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Synthesis and Microbial Activity of Novel Quinazoline Derivatives

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Abstract: A series of new 1-allyl-6-bromo-2,3-dihydro-3-methylbenzo(h)quinazolin-4(1H)-one, 1-benzyl-6-bromo-2,3-dihydro-3-methylbenzo(h)quinazolin-4(1H)-one and 6-bromo-2,3-dihydro-3-methyl-1-propylbenzo(h)quinazolin-4(1H)-one were synthesized by the reaction of substituted methyl-1-aminonaphthalene-2-carboxylate. The biological screening showed that above compounds have shown most potent biological activity. The functional groups were identified with the help of FT-IR spectra. Nature of protons present was examined by using ^{1}HNMR.
Keywords: Naphthalene, quinazoline, biological activity.

Introduction:

In the recent years, the problem of multidrug resistant micro-organisms has reached on alarming level around the world and the synthesis of new anti-infective compounds has become an urgent need for the treatment of microbial infections. Naphthalene, quinazoline and their heterocyclised products exhibit miscellaneous biological activity, as well as antibacterial, anti fungicidal, analgesic, anti-inflammatory activity [(1-5)]. These heterocyclic systems find wide use in medicine, agriculture and industry. The core structure is widely used in clinically very important antibiotics like penicillin, thenamycins and quinoline-based compound. Among them fluoroquinolones are known to display anti- tubercular activity, mefloquine is known for its antibacterial and anti-tubercular activity [(6-7)]. A large number of heterocyclic compounds have been investigated for their various biological activities. In view of above facts, this research work is aimed to design and synthesis of series of new 1-allyl-6-bromo-2, 3-dihydro-3-methylbenzo (h) quinazolin-4(1H)-one, 1-benzyl-6-bromo-2,3-dihydro-3-methylbenzo(h)quinazoline-4(1H)-one and 6-bromo-2,3-dihydro-3-methyl-1-propyl benzo (h) quinazolin -4(1H)-one compounds. Their biological activities were examined and reported in this paper.

Experimental methods:

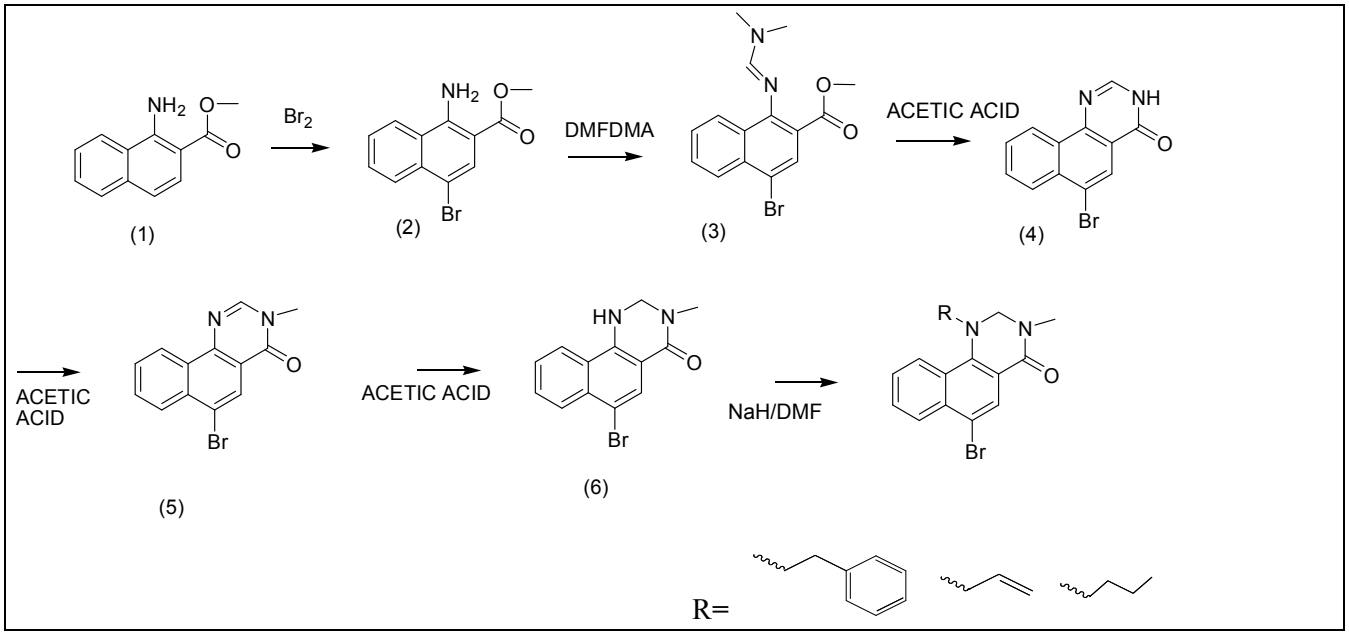
The synthesis of novel quinazoline derivatives involved in multiple steps (Scheme-1) and their microbial studies were described below.

