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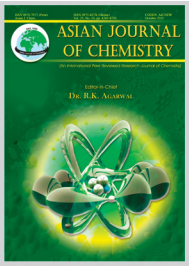

Synthesis and Evaluation of Quinazoline Derivative as Antimicrobial and Surface Active Agent

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Anthranilic acid reacted with benzoyl chloride to produce 2-substituted 3,1-benzoxazin-4-one which was used as starting material to synthesize 3-{[*bis*(4-fluorophenyl)methylidene]amino}-2-phenylquinazolin-4(3*H*)-one. The products were subjected to reaction with required mole of sodium lauryl sulfate to produce a novel surfactant having antibacterial and surface active properties which can be used in the manufacturing of drugs, cosmetics, pesticides or can be used as antibacterial additives. The surface active properties as surface and interfacial tension, cloud point, foaming height, wetting time and emulsification power were determined. The antimicrobial activities were also screened.

Key Words: Quinazoline derivative, Surfactant, Antimicrobial activity.

INTRODUCTION

One of the most important groups of surfactants with growing industrial interest is the nonionics, which are second largest class of surfactants. These are compatible with other surfactant also. Sodium lauryl sulphate is non-ionic surfactant commonly used in cosmetic cleansers, hair shampoos, bath and shower gels, bubble baths, *etc*. Several quinazoline derivatives have pharmaceutical and industrial applications. Sodium lauryl sulfate has very well water solubility and have 40 HLB value. This encouraged us to synthesize a novel surface active agent containing quinazoline nucleus because quinazoline derivative has poor water solubility. Low water solubility of the quinazoline derivatives is the major impediment to achieve lower MIC values. These compounds have a double function such as antimicrobial and surface active agents which may serve in the manufacturing of drugs, cosmetics, pesticides or as antibacterial and/or antifungal agents. The surface properties such as surface and interfacial tension, cloud point, foaming height, wetting time and emulsification power were determined. Their antimicrobial properties were also screened.

EXPERIMENTAL

The melting points of newly synthesized compounds were determined with an electro thermal melting point apparatus. The homogeneity of all newly synthesized compounds was checked by TLC on silica gel-G coated plates using petroleum ether:ethylacetate:methanol (1:1:0.3) solvent system.

The purity of compound was checked by IR, NMR and mass of compounds. IR spectra (KBr pellet) were recorded on FTIR 500 (Perkin-Elmer) instrument. ^{1}H NMR spectra were recorded on 400 FT NMR instrument at 400 MHz in $CDCl_3$ are reported in ppm.

Synthesis of 2-phenyl-3, l-benzoxazin-4-one: To a solution of anthranilic acid (0.1 mol) dissolved in pyridine (60 mL), benzoyl chloride (0.2 M) was added. The mixture was stirred for 0.5 h followed by treatment with 5 % $NaHCO_3$ (15 mL). The solid obtained was finally crystallized from ethanol, yield: 80 %, m.p. 120 °C; IR (KBr, ν_{max}, cm^{-1}): 3350 (NH), 1780 (C=O) 1680 (cyclic C=O) and 1620 (C=N); NMR ($CDCl_3$): 6.8-7.5 (m, 9H, ArH); MS (m/z) 223 (M1).

Synthesis of 3-amino-2-phenyl quinazolin-4(3*H*)-one: A mixture of 2-phenyl-3-benzoxazin-4-one (0.05 mol) and hydrazine hydrate (0.05 M) in ethanol was refluxed for 3 h and cooled. The separated solid was crystallized from ethanol, yield: 85 %, m.p. 196 °C; IR (KBr, ν_{max}, cm^{-1}): 3300 (NH_2), 1680 (cyclic C=O), 1620 (C=N) and 1600 (C=C); ^{1}H NMR ($CdCl_3$): 4.5 (2H, NH_2), 6.7-7.4 (9H, ArH); MS (m/z) 237 (M1).

