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Synthesis and biological activities of some novel substituted quinazoline derivatives

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ABSTRACT

A simple method for the synthesis of title compounds is reported, which were isolated from a series of reactions. After nucleophilic reaction of 2-phenyl-3, 1benzoxazin-4(3H)-one with thiosemicarbazide and hydrazinehydrate to furnish quinazolinylthiourea, followed by aromatic acidchloride, all the compounds synthesized were screened for their potential anticancer, anti-diabetic, anti tumor and anti asthmatic properties, which exhibited some authentic results towards testing organism in vitro and in vivo studies.

Key Words: anthranilic acid, thiosemicarbazide, hydrazinehydrate and benzoyl chloride.

INTRODUCTION

Many modern pharmaceuticals are totally synthetic compounds and a large proportion of these are heterocyclic. In other areas in which organic compounds are widely used, such as the pesticides and dyestuffs industries heterocyclic compounds are also predominant. In laboratory synthesis, heterocyclic compounds are frequently a source of latent functionality. The ring system can be carried through many stages of a synthetic sequence and they cleaved to produce delicate functional groups, often in a highly stereo selective manner.

The pharmacological activity of the compounds due to the function of specific groups that occupied the position of that group or atom or bond or stereo chemical orientation. The whole pharmacological activity of the compounds has been decided by the above groups. Hence the determination of the structure of a biologically active molecule provides a two-fold benefit to modification of the structure. Pharmacological research plays an important role in its contribution to pharmacy and medicine.

Quinazoline-4-one derivatives have been reported for diverse potential biological activities like anti hypertension[1,2], antiproloferative[3], anti convulsant[4], antifungal, and anti bacterial activity[5,6], anti cancer[7], anti HIV[8]and methaquinone having Quinazoline-4one nucleus is used as a sedative and hypnotic agent[9].

The present work is to synthesis some novel 2-Phenyl-3,1-benzoxazin-4-(3H)one derivatives was synthesized by literature method[10].

MATERIALS AND METHODS

Experimental Section

General procedures: Melting points are uncorrected and were recorded on a REMI series, lab India instrument. TLC analysis was done using pre-coated silica gel plates and visualization was done using iodine. IR spectra were recorded in KBr on schimadzu FT-IR Spectrometer. 1H & 13C-NMR spectra were recorded on a Bruker (AC 400MHz) using TMS as an internal standard. Elemental analysis was carried out on a Perkin-Elmer series –II CHNS/O Analyzer 2400. All the chemicals were obtained from Aldrich; all the solvents used were of commercial grade only.

Synthesis of 2-phenyl-3,1-benzoxazin-4-(3H)one: (ABP) [10]

To a stirred solution of anthranilic acid (0.01 mole) in pyridine (60 ml), benzoyl chloride (0.01 mole) was added drop wise maintaining the temperature near 8°C for 1.5 hours. Reaction mixture was stirred for another 3 hours at room temperature while stirring a solid product separate out. Whole reaction mixture was neutralized with $NaHCO_3$ solution. A pale yellow solid deposited which was filtered washed with water and recrystallized from ethanol.

Yield: 78%; m.p:117-120°C, Compound ABP (Found: C, 75.33; H, 4.03; N, 6.27; O, 14.34; $C_{14}H_9NO_2$) IR (KBr): 3437 (N-H stretching), 1762 (C=O), 1611 Cyclic (C=O), 1572 (C=N). ^{1}H NMR: δ 7.0-7.5 (m, 9H, Ar-H),

Synthesis of N-[2-phenyl-4(3H)-oxo-quinazoline-3-yl]thiourea: (BTS) [10]

Compound ABP (0.01 mole) was dissolved in ethanol and thiosemicarbazide (0.01 mole) in ethanol was added to with a catalyst amount of pyridine reaction mixture was refluxed for 4 hours and after cooling a crystalline product was obtained. It was filtered and recrystallized from ethanol to yield needle shaped shining white crystals to compound (BTS).

Yield: 70%; m.p:165°C, Compound BTS (Found: C, 60.8; H, 4.05; N, 18.9; O, 5.4; S, 10.8; $C_{15}H_{12}N_4OS$) IR (KBr): 3438 (N-H stretching), 1669 (C=O), 694 (C=S), 1606 (C=N). ^{1}H NMR: δ 8.8 (m, 3H, NH, C=S, NH_2), 7.7 (m, 9H, Ar-H),

Synthesis of 3-amino-2-phenylquinazolin-4(3H)-one: (BHH)

A mixture of 2-phenyl-3-benzoxazin-4-one (0.05 mole) and hydrazine hydrate (0.05 mole) in ethanol was refluxed for 3 h and cooled. The separate solid was crystallized form ethanol.