Preparation of 6-bromo-2, 3-dihydro-3-methylbenzo (h) quinazolin-4(1H)-one.

A stirred solution of methyl 1-aminonaphthalene-2-carboxylate **(1)** (350mg, 1.73mmol) was mixed in the solution of 1, 4-dioxane and t-butanol. It was cooled to 0°C. Bromine (320mg, 2mmol) was added slowly

in the above solution under nitrogen atmosphere. The reaction mixture was stirred well for 3 hours at room temperature. After completion of reaction, the obtained product was washed with water. Then it was filtered and dried to get methyl 1-amino-4-bromonaphthalene-2-carboxylate **(2)**. A stirred solution of methyl 1-amino-4-bromonaphthalene-2-carboxylate (350 mg, 1.2mmol) was added with N, N-dimethylformamide dimethylacetal (1.19ml, 8.9mmol) and heated to 100°C for 16 hours. After completion of reaction, the obtained product was washed with diethyl ether to get pure methyl 4-bromo-1-((E)-formamido) naphthalene-2-carboxylate **(3)**. A stirred solution of methyl 4-bromo-1-((E)-formamido) naphthalene-2-carboxylate (250mg, 0.74mmol) in ammonium acetate, acetic acid and heated to 50°C for 16 hours. After completion of reaction, the obtained product was washed with water, filtered and dried to get pure 6-bromobenzo (h) quinazolin-4(3H)-one **(4)**. A stirred solution of 6-bromobenzo (h) quinazolin-4(3H)-one (200mg, 0.72mmol) in dimethylformamide (5ml) and the solution was cooled to 0°C. Then NaH (35mg, 0.86mmol) was added and stirred for 30min. After methyl iodide (103mg, 0.72mmol) was added and stirred for 1hour at room temperature. After completion of reaction, saturated ammonium chloride solution was quenched and extracted to dichloromethane. It was washed with water and dried to over sodium sulphate to get 6-bromo-3-methylbenzo (h) quinazolin-4(3H)-one **(5)**. The crude product was preceding next step without further purification.

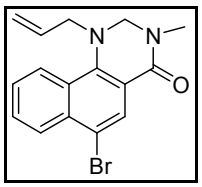
The stirred solution of 6-bromo-3-methylbenzo (h) quinazolin-4(3H)-one (200mg, 0.69mmol) in acetic acid and zinc dust (50mg, 0.69mmol) were added and stirred for 2 hours at room temperature. After completion of reaction, the reaction mass was diluted with ethyl acetate and filtered through celite pad, washed with excess of ethyl acetate. The filtrate was concentrated and purified by column chromatography to get pure 6-bromo-2, 3-dihydro-3-methylbenzo (h) quinazolin-4(1H)-one **(6)**.



Scheme-1

Preparation of 1-allyl-6-bromo-2, 3-dihydro-3-methylbenzo (h) quinazolin-4(1H)-one (6a)

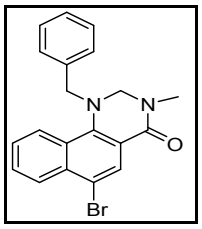
The stirred solution of 6-bromo-2, 3-dihydro-3-methylbenzo (h) quinazolin-4(1H)-one (40mg, 0.68mmol) is added in dimethylformamide (1ml) and cooled to 0°C. Then NaH (24mg, 1.02mmol) was added and stirred for 30 min. Allyl bromide (1.02mmol) was added and stirred for 1 hour at room temperature. After completion of reaction, saturated ammonium chloride solution was quenched and extracted to dichloromethane, washed with water and dried. The combined organic layer was concentrated. The residue was purified by column chromatography to get pure 6-bromo-2, 3-dihydro-1, 3-dimethylbenzo (h) quinazolin-4(1H)-one **(6a)**.