Synthesis of 3-{[*bis*(4-fluorophenyl)methylidene]-amino}-2-phenylquinazolin-4(3*H*)-one (QD): A mixture of 3-amino-2-phenylquinazoline-4(3*H*)-ones (0.01 mol), ethanol (10-15 mL) and substituted difluoro benzophenone (0.01 mol) were refluxed with stirring on water bath for 8-9 h. The resulting mixture was transferred to the beaker and ice-cooled water was added to it. The separated solid was filtered, washed with water and recrystallized from solvent to give compounds. General scheme is given in **Chart-I**.

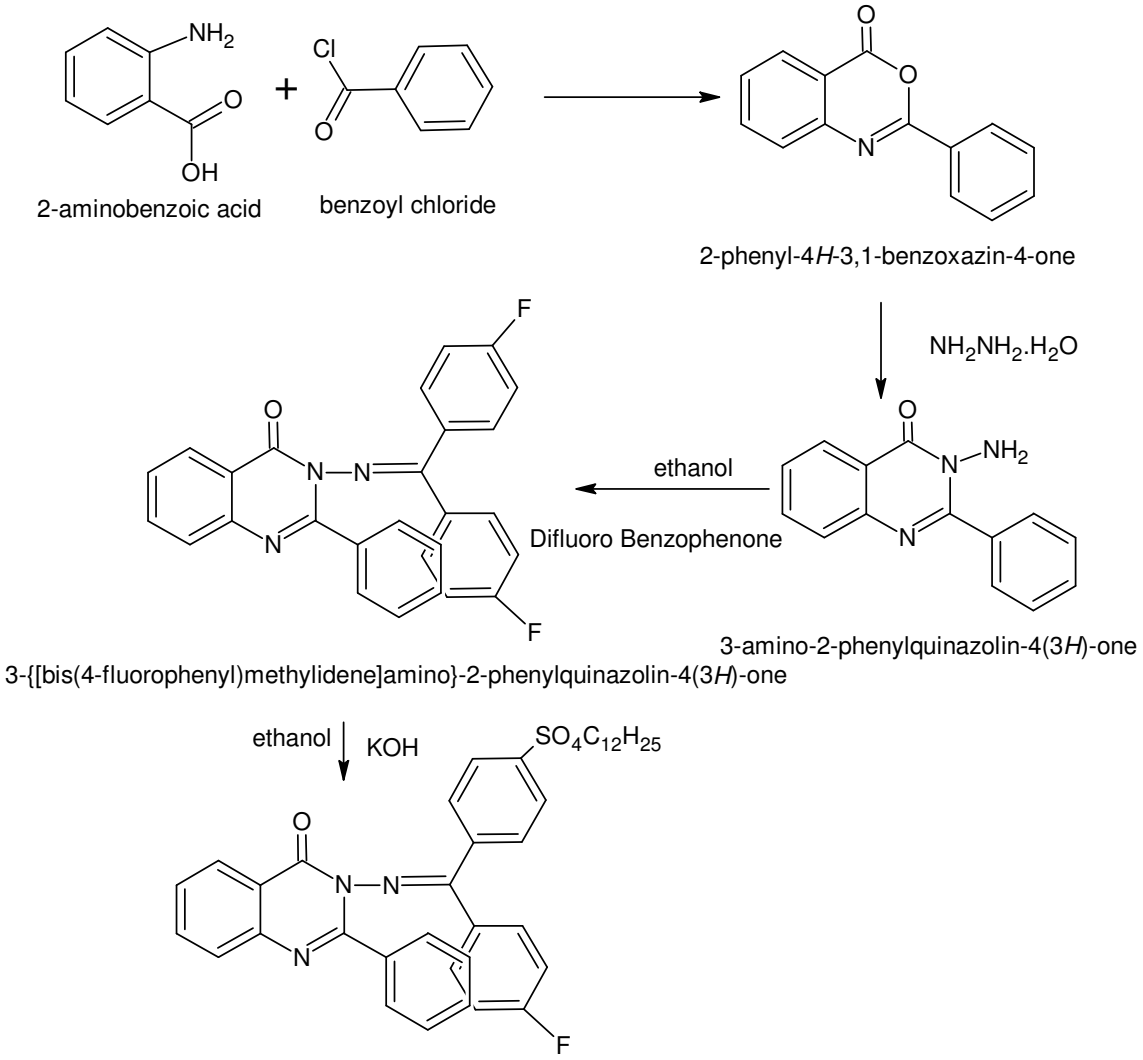

Chart-I: General scheme for synthesis of surfactant

Recrystallization solvent: Ethanol, IR (cm^{-1}): 1674 (C=O), 1614 (C=C), 1593 (C=N), 1554 (ar C=C), 1469 (C=C), 1373 (C-N), 1184 (Ar-F); ^1H NMR ($CdCl_3$): 7.1 (Ar-H), 6.5 (Ar-F); MS m/z 437 (M+).

Conversion of the prepared compound to surfactant: The synthesized compound was screened on their antimicrobial activity. The procedure was tried with other quinazoline derivatives but yield was very poor and difficult to synthesize. A solution of compounds (0.01) and sodium lauryl sulphate (0.01 mol) were refluxed 12 h in boiling ethanol (20 mL) in the presence of potassium hydroxide. Then mixtures were evaporated on water bath and excess ethanol was removed and crystallized by ethanol. Structure was confirmed by TLC, IR, CH analysis, mass and NMR. Yield: 45 %, UV λ_{max}: 245 nm R_f: 0.77 (Petroleum ether:ethyl acetate:methanol) m.p. 160 ºC; ^1H NMR ($CdCl_3$): MS m/z 683 (M^+).

Evaluation of physical properties

Surface and interfacial tension: Surface tension was measured using stalgmometer with 0.1% w/v aqueous solution at room temperature (25 ºC)[1].

Cloud point: Cloud point was determined by gradually heating 1 % w/v solution in a controlled temperature bath and recording the time at which the clear or nearly clear solutions became definitely turbid. The reproducibility of this temperature was checked by cooling the solutions until they become clear again[2].