Yield: 75%; m.p:194°C, Compound BHH (Found: C, 70.88; H, 4.64; N, 17.72; O, 6.75; $C_{15}H_{11}N_3O$) IR (KBr): 3307 (NH_2), 1761 (C=O), 1594 (C=O), 1531 (C=C), ^{1}H NMR: δ 4.4 (S, 2H, NH_2), 6.7-7.4 (m,9H, Ar-H)

Synthesis of N-(4-oxo-2-phenyl quinazolin-3(4H)-yl carbamothioyl) benzamide: (TSCB)
A mixture of compound BTS (0.01 mole) one equal molar and benzoylchloride (0.01 mole) was refluxed in pyridine (40 ml) for 4 hours. The reaction mixture was cooled treated with cold ice-cold HCl. The separated solid was filtered washed with water and dried, recrystallized from ethanol.

Yield: 70%; m.p:165°C, Compound TSCB (Found: C, 66; H, 4.0; N, 14; O, 8; S, 8; $C_{22}H_{16}N_4O_2S$) IR(KBr): 3428 (NH), 3279 (CH, Ar-H), 2923 (C-H, CH_2), 1667 (C=O), 694 (C=S), ^{1}H NMR: δ 8.13 (2° Amide) (m, 3H, NH, C=S) 7.8-7.5 (m,9H, Ar-H)

Synthesis of N-(4-oxo-2-phenyl quinazolin-3(4H)-yl)benzamide: (HHB)
A mixture of compound BHH (0.01 mole) one equal molar and benzoyl chloride (0.01 mole) was refluxed in pyridine (40 ml) for 4 h. The reaction mixture was cooled treated with cold ice-cold HCl. The separated solid was filtered washed with water and dried and recrystallized from ethanol.

Yield:50%; m.p:207°C, Compound HHB (Found: C, 74.1; H, 4.1; N, 12.3; O, 9.4; $C_{21}H_{14}N_3O_2$) IR (KBr): 3439 (NH_2), 1651 Cyclic(C=O), 1552 (C=N), ^{1}H NMR: δ 8.0 (2°Amide), 7.6-7.2 (m,9H, Ar-H)

RESULTS AND DISCUSSION

We elicited a new method for the synthesis of Quinazoline derivatives with aromatic acidchloride.In continuation of our work on this different aromatic acidchlorides, we wish to report in the paper synthesis of 2-substituted Quinazoline by the reaction between an aromatic acidchlorides. The reactions were carried out at room temperature, using aromatic acidchloride in the presence of pyridine.

Table-1: Physical and Analytical Data of Compounds

Compounds	Time in Hours	m.p (°C)	Yield %	Molecular Formula	Analysis % calcd.(Found)				
					C	H	N	O	S
ABP	1.5	117-120°C	78	$C_{14}H_9NO_2$	75.33	4.03	6.27	14.34	-
BTS	4	165	70	$C_{15}H_{12}N_4OS$	60.8	4.05	18.9	5.4	10.8
BHH	3	194	75	$C_{15}H_{11}N_3O$	70.88	4.64	17.72	6.75	-
TSCB	4	165	70	$C_{22}H_{16}N_4O_2S$	66	4.0	14	8	8
HHB	4	207	50	$C_{21}H_{14}N_3O_2$	74.1	4.1	12.3	9.4	-

Biological Activities
Antimicrobial Activity Studies
Discs impregnated with known concentration of antibiotics are placed on agar plate that has been inoculated (or) seeded uniformly over the entire plate with a culture of the bacterium to be tested. The plate is incubated for 18-25 h at 37°C. During this period, the antibacterial agent diffuses through the agar and may prevent the growth of organism. Effectiveness of susceptibility is proportional to the diameter of zone of zone of inhibition of zone around the disc. Organism which grow up to edge of the disc are resistant.
Report On Anti Microbial Activity of the Given Samples

The anti-microbial activity for the given samples was carried out by disc diffusion technique (Indian Pharmacopocia 1996, Vol II-A, 105). The test micro organism of gram positive *staphylococcus aurous* and gram negative *Escherichia co*li, and fungus *Candida albicans* and *Aspergullus Niger* were obtained from National Chemical Laboratory (NCL), Pune and maintained by periodical sub culturing on Nutrient agar and Sabouraued Dextrose Medium for bacteria and fungi respectively. The effect produced by the positive control (reference standard Ciprofloxacin 5 µg/disc for bacteria and Fluconazole 10 µg/disc for fungi.

