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Synthesis and antimicrobial screening of some novel quinazolinones and its derivatives

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Abstract

Various novel quinazolinones and quinazolidine dione derivatives were prepared by using anthranilic acid. Anthranilic acid was synthesized by treating phthalimide with sodium hypobromide solution. The synthesized anthranilic acid was treated with urea, thiourea, acetamide and benzamide to give corresponding titled compounds in good yields. The synthesized compounds were characterized by physical properties and spectral studies (IR, ^{1}H-NMR) and tested for antimicrobial activity.

Keywords: Anthranilic acid, Urea, Thiourea, Benzamide, Quinqzolinones and Quinazolidine diones.

Introduction

Quinazoline and quinazolinones are a type of heterocyclic fused rings possesses various uses in the field of pharmacy. Quinazolines and quinazolinones are active compounds that shows numerous biological activities[(1)] such as antioxidant,[(2)] antileukemic,[(3)] antileishmanial and other activities. It is considered as a useful entity, the alteration is made with different substituents.

Therefore, it seems promising to synthesize some new substituted quinazolinones, quinazolidine diones using compounds like urea/ thiourea/ substituted amides and antranilic acid. Substituted quinazolinones, quinazolidine diones possess numerous activities.[(4,5)] As part of ongoing studies in developing new antimicrobials, we are reporting the synthesis of a novel quinazolinones with interesting antimicrobial activity (Fig. 1-3).

Materials and Method

Materials and reagents were purchased from commercial suppliers (Merck grade) and they were used without purification. Melting points were determined by using electrical melting point apparatus and are uncorrected. The progress of the reaction was monitored by TLC using Silica Gel G (Merck). IR spectra were recorded in KBr discs on a Bruker analyzer. ^{1}H-NMR spectra were recorded on a Bruker (400 MHz) spectrometer (chemical shifts in γ, ppm) in DMSO using TMS as internal standard.

Experimental work: Scheme shown in Fig. 4.

Phthalimide[(6,7)] synthetic procedure: A mixture of pthalic anhydride (2.5 g), urea (0.55 g) were taken in a RBF and refluxed at 130-135^{o}C. When temperature raises to 150-160^{o}C solution becomes solid. Then cool it and 40 ml of water was added to form pthalimide. The obtained precipitate was filtered and dried at 100^{o}C.

Anthranilic acid[(8)] synthetic procedure: A mixture of 1.5 gms of NaOH and 1.5 ml of water were taken in a beaker and add 0.5 ml of bromine with continuous stirring. Now add 1.2 gms of finely powdered phthalimide and 1.1 gms of NaOH in 4 ml of water was added with stirring. Clear solution was formed after heating the mixture at 80^{o}C. The obtained clear solution was cooled in ice bath and 30 ml of conc. HCl was added with stirring until the solution becomes neutral. Finally 10-12 ml of glacial acetic acid was added and the obtained precipitate was filtered and dried.

General procedure for synthesis of quinazolinones and quinazolidine diones:[(9,10)] A mixture of anthranilic acid (0.01 mol), benzamide/acetamide/urea/thiourea (0.01 mol) and glacial acetic acid (0.54 ml) were taken in RBF and refluxed for 30-45 minutes at a temperature of 120-130^{o}C. The reaction was checked by TLC. After completion of reaction cool the solution and add cold water. The obtained precipitate was filtered and dried.

Various titled compounds synthesized from Anthranilic acid are

- 2-phenyl–4(3*H*)quinazolinone (3a)
- 2-methyl–4(3*H*)quinazolinone (3b)
- 4(1*H*,3*H*)quinqzolinedione (3c)
- 4(1*H*,3*H*)quinazolinone-2-thione (3d)

Physical characterization of the synthesized Compounds: Melting points were determined by open ended capillary tube and are uncorrected. Purity of the compounds was checked by the TLC. Physical data results were shown in Table 1.