(6a)

Preparation of 1-benzyl-6-bromo-2, 3-dihydro-3-methylbenzo (h) quinazolin-4(1H)-one (6b)

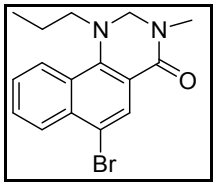
The stirred solution of 6-bromo-2, 3-dihydro-3-methylbenzo (h) quinazolin-4(1H)-one (40mg, 0.68mmol) is added with dimethylformamide (1ml) and cooled to 0°C. Then NaH (24mg, 1.02mmol) was added and stirred for 30min. Benzyl bromide (1.02mmol) was added and stirred for 1hour at room temperature. After completion of reaction, saturated ammonium chloride solution was quenched and extracted to dichloromethane, washed with water and dried. The combined organic layer was concentrated. The residue was purified by column chromatography to get pure 1-benzyl-6-bromo-2, 3-dihydro-3-methylbenzo (h) quinazolin-4(1H)-one **(6b)**.



6b)

Preparation of 6-bromo-2, 3-dihydro-3-methyl-1-propylbenzo (h) quinazolin-4(1H)-one (6c)

The stirred solution of 6-bromo-2, 3-dihydro-3-methylbenzo (h) quinazolin-4(1H)-one (40mg, 0.68mmol) is added with dimethylformamide (1ml) and cooled to 0°C. Then NaH (24mg, 1.02mmol) was added and stirred for 30min. Bromo propane (1.02mmol) was added and stirred for 1hr at room temperature. After completion of reaction, small amount of saturated ammonium chloride solution was quenched and extracted to dichloromethane, washed with water and dried. The combined organic layer was concentrated. The residue was purified by column chromatography to get pure 6-bromo-2, 3-dihydro-3-methyl-1-propylbenzo (h) quinazolin-4(1H)-one **(6c)**.



(6c)

Results and discussion:

For industrial applications of compound information of melting point is mandatory. The melting points of synthesized compounds (6a – 6c) were found with the help of Gallenkamp apparatus in open capillaries. In order to confirm the functional groups present in these compounds, FT-IR spectra were recorded on Perkin Elmer spectrum RXI spectrophotometer. To identify the nature of proton present in these compounds, NMR spectra were recorded by using Brucker FT-NMR 500MHz. As these compounds were to be used for pharmaceuticals applications, there should not be any impurities present in these compounds. The purity of these compounds was tested by TLC was identified by UV, $KMnO_4$ and iodine chamber.

The reaction scheme for the synthesis of compound (6a-6c) is shown in above. The yield, physical and spectral data are tabulated in Table 1.

Antibacterial Activities:

Agar well diffusion method was employed to ascertain the antimicrobial activity of newly synthesized compounds. All the compounds were tested for their antibacterial activity against *Bacillus substilis, Staphylococcus aureus* (Gram positive bacteria), *Escherichia coli*, and *Pseudomonas aeruginosa* (Gram negative bacteria) using nutrient agar medium (Table 3). Antifungal activity was carried out against *Aspergillus niger* and *Fusarium oxyporium* using potato dextrose agar medium (Table 4). DMSO was used as solvent control. The compounds were tested at a concentration of 100 µg/ ml against both bacterial and fungal strains.

Mass spectrum analysis:

The molecular weight of the compounds were estimated as given in Table.2

Table.1 Yield, physical and spectral data

Comp.	Formula	M.P	Yield	Spectral data
6a	C16H15BrN2O	96-98^{0}C	55%	IR (%T, cm^{-1}): 3435 (NH), 2833. (- CH3), 2719 (-NCH_3), 1591(C=O), 1364 (CN), 768 (C-Br). ^{1}H NMR: (DMSO, 500 MHz, δ ppm) 3.01(s, 3H, -CH3), 3.63(s,3H,-NCH_3), 3.76-3.77(d,2H,6Hz, -CH_2), 5.28-5.30(m,1H, Ar-H), 5.36-5.42(m,1H,Ar-H), 6.02-6.12(m,1H,Ar-H), 7.72-7.76(m,1H, Ar-H), 7.80-7.83(m,1H, Ar-H), 8.14(s, 1H, Ar-H), 8.17-8.21(m, 2H, Ar-H).
6b	C20H17BrN2O	89-90^{0}C	70%	IR (%T, cm^{-1}): 3434(NH), 2965(Ar-CH), 1362 (CH_3), 771(C-Br). ^{1}H NMR: (DMSO, 500 MHz, δ ppm) 2.86(s, 3H, -CH3), 4.32(s,3H,-NCH_3), 4.55(s,2H, -CH_2), 7.30-7.31(m,1H, Ar-H), 7.34-7.37(m,1H,Ar-H), 7.40-7.45(m,4H,Ar-H), 7.76-7.79(m,1H, Ar-H), 7.82-7.85(m,1H, Ar-H), 8.15(s,1H, Ar-H), 8.21-8.27(m,1H, Ar-H), 8.36-8.38(m, 1H, Ar-H).
6c	C16H17BrN2O	103-105^{0}C	62%	IR (%T, cm^{-1}): 3429(NH), 2834(-CH), 2720 (-NCH_3), 1593 (C=O), 1367 (CH_3), 765 (C-Br). ^{1}H NMR: (DMSO, 500 MHz, δ ppm) 3.25(s, 3H, -CH3), 3.60(s, 3H,-NCH_3), 3.70-3.71(d, 2H, 5.8Hz, -CH_2), 5.22-5.26 (m, 1H, Ar-H), 5.38-5.42(m, 1H, Ar-H), 6.22-6.24(m, 1H, Ar-H), 7.71-7.74 (m,1H, Ar-H), 7.88-7.89(m, 1H, Ar-H), 8.14 (s, 1H, Ar-H), 8.19-8.21(m, 2H, Ar-H).

Table.2 Molecular weight

Compound	Molecular weight	
	Calculated value	Observed value (M+1)
6a	331.21	332.10
6b	381.12	382.00
6c	333.22	335.21

About 15-20 ml of the sterilized media was poured onto the sterilized petri dishes and allowed to solidify. Wells of 6 mm diameter was made in the solidified media with the help of sterile borer and solutions of the test compounds were added with the help of micropipette. A sterile swab was used to evenly distribute microbial suspension over the surface of solidified media. The plates were incubated at 37°C for 24 hrs in the

case of antibacterial activity and 72 hrs at 25°C for antifungal activity. The zone of inhibition was measured in mm scale.

Table: 3. Antibacterial activity of synthesized compound

Compound	Zone of inhibition (mm) at 100µg/ml concentration			
	Bacillus Substilis	***Staphylococcus aureus***	***Escherichia coli***	***Pseudomonas aeruginosa***
6	11	10	10	-
6a	15	16	15	15
6b	17	15	18	19
6c	13	-	13	11

Table: 4. Antifungal activity of synthesized compounds

Compound	Zone of inhibition (mm) at 100µg/ml concentration	
	Fusarium oxyporium	***Aspergillus niger***
6	15	15
6a	12	14
6b	12	14
6c	-	12

Biological activity:

Antimicrobial studies:

All the synthesized compounds were screened for antimicrobial activity by agar well diffusion method. The results showed that among the tested compounds 6a, 6b exhibited good activity against both gram positive and gram negative bacteria. Compound 6 is less active against *Staphylococcus aureus* and *Escherichia coli*. Compound 6 and 6c show inactive against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The compounds 6, 6b are well active against *Aspergillus niger* and *Fusarium oxyporium*. Compound 6c do not exhibited antifungal activity. Compound 6a showed least activity towards *Aspergillus niger* and *Staphylococcus aureus* and remaining compounds showed moderate activity.

Conclusion:

In this study a series of novel heterocyclic compounds containing quinazoline derivatives were synthesized .The presence of functional groups were identified with the help of FT-IR and ^{1}HNMR spectral analysis. The molecular weights of the synthesized compounds were estimated by Mass Spectrum. Melting points of these compounds were found and reported. These compounds were also undergone for antimicrobial activity. The synthesized series showed excellent to good activity against Gram-negative micro-organisms (*Pseudomonas aeruginosa* and *Escherichia coli*) and the least activity against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus substilis*). All compounds of the series exhibited moderate to less antifungal activity against *Aspergillus niger* and *Fusarium oxyporium*. The screening results revealed that most of the compounds were found to exhibit significant antimicrobial activity.

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