The results obtained are tabulated as follows:

Table-2

S.No.	Name of the Micro Organism	Diameter of Zone of inhibition in mm				
		BTS	TSCB	BHH	HHB	Standard
1.	*Staphylococcus aurous* (NCIM2079)	36	42	33	41	46
2.	*Escherichia coli* (NCIM 2065)	29	39	37	27	40
3.	*Candida albicans* (NCIM 3102)	18	16	19	18	20
4.	*Aspergillus niger* (NCIM 105)	15	19	17	16	20

Anti-Asthmatic Report by *in vitro* Studies

The Anti-Asthmatic Screening

All the compounds prepared herein were screened for their potential anti-asthmatic activities such as; they were tested against PDE-IV for potential anti-asthmatic effect, against DDP-IV. Good activity was found the anti-asthmatic activity was carried out using *Phosphodiesterase* IV enzyme (PDE-IV) [11] and the primary screening of the compound was done at 1 µ concentration using human PDE- IV enzyme, where Rolipram & Ariflo were used as standard compounds.

Protocol for PDE-IV- inhibition assay

Phophodiesterase IV enzyme converts [^{3}H] cAMP to the corresponding [^{3}H] 5'-AMP in proportion to the amount of *Phosphodiesterase* IV present. The [^{3}H] adenosine and phosphate by the action of snake venom 5'-nucleotidase hence the amount of [^{3}H] adenosine librated is proportional to *phosphodiesterase* IV activity.

The assay was performed at 34°C in a 200 ml total reaction mixture. The reaction mixture contained 25m µ of tris buffer, 10 m µ $MgCl_2$; 1µM cAMP (0.1µCi) stock solutions of the compounds to be investigated were prepared in dimethylsulfoxide in concentrations such that the dimethylsulfoxide content in the test samples did not exceed 0.05% by volume to avoid affecting the *phosphodiesterase* IV activity. Compound was then added in the reaction mixture (25µL/tube).

The assay was initiated by addition of enzyme mix (75µL) and the mixture was incubated for 20 minutes at 34ºC, the reaction was stopped by boiling the tubes for 2 min at 100°C in a water bath. After cooling on ice for 5 minutes and addition of 50 µg 5' nucleotidase snake venom from crotalus atrox incubation was carried out aganin for 20 min at 34°C the unreacted substrate was separated form [^{3}H] adenosine by addition of Dowex AG IX-8 (400 µL), which was pre equilibrated in (1:1) water:ethanol. Reaction mixture was then thoroughly mixed, placed on ice for 15 minutes. Vertexed and centrifuged at 14,000 rpm for 2 min, after centrifugation a sample

of the supernatant (150 µL) was taken and added in 24 well optiplates containing scinillant (1 mL) and mixed well. The sample in the plates were then determined for radioactivity in a Top counter and the *Phosphodiesterase* IV activity was calculated. *Phosphodiesterase* IV enzyme was present in quantities that yield < 30% total hydrolysis of substrate (linear assay conditions). Rolipram and cilomilast were used as standard in all assays.

Table-3: Anti-Asthmatic Report by *invitro* Studies

Compounds (1µM) % inihibition	PDE-IV (0.03µM) % inihibition
BTS	24
TSCB	27
BHH	25
HHB	20

CONCLUSION

The present work describes the cyclization reaction of 2-phenyl-3, 1-benzoxazin-4(3H) one. The derivatives, synthesized are hydrazinecarbothioamide compound with 2-phenyl-4H-benzo[d][1,3]oxazin-4-one (ABP), 1-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiourea (BTS), N-(4-oxo-2-phenylquinazolin-3(4H)-ylcarbamothioyl)benzamide (TSCB), 3-amino-2-phenylquinazolin-4(3H)-one (BHH), N-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzamide (HHB). Biological screening for all the compounds were carried out and reported.

The spectral data of synthesized compounds showed the expected adsorption frequency range and signals. The compounds were subjected to antimicrobial activity by disc diffusion method and anti-asthmatic activity *invitro* studies. They showed good inhibition power.

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