IR Spectral Data of synthesized compounds:

Spectral data of 2-phenyl–4(3*H*)quinazolinone (3a)

IR (Cm^{-1}, KBr): 3358.20 (NH), 1651.39 (C=O of Amide group), 1614.75 (C=N), 1570.70 (C=C).

Spectral data of 2-methyl–4(3*H*)quinazolinone (3b)

IR (Cm^{-1}, KBr): 3348.20 (NH), 1631.29 (C=O of Amide group), 1620.65 (C=N), 1560.70 (C=C).

Spectral data of 4(1*H*,3*H*) quinqzolinedione (3c)

IR (Cm^{-1}, KBr): 3360.08 (NH), 3254.81(NH), 1699.46 (C=O of Amide group), 1400.18 (C-N), 1557.48 (C=C).

Spectral data of 4(1*H*,3*H*) quinazolinone-2-thione (3d)

IR (Cm^{-1}, KBr): 3179.09 (NH), 3394.74 (NH), 1745.28 (C=S), 1598.02 (C=O of Amide group), 1303.34 (C-N), 1554.04 (C=C).

H^1 NMR spectral data of 2-phenyl-4(3*H*)quinazolinone (3a): δ 7.41 (d, *J* = 6.9 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 6.52 (t, *J* = 6.9 Hz, 3H), 7.74 (t, *J* = 7.4 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 8.09 (s, 1H), 8.24 (d, *J* = 7.6 Hz, 1H).

Antimicrobial activity of synthesised compounds:[11-13] In the present work the antimicrobial activity was tested by cup plate method. The antimicrobial activity of substituted quinazolinones and quinazoline diones was tested and compared with the standard drug Streptomycin. The concentration of different test solutions is 2 mg/ml compared with standard solution at a concentration of 5 mg/ml. Acetone, chloroform were used as a solvent.

Test organisms: *Escherichia coli*, *Bacillus cereus*, *Staphylococcus aureus.*

Procedure for Antimicrobial activity: Agar medium was inoculated at 1% level with 18 hrs old cultures of the above mentioned test organisms and were transferred into sterile petri dishes. The medium in the plates was allowed to set at room temperature for about 10 min and they were set to solidify in a refrigerator for 30 min. After that cylinders were made in the medium. The test solutions which were prepared in acetone and chloroform along with the standard solution of Streptomycin were placed in their respective cylinders. The plates thus prepared were left to stand in a refrigerator for about 1 hr to allow the test solution for diffusion. Then incubation of the above plates was done for 24 hrs at 37^{0}C. Then zones of inhibition were examined and the inhibition zone diameters were measured.

Results and Discussion

The present study aimed to synthesize quinazolinones and quinazolidine diones using the appropriate synthetic procedure i.e. reaction of anthranilic acid, urea/thiourea/acetamide/benzamide in presence of glacial acetic acid.

A mixture of anthranilic acid and benzamide/ acetamide/ urea/ thiourea and glacial acetic acid were taken in round bottomed flask and refluxed for 30-45 minutes at a temperature 120-130^{o}C. The forward movement of the reaction was checked by TLC. After completion of reaction cool the solution and add cold water. The formed precipitate was filtered and dried.

Quinazolinones and quinazolidine diones tested for antimicrobial activity against *Escherichia coli*, *Bacillus cereus*, *Staphylococcus aureus* by using cup plate method with reference to the standard Streptomycin. After 24 hrs of incubation, zone of inhibition was measured (Table 2) and compare the antimicrobial activity of synthesized compounds (3a-3d) with standard (Fig. 5).