Wetting time: Wetting time was determined by immersing a sample of cotton fabric in a 1 % w/v aqueous solution of surfactants[3]. Thus, they can find a wide application in textile industry.

Foaming properties: Foaming properties were measured by known procedure[4]. In this procedure, a 25 mL solution (0.1 w/v %) was shaken vigorously for 10 s in a 100 mL glass stopper, graduated cylinder at 25 ºC. the solution was allowed to stand for 30 s and the foam height was measured.

Emulsification stability: Emulsification stability was prepared from 10 mL of a (0.1 % w/v) aqueous solution of surfactant and 5 mL of liquid paraffin at 40 ºC. The emulsifying property was determined by the time it took for an aqueous volume separating from the emulsion layer to reach 9 mL counting from the moment the shaking was stopped[5].

Determination of critical micelle concentration (CMC): The critical micelle concentration of surfactant was determined by plotting surface tension values against the concentration of each surfactant.

Antibacterial testing by disc diffusion: The antibacterial activity of the surfactant was tested *in vitro* using disc diffusion method[6]. Bacterial inoculums were prepared from overnight grown cultures (24 h) in nutrient broth (Himedia) and turbidity was adjusted equivalent to 0.5 McFarland units (*ca.* 10^8 cfu/mL). Aliquots (100 µL) of inoculums were spread over the surface of Mueller Hinton Agar (Difco) plates with a sterile glass spreader. Sterilized paper discs (Oxoid, 6 mm diameter) were wetted with 10 µL of a solution of each compound to be tested, in the concentration of 0.02 g/mL in DMF. The plates were then incubated 24 h at 37 °C. The formed inhibition zones were measured in mm. The values are reported at Table-2 as a mean of three replicates.

RESULTS AND DISCUSSION

A number of research programs are aimed at increasing the antimicrobial performances of molecules by introducing new molecular parameter such as heteroatoms[7], chemical functions[8-11], aromatics[12] or non aromatic cyclic substituents[13]. Formulation studies are also an active field of research[14].

