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Synthesis of Quinazoline Derivatives and their Biological Activities

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A series of novel 4-oxo-2-phenyl-4*H*-quinazoline-3-carboxylic acid (4-substituted phenyl amides) have been synthesized by condensing 2-phenyl-3,1-benzoxazine-4-one and 4-substiuted phenyl ureas. A mixture of N-benzoyl anthranilic acid and acetic anhydride was condensed to form 2-phenyl-3,1-benzoxazine-4-one and various 4-substituted anilines were condensed with sodium cyanide to form 4-substituted phenyl ureas. The structures of the synthesized compounds were also elucidated. The synthesized compounds were found to have significant effect against the tested microorganisms.

Key Words: Synthesis, Quinazolines, Antibacterial, Antifungal.

INTRODUCTION

Quinazoline nucleus has attracted attention of medicinal chemists, due to wide spectrum of biological activities exhibited by them. Quinazoline and condensed quinazolines have exhibited a variety of biological activities like analgesic, antiinflammatory[1], antihypertensive[2], antihistaminic, anticancer[3-5], sedative, hypnotic and antimicrobial activities[6,7]. From the various quinazolines reported the C-2 and N3 disubstituted quinazolines exhibited interacting pharmacological activities. The literature reveals that the phenyl ureas show a wide range of biological spectrum like anticonvulsant, anticancer, antiviral and antimicrobial activities.

In spite of large number of quinazoline and phenyl ureas have been synthesized and studies have done for various pharmacological activities, however, quinazolinyl amide derivatives were not reported so far. Hence, the present study is devoted to synthesize some quinazolinyl amide derivatives and to explore their possible biological activities.

EXPERIMENTAL

The melting points were taken in open capillary tubes in concentrated sulphuric acid melting point bath and therefore the values reported are uncorrected. UV spectra were recorded on Shimadzu 1700, UV-Vis spectrophotometer and spectral grade

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ethanol was used as solvent. The IR spectra of the compounds were recorded in the region, 4000-400 cm^{-1} using KBr discs on JASCO 4100 FTIR and the NMR spectral study was done using DMSO as solvent on JOEL FX90Q, FOURIER transform-NMR spectrometer. The purity of the compounds was checked by TLC, using plates coated with silica gel G, benzene:chloroform as mobile phase and iodine vapour as detection method.

Preparation of N-benzoyl anthranilic acid: Benzoyl chloride (0.05 mol) was added dropwise to a stirred solution of anthranilic acid (0.05 mol) in dimethyl formamide (70 mL) and the reaction mixture was stirred at room temperature for 2 h. Water (100 mL) was then added with stirring and the separated solid was washed with water, dried and recrystallized from ethanol.