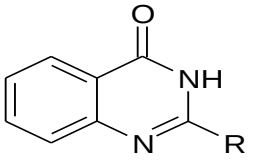

Fig. 1: 4(3*H*) quinazolinone

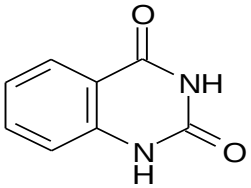

Fig. 2: 4(1*H*,3*H*) quinazolinedione

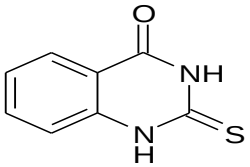

Fig. 3: 4(1*H*,3*H*) quinazolinone-2-thione

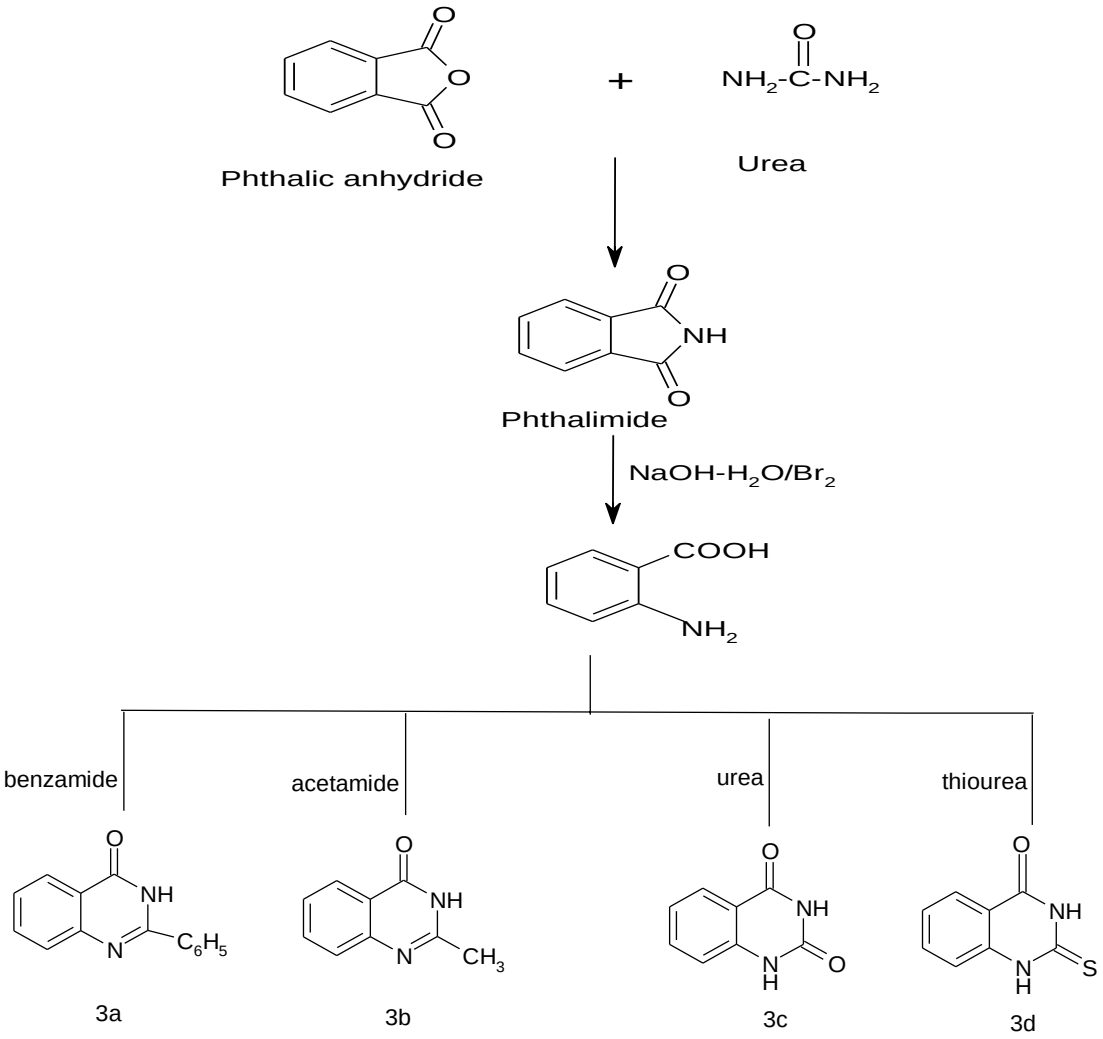

Fig. 4: Schematic representation

Table 1: Physical data of the synthesized compounds

Compound	Molecular formula	Molecular weight (gm)	Melting point (˚C)	% yield	R_f value
3a	$C_{14}H_{10}N_2O$	222	130	32	0.72
3b	$C_9H_8N_2O$	160	125	50	0.80
3c	$C_8H_6N_2O_2$	164	200	45	0.73
3d	$C_8H_6ON_2S$	178	170	40	0.88

