{-1} , C=N stretching. The NMR spectrum of the compound **6a** showed a singlet at δ 5.44 indicating the presence of OCH_2 protons. In the aromatic region complex multiplet at δ 7.23-7.67 was observed indicating the presence of ten aromatic protons. A singlet at δ 7.98 was observed for one NH protons. The NMR spectrum of the compound **6f** showed a singlet at δ 5.46 indicating the presence of OCH_2 protons. In the aromatic region complex multiplet at δ 7.28-7.97 was observed indicating the presence of ten aromatic protons. Furthermore a singlet at δ 7.96 was observed for one NH protons.

Antimicrobial activity

The synthesized compounds were evaluated for their antimicrobial activity against bacterial strain *S. aureus* (gram-positive), *E. coli* (gram-negative) and fungal strain *A. niger* by cup plate method¹⁵ at 200, 100, 50 and 25 $\mu\text{g/mL}$ concentration. Ofloxacin and Ketoconazole were used as standard drugs for antibacterial and antifungal activity respectively. The minimal inhibitory concentration (MIC, $\mu\text{g mL}^{-1}$) of the tested compounds are recorded in Table 2

The 1,2,4-triazole derivative **4c** having chloro group at *para* position of phenyl ring exhibited a MIC of 50 $\mu\text{g/mL}$ against, *S. aureus*, *E. coli* and *A. niger*, whereas **4b** exhibited significant antimicrobial activity (MIC 25 $\mu\text{g/mL}$) against *S. aureus* and *A. niger*. The compound **5a** exhibited promising antibacterial activity (MIC 25 $\mu\text{g/mL}$) against *S. aureus*, *E. coli* and *A. niger* strains. Compound **5b** exhibited (MIC 25 $\mu\text{g/mL}$) against *E. coli* and *A. niger*. The 2-(quinolin-8-yloxy) acetohydrazide derivative **6e** having 3-chloro-4-fluorophenyl amino group at 2nd position of thiadiazole ring was found to have MIC 25 $\mu\text{g/mL}$ against *S. aureus*, *E. coli*. and *A. niger*. 1,3,4-thiadiazole derivative **6f** also exhibited promising antibacterial activity (MIC 25 $\mu\text{g/mL}$) against *E. coli*.

Table 2. Antimicrobial activities of the compounds.

Compound No.	MIC, µg/mL		
	<i>S.aureus</i>	<i>E.coli</i>	<i>Aniger</i>
Ofloxacin	10	12.5	--
Ketoconazole	--	--	12.5
4a	100	100	100
4b	25	50	25
4c	50	50	50
5a	25	25	25
5b	50	25	25
5c	50	50	100
6a	100	100	100
6b	100	100	100
6c	50	100	50
6d	100	100	100
6e	25	25	25
6f	50	25	50
6g	100	50	50

-- Not tested

Conclusion

In summary, we have described the genesis and synthesis of antimicrobially active 4-(substituted phenyl)-5-[(quinolin-8-yloxy) methyl]-4H-1,2,4-triazole-3-thiol, N³-(4-substituted phenyl)-5-[(quinolin-8-yloxy) methyl]-4H-1,2,4-triazole-3,4-diamine and N-(4-substituted phenyl)-5-[(quinolin-8-yloxy) methyl]-1,3,4-thiadiazol-2-amine derivatives. The antimicrobial screening results revealed that some of the compounds are moderately active. However, the activities of the tested compounds are less than those of standard antibacterial and antifungal agents used.

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