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Synthesis and evaluation of quinolone derivatives as potential antibacterial agents

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ABSTRACT

A series of 1-(substituted -2-oxoquinolin-1(2H)-yl) urea and thiourea have been synthesized by using coumarin derivatives and semicarbazide in presence of ethanol as a solvent. Coumarin derivatives were prepared via pechmann condensation by adding a mixture of substituted phenol and ethyl acetoacetate in concentrated sulfuric acid. Coumarin derivatives then subjected to condensation with semicarbazide and thiosemicarbazide. The structure of all these synthesized compounds has been established on the basis of chemical transformation, IR and ^{1}HNMR spectral studies. Synthesized compounds are showing amazing antibacterial activity for common food borne pathogens such as *Escherichia coli, Shigella flexneri, Staphylococcus aureus, and Bacillus cereus.*

Keywords: Coumarin, Quinolone, Oxoquinolone, Anti-bacterial activity.

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INTRODUCTION

Quinolones are some of the few heterocyclic that have gained importance recently as they are a family of synthetic broad-spectrum antibiotics[1]. The quinolones not only offer interesting chemistry but their derivatives possess diverse chemotherapeutic properties. Quinolones and fluoroquinolones are chemotherapeutic bactericidal drugs, eradicating bacteria by interfering with DNA replication[2]. Nowadays, the quantitative structure activity relationships (QSAR) associated with the quinolones has been increasingly used in drug design. Typically, the predominant variables which are evaluated for correction with biological activity are usually physicochemical parameter[3]. The successful application of the computer automated structure evaluation (CASE) which utilized molecular features inherent within the chemical structure were recently reported by Klopman *et al*[4].

Urea derivatives of quinolones has been medically proven in various clinical studies to have extraordinary anti microbial properties that promote fast healing of dry cracked split skin, eczema , psoriasis, rashes, burns and other types of skin problems. A large number of studies have confirmed the beneficial effect of urea compounds for many of the skin problems people face today. Evidence shows that urea compounds are useful for all degree of dry skin[5]. Quinolone compounds found to inhibit microbial growth at the site of an infection to be treated in a human or lower animal subject, without undue adverse side effects (such as toxicity, irritation, or allergic response), Commensurate with a reasonable benefit/risk ratio when used in the manner of this invention[6]. In recent years effort has been directed towards the synthesis of new quinolones that can provide improved antibacterial activity. In this work, we wish to describe the design, synthesis of a series of new quinolone urea derivatives. These quinolone compounds were structurally unprecedented, having different functional groups at different positions.

MATERIALS AND METHOD

All reagents were purchased from commercial suppliers and used without further purification. Melting points were determined in open capillaries and are uncorrected. IR (KBr) spectra were recorded on Perkin Elmer-577 spectrophotometer, NMR spectra on Varian Mercury YH-300 spectrometer with TMS as internal standard using $CDCl_3$ and DMSO as solvent. Purity of the compounds was checked by TLC.

The bacterial strains studied are identified strains and were purchased from the Himedia Pvt Ltd. culture collection, Mumbai. The investigated microorganisms were Escherichia coli ATCC 25922, Shigella flexneri ATCC9199, and Staphylococcus aureus ATCC 12600, Bacillus cereus ATCC

10876. All four bacterial strains used were common food borne pathogens, including two Gram – ve bacteria such as Escherichia coli ATCC 25922 & Shigella flexneri ATCC9199, and two Gram +ve bacteria such as Staphylococcus aureus ATCC 12600 & Bacillus cereus ATCC 10876. The compounds were dissolved at a concentration of 1.0 mg/ml in Di-methyl Formamide (DMF). The synthesized compounds are soluble only in DMF[17].