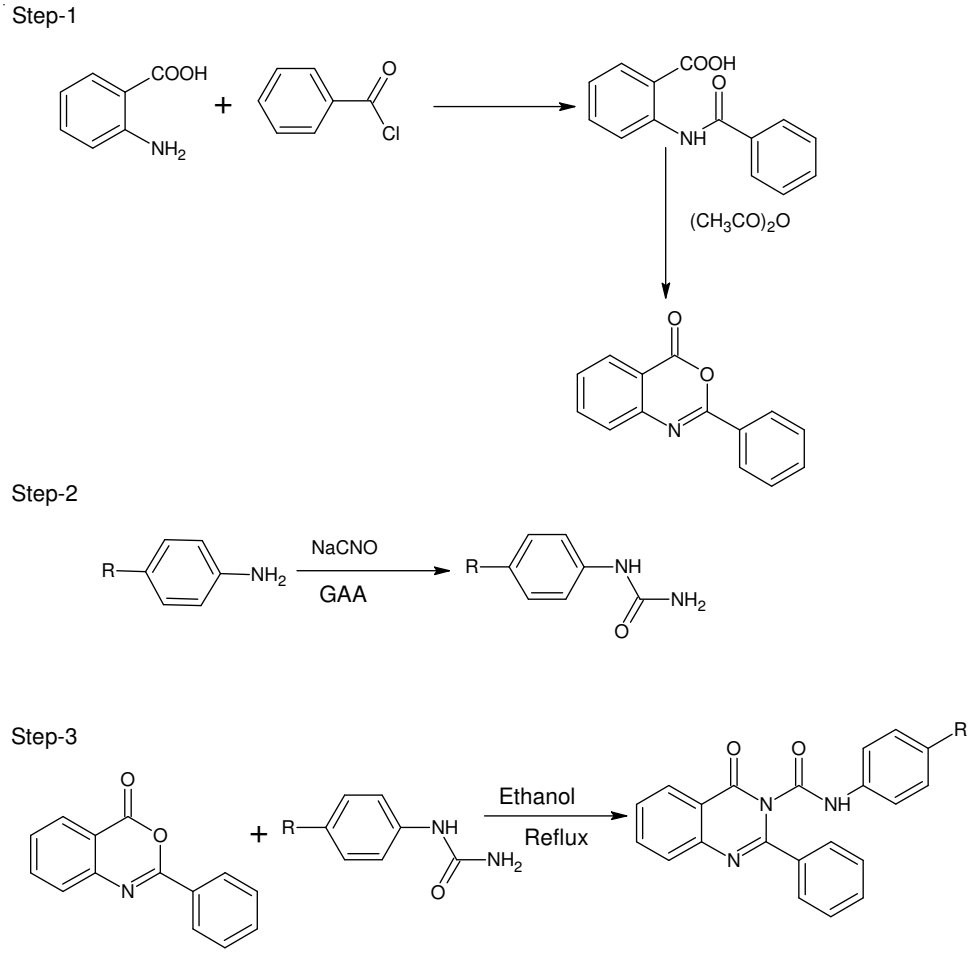
Preparation of 2-phenyl-4*H*-3,1-benzoxazin-4-one: A mixture of N-benzoyl anthranilic acid (0.0l mol) and acetic anhydride (10 mL) was heated under reflux for 3 h at 80 °C. Excess acetic anhydride was evaporated under reduced pressure and the obtained solid was recrystallized with petroleum ether.

Preparation of 4-substituted phenyl ureas[8]: 4-Substituted aniline (0.1 mol) was grind well in a glass mortar and dissolved in a mixture of 10 mL glacial acetic acid and 90 mL water. A solution of sodium cyanate (0.1 mol) in 50 mL hot water was slowly added to the amine solution with continuous shaking and allowed to stand for 0.5 h then, cooled in ice for another 0.5 h. A white solid was obtained and recrystallized by using absolute ethanol.

Preparation of quinazolines: A mixture of 2-phenyl-4*H*-3,1-benzoxazin-4-one and 4-substituted phenyl urea was dissolved in 50 mL of absolute ethanol and heated under reflux for 3 h. On cooling the separated solid was washed with water and recrystallized by using a mixture of water and acetic acid (**Scheme-I**).

Antibacterial activity: Muller Hinton agar medium was prepared and transferred into sterile Petri plates. l00 µL of the standardized bacterial inoculum was spread on agar medium using sterile cotton swab. The sample impregnated discs were placed on the inoculated agar medium. Negative control was prepared by using the same solvent employed to dissolve the CODE plant extracts. Ofloxacin 5 µg/disc was used as positive reference standard to determine the sensitivity of each microbial species tested. All the Petri plates were incubated at 37 °C for 24 h. After the incubation, the diameter of zone of incubation was measured.

Antifungal activity: Sabouraud dextrose agar medium was prepared and transferred into sterile Petri plates. l00 µL of the standardized fungal inoculum was spread on agar medium using sterile cotton swab. The sample impregnated discs were placed on the inoculated agar medium. Negative control was prepared using the same solvent employed to dissolve the plant extracts. Clotrimazole 10 µg/disc was used as positive reference standard to determine the sensitivity of each microbial species tested. All the Petri plates were incubated at 27 °C for 72 h. After the incubation, the diameter of zone of incubation was measured.