Table 2: Anti-microbial activity results

S. No.	Name of organism	Average zone of inhibition (mm)				
		Standard (5 mg/ml)	3a (2 mg/ml)	3 b (2 mg/ml)	3 c (2 mg/ml)	3d (2 mg/ml)
1.	E. coli	10.8	10.6	10.3	10.5	10.8
2.	B. cereus	10.5	20	10.4	10.6	20.1
3.	S. aureus	10.4	10.2	10.5	10.7	20

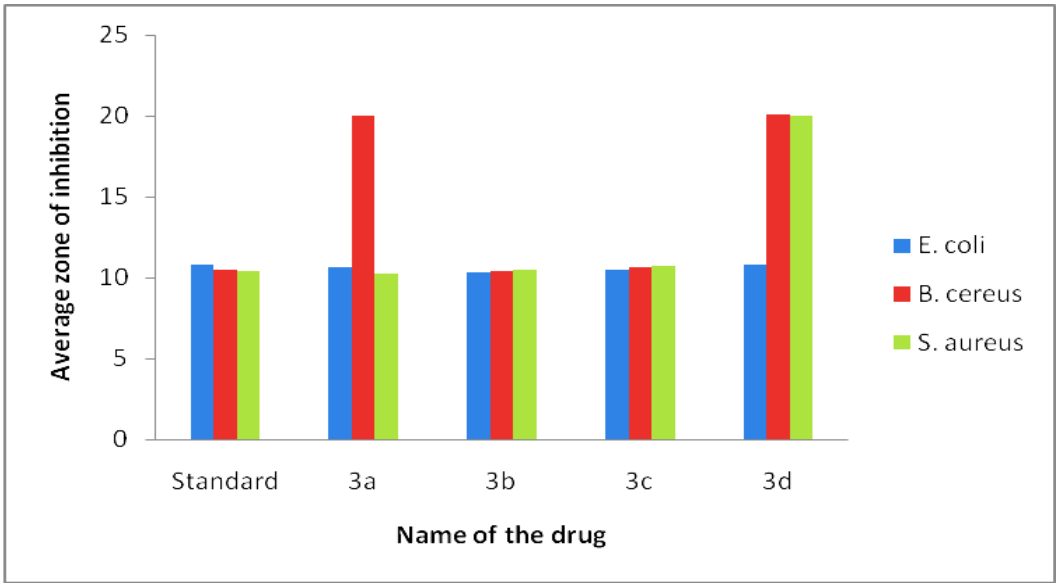

Fig. 5: Comparative antimicrobial activity of synthesized compounds (3a, 3b, 3c, 3d)

Conclusion

Anthranilic acid was synthesized from phthalimide. Synthesized anthranilic acid was treated with urea, thiourea, benzamide and acetamide to give corresponding titled compounds (3a-3d) in good yields. Synthesized compounds were characterized by physical data (Molecular formula, Molecular weight, Melting point and R_f value) and spectral data (IR spectra & H^1 NMR). Further titled compounds (3a-3d) tested for antimicrobial activity. All the titled compounds show good antimicrobial activity against *Escherichia coli*, *Bacillus cereus*, *Staphylococcus aureus* with respect to standard. Specifically 3a compound possess good antimicrobial activity against *Bacillus cereus* where as 3d compound shows very good antimicrobial activity against *Bacillus cereus*, *Staphylococcus aureus.*

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