Experimental Procedure

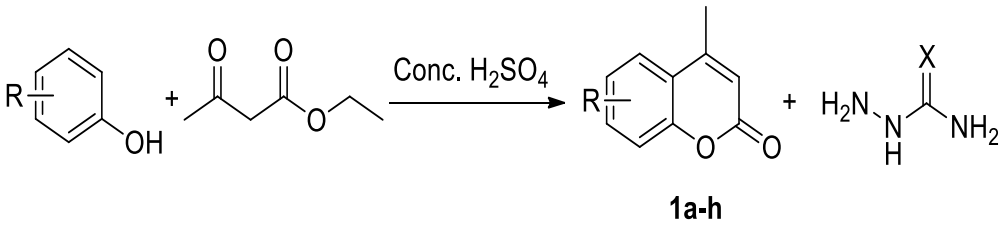
Synthesis of Coumarin derivatives

A mixture of derivatives of phenol and ethyl acetoacetate was stirred in concentrated sulfuric at room temperature. As the phenol was consumed pour the mixture in crushed ice to recovered the solid that was collected by filtration and washed with water giving corresponding coumarin derivatives (**1a-h**) and crystallized from ethanol[7-8].

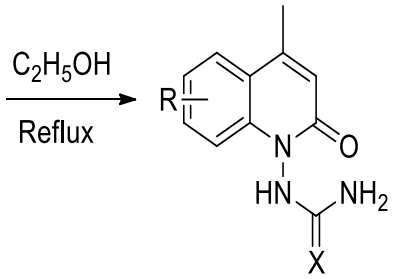
Synthesis of Quinolone derivatives

A mixture of coumarin derivatives **(1a-h)** and semicarbazide or thiosemicarbazide in ethanol was refluxed for about 5 hours. The reaction mixture was cooled and poured into ice to obtained solid which was again collected by filtration and recrystallized from suitable solvent[9-10]. (Scheme 1)

Scheme 1



1a-h



2a-h (X=O, S)

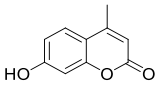
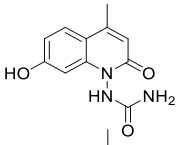
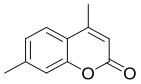
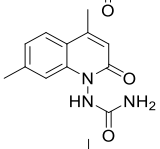
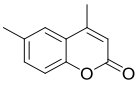
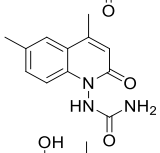
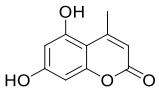
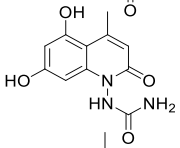
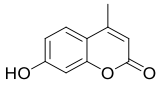
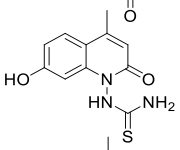
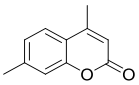
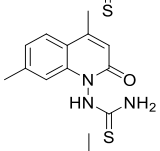
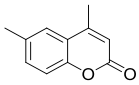
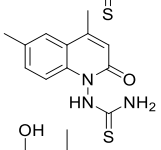
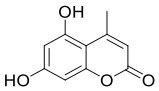
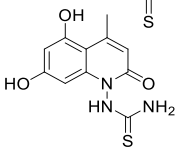
After getting the result, we generalized the reaction using different coumarin derivatives **(1a-h)** and semicarbazide or thiosemicarbazide in ethanol observed the corresponding products **(2a-h)** in excellent yields (Table 1). The reaction was very clean at room temperature and completed in around 5h.

Antibacterial Activity

A loop full of the given test strain was inoculated into 25 ml of Luria Bertani broth (LB Broth) and incubated for 24 in an incubator at 37^{o}C in order to activate the bacterial strain. A Petri dish of 100 mm diameter was filled with 28-30 ml of Luria Bertani (LB) media. Inoculation was performed by the pour plate technique. 0.2 ml of the activated strain was inoculated into the media when it had reached a temperature of 40-45^{o}C. The complete procedure of the ditch preparation was done in a laminar airflow to maintain strict sterile and aseptic condition. The media was allowed to solidify. After solidification of the media, a well was made in the media with help of a cup-borer (0.5 cm) and then 0.03 ml of the synthetic compound (dissolved in DMF) was inoculated into the well. Controls were performed (for each bacterial strain), where 0.03 ml of the pure solvent was inoculated into each well. The plates were incubated for 24 h at 37^{o}C. The inhibition zone formed by the compounds against the particular test bacterial strain determined the antibacterial activities of the synthetic compounds[18].