Scheme-I

RESULTS AND DISCUSSION

The physical characterization data of all the synthesized compounds *viz.,* 4-oxo-2-phenyl-4*H*-quinazoline-3-carboxylic acid (4-chloro phenyl)amide (C1Q), 4-oxo-2-phenyl-4*H*-quinazoline-3-carboxylic acid (4-bromo phenyl)amide (BrQ), 4-oxo-2-phenyl-4*H*-quinazoline-3-carboxylic acid (4-nitro phenyl)amide (NO_2Q), 4-[(4-oxo-2-phenyl-4*H*-quinazoline-3-carbonyl)amino]benzoic acid (PABAQ) and 4-oxo-2-phenyl-4*H*-quinazoline-3-carboxylic acid (4-sulfanoyl phenyl)amide (SO_2Q) are given in Table-1.

Spectral studies

UV spectra: All newly synthesized compounds λ_{max} were recorded by using ethanol as solvent. It proves further confirmation of the compound formed (Table-1).

TABLE-1
PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS

Compound	m.f.	m.w.	m.p. (ºC)	R_f value	λ_{max} (nm)
C1Q	$C_{21}H_{14}N_3O_2Cl$	375.81	135-137	0.702	312
NO_2Q	$C_{21}H_{14}N_4O_4$	386.37	130-132	0.785	311
B_rQ	$C_{21}H_{14}N_3O_2Br$	420.46	120-122	0.545	313
PABAQ	$C_{21}H_{15}N_3O_4$	373.37	165-170	0.492	294
SO_2Q	$C_{21}H_{16}N_4O_4S$	420.44	238-240	0.412	242

IR spectra: The characteristic absorption peaks were observed for all relevant groups. The absorption peaks around 1600 cm^{-1} indicates the formation of C=N ring atoms of quinazoline, amide N-H stretching vibrations were observed in the region of 3500-3140 cm^{-1}. Amide C=O stretching vibrations were observed near 1690-1640 cm^{-1} and all other relevant groups absorption were observed for all the synthesized compounds.

NMR spectra: Aromatic protons were observed 6.68- 8.13 δ ppm. Amide N-H proton were observed at 6.05-6.40 δ ppm, for all the synthesized compounds.

Antibacterial screening: All synthesized compounds were evaluated for *in vitro* antibacterial activity against seven pathogenic bacterial by standard agar dilution method. The zone of inhibition was determined using ofloxacin as reference standard. All quinazoline derivatives showed significant antibacterial activity against tested pathogens. However, none of the synthesized compounds were superior to the standard ofloxacin (Table-2). All the compounds were active against *Klebsiella aerugenes* and *Salmonella typhi*. Compounds BrQ, NO_2Q and C1Q were not active against *Staphylococus aures*. Among the synthesized compounds NO_2Q and C1Q were found to be more potent compounds in the series.

TABLE-2
ANTIMICROBIAL SCREENING-ZONE OF INHIBITION (nm)

Microorganism (Bacteria)	ClQ	NO_2Q	BrQ	PABAQ	SO_2Q	Std.*
Pseudomonas aerogenosa	11	10	8	-	8	22
Eschericha coli	11	14	11	10	8	23
Staphylococus aureus	-	-	-	10	10	25
Bacillus cereus	11	-	10	10	5	19
Bacillus subtillus	11	8	7	-	-	24
Klebsiella aerugenes	8	10	8	9	10	21
Salmonella typhi	11	10	9	8	9	21
Microorganism (Fungi)	ClQ	NO_2Q	BrQ	PABAQ	SO_2Q	Std.**
Lipomyces lopofera	14	11	9	12	10	18
Rhodotorula rubra	-	16	11	11	-	17
Aspergillus fumigatus	-	-	-	-	-	17
Aspergillus flavus	-	-	-	10	-	16

*Ofloxacin, **Clotrimazole.

Antifungal screening: All the synthesized compounds were evaluated for their *in vitro* antifungal activity against four pathogenic fungi by standard agar dilution method and the zone of inhibition was determined. Clotrimazole was taken as reference standard. All the compounds were not active against *Aspergillus fumigatus* (Table-2).

Conclusion

A further modification on these molecules can be initiated which would open a new era in developing more therapeutically effective agent against microbial infection of HIV associated tuberculosis in future.

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