Surface active properties: The investigation of the surface active properties of the compounds has been done in the neutral medium (pH 7.3), at a concentration of 0.3 w/v %. These types of surfactants are especially interesting because they are not the most common. Therefore the traditional procedure was used to follow up the properties. The physical properties are represented in Table-1.

TABLE-1
PHYSICAL PROPERTIES OF SURFACTANT

Physical properties	Value
Colour	White crystal
Surface tension (0.3 %)	27 (dyne/cm)
Foam height (0.1 %)	3 ± 1 cm
Emulsion stability (0.1 %)	25 ± 2 min
Wetting time	10 ± 2 sec
Cloud point	60 ± 5 ºC
pH	7.3 ± 0.1

Surface tension: It is evident that the products obtained have pronounced surface activity.

Cloud point: A very important factor in making the most efficient use of nonionic surfactants in aqueous system is an understanding of the property called cloud point. The cloud point of the prepared surfactants is less than 100 ºC.

Wetting time: For the prepared compounds, at all points of the investigation, the synthesized surfactants were efficient wetting agents.

Foam power: Foam power was also investigated for the nonionic compounds and is generally rated as foamy. The foam height of the prepared surfactants was measured. A low foaming power has an application in the dyeing industry[15].

Emulsion stability: Studies are still being carried out on the use of surfactants in emulsion formation which is of immense importance to technological development. It was proven that the emulsifying stability of the prepared surfactants those containing heterocyclic nucleus exhibit moderate emulsifying properties. The results might lead to the application of the surfactants of choice in the manufacturing of pesticides and cosmetics.

Critical micelle concentration (CMC): Fig. 1 shows the effect of varying the concentration of drug on the surface tension of their solution at a constant temperature (25 ºC). The value of CMC for drug was found to be 0.3 %. Hydrophobic group is an important driving force in micellization. Increase in hydrophobic character, decrease in CMC value. The number of carbon atoms was found to be a determining factor in the values of CMC[16].

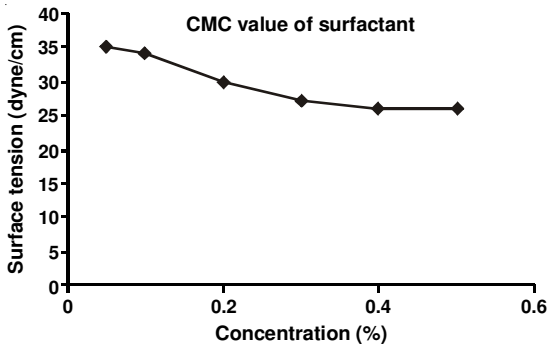

Fig. 1. Effect of concentration of drug on surface tension

Biological activity: It has been observed that, surfactant has remarkable antimicrobial activity towards the selected bacteria than quinazoline derivative. The presence of heterocyclic moiety in the prepared nonionic surfactant molecule revealed an increase in the biological activity. It is therefore clear that this surfactant is effective and inhibited the growth of all tested microorganisms. Introducing lauryl sulphate increase hydrophillicity of compound which help in enhancement of antimicrobial property shown in Table-2.

TABLE-2
ZONE OF INHIBITION WITH DIFFERENT MICROBES

Compound	Zone of inhibition (mm)			
	S. aureus	*B. subtilis*	*S. dysentriae*	*E. coli*
QD	19	15	21	18
Surfactant	25	21	29	20
DMF (control)	–	–	–	–
Standard (ciprofloxacin)	25	20	28	22

*Conc. 100 µg/mL; QD = Quinazoline derivatives; DMF = Dimethyl formamide

Conclusion

From the results, one may concluded that prepared surfactants have good emulsifier properties in non edible media such as cosmetic, detergent and Soaps. New quinazoline derivative bearing long alkyl chain with hydrophilic center in a single molecular framework likely to constitute a new biologically active surfactants compounds which may serves in the manufacture of drugs, cosmetics, pesticide, antibacterial and/or antifungal.

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