RESULTS AND DISCUSSION

Table 1: Synthesis of quinolone derivatives [a,b]

Entry	Coumarin	Time (h)	Product	Yield (%)	M.P. (°C)
a		4.5		82	194
b		3.5		77	153
c		5.0		70	170
d		4.5		76	170
e		3.5		86	122
f		5.0		69	128
g		4.0		87	182
h		3.0		83	180

[a] Reaction condition: 1.0 mmol of coumarin, 1.0 mmol of semicarbazide or thiosemicarbazide in ethanol DMF at refluxed condition.

[b] Confirmed by (TLC, ^{1}H NMR).

The advantage of this reaction is that the reaction completed in short time and the product obtained without any work up and purification leaving the byproducts in water. There is no requirement of extraction in organic solvents and purification by chromatography.

Table 2 : **showing antibacterial zones values observed for different synthetic test compounds (2a-2h) each having 30 µg/ml concentrations.**

Compounds (30 µg/ml)	Escherichia coli ATCC 25922	Shigella flexneri ATCC9199	Staphylococcus aureus ATCC 12600	Bacillus cereus ATCC9199
2a	++	+	++	+
2b	++	+	++	+
2c	++	++	-	++

2d	++	-	+	+
2e	+	-	++	+
2f	++	-	+	+
2g	++	+	-	+
2h	++	++	-	+

++ Zone of inhibition (0. 5 -1.5 cm diameter); + zone of inhibition (>1.0 cm diameter); - no zone of inhibition

2a:1-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl) urea:

Light brown crystals, yield 82%, mp 194 °C; IR (ν_{max}, cm^{-1}): 1709 (C=O), ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (3H, *s*, CH_3CH), 2.50 (1H, s, NH), 3.42 (2H, s, NH_2), 6.09 ($1H_{arom}$, s, CH), 6.68 ($1H_{arom}$, d, CH), 6.79 (1H, s, CH-C), 7.56 ($1H_{arom}$, d, CH), 10.52 (1H, s, OH-Ar). Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02; O, 20.58; Found: C, 56.62; H, 4.71; N, 18.03; O, 20.57.

2b:1-(4,7-dimethyl-2-oxoquinolin-1(2H)-yl)urea: White crystals, yield 77%, mp 153 °C; IR (ν_{max}, cm^{-1}): 1703 (C=O), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (1H, s, NH), 1.65 (2H, s, NH_2), 2.42 (3H, s, CH_3CH), 2.45 (3H, s, CH_3CH), 6.22 (1H, s, CH-C), 7.13 ($1H_{arom}$, d, CH), 7.46 ($1H_{arom}$, s, CH), 7.49 ($1H_{arom}$, d, CH). Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17; O, 13.84; Found: C, 62.30; H, 5.68; N, 18.16; O, 13.81.

2c:1-(4,6-dimethyl-2-oxoquinolin-1(2H)-yl)urea: White crystals, yield 70%, mp 170 °C; IR (ν_{max}, cm^{-1}): 1701 (C=O), ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 ($1H_{arom}$, s, CH),2.45 (3H, s, CH_3 CH), 7.44 ($1H_{arom}$, d, CH), 7.10 ($1H_{arom}$, d, CH). Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17; O, 13.84; Found: C C, 62.33; H, 5.66; N, 18.14; O, 13.86.

2d:1-(5,7-dihydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)urea:

Grey crystals, yield 76%, mp 170 °C; IR (ν_{max}, cm^{-1}): 1711 (C=O)^{1}H NMR (300 MHz, DMSO-d_6): δ ^{1}H NMR ($CDCl_3$): 2 (NH, NH_2), 7.10 ($1H_{arom}$, d, CH), 6.11($1H_{arom}$, s, CH), 1.71 (3H, s, CH_3), 5.0 (OH), 6.42 (1H, s). Anal. Calcd. for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86; O, 25.68; Found: C, 53.03; H, 4.42; N, 16.87; O, 25.70.

2e:1-(7-hydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)thiourea:

Light brown crystals, yield 86%, mp 122 °C; IR (ν_{max}, cm^{-1}): 1713 (C=S) ^{1}H NMR (300 MHz, $CDCl_3$): δ 2 (NH, NH_2), 7.05 ($1H_{arom}$, d, CH), 6.46($1H_{arom}$, s, CH), 1.71 (3H, s, CH_3), 2.35 (3H, s, CH_3), 6.35 (1H, s). Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45; N, 16.86; O, 12.84; S, 12.86; Found: C, 53.02; H, 4.44; N, 16.87; O, 12.84; S, 12.83.

2f:1-(4,7-dimethyl-2-oxoquinolin-1(2H)-yl)thiourea:

White crystals, yield 69%, mp 128 °C; IR (ν_{max}, cm^{-1}): 1701 (C=S), ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.3 (NH, NH_2), 7.02 ($1H_{arom}$, s, CH), 6.86 ($1H_{arom}$, d, CH), 1.74 (3H, s, CH_3), 2.30 (3H, s,

CH_3, 6.51 (1H, s). Anal. Calcd. for $C_{12}H_{13}N_3OS$: C, C, 58.28; H, 5.30; N, 16.99; O, 6.47; S, 12.97; Found: C, 58.25; H, 5.27; N, 16.97; O, 6.48; S, 12.94.

2g:1-(4,6-dimethyl-2-oxoquinolin-1(2H)-yl)thiourea):

White crystals, yield 87%, mp 182 °C; IR (ν_{max}, cm^{-1}): 1654 (C=S), ^1H NMR (300 MHz, $CDCl_3$): δ 26 (1H, s, NH), 1.81 (2H, s, NH_2,), 6.20 (1H, s, CH-C), 2.42 (3H, s, CH_3). Anal. Calcd. for $C_{12}H_{13}N_3OS$: C, 58.28; H, 5.30; N, 16.99; O, 6.47; S, 12.97; Found: C, 58.31; H, 5.29; N, 16.99; O, 6.48; S, 12.95.

2h:1-(5,7-dihydroxy-4-methyl-2-oxoquinolin-1(2H)-yl)thiourea:

Light green crystals, yield 83%, mp 182 °C; IR (ν_{max}, cm^{-1}): 1659 (C=S), ^1H NMR (300 MHz, DMSO-d_6): δ 1.28 (1H, s, NH), 1.86 (2H, s, NH_2,), 6.20 (1H, s, CH-C), 2.22 (3H, s, CH_3), 7.53 ($1H_{arom}$, d, CH), 10.58 (1H, s, OH-Ar). Anal. Calcd. for $C_{11}H_{11}N_3O_3S$: C, 49.80; H, 4.18; N, 15.84; O, 18.09; S, 12.09; Found: C, 49.81; H, 4.15; N, 15.85; O, 18.06; S, 12.11.

CONCLUSION

The inhibition zone formed by the compounds against the particular test bacterial strain determined the antibacterial activities of the synthetic compounds. Test compounds viz; 2a and 2b were found to show antibacterial activity against Gram +ve and Gram –ve bacteria, indicating broad range spectrum of activity. Compound 2h and 2c was found to show antibacterial activity (zone of inhibition more than 1.0 cm) against Escherichia coli and Shigella flexneri both belonging to Gm – ve genotypes. However growth of Bacillus cereus (Gram +ve) was also inhibited by 2h and 2c compound but Staphylococcus aureus (Gram +ve) growth was not affected, indicating narrow spectrum of antibacterial activity. Other compounds viz; 2d, 2e, 2f, and 2g showed variable antibacterial activity.

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