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A STUDY ON SYNTHESIS AND CHARACTERISATION OF SOME NOVEL QUINAZOLINONES

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ABSTRACT
Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. The heterocyclic compounds are fundamentals of life, like haeme derivatives in blood & chlorophyll essential for photosynthesis in plants. Also the DNA & RNA are containing heterocycles. The study aims to synthesize simple derivatives of quinazoline by combining with aromatic primary amine, hydrazine hydrate and benzoxazine. The synthesized compounds were characterized by melting point analysis. Melting point was recorded and compared with the standard references. The characterization of compounds provided further scope in the research towards the discovery of new derivatives for several ailments. The biological evaluation could be beneficial for future studies.

KEYWORDS: Heterocyclic compounds, benzoxazine, quinazoline, primary amine, hydrazine hydrate and benzoxazine.

INTRODUCTION
Any of a class of organic compounds whose molecules contain one or more rings of atoms with at least one atom being an element other than carbon, most frequently oxygen, nitrogen, or sulfur are called heterocyclic compounds. Heterocyclic chemistry is the branch of chemistry dealing with the synthesis, properties, and applications of heterocycles. Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. The word hetero means "different from carbon and hydrogen". Many heterocyclic compounds are biosynthesized by plants & animals are biologically active. Some heterocyclic compounds are fundamentals of life, like haeme derivatives in blood & chlorophyll essential for photosynthesis in plants. Also the DNA & RNA are containing heterocycles. Dyestuffs of plant origins include indigo blue used to dye jeans. Several heterocycles are the basic structure nucleus for nicotine, pyridoxine, cocaine, morphine etc. Among a wide variety of nitrogen heterocycles that have been explored for developing pharmaceutically, quinazolinone plays an important role in medicinal chemistry and subsequently has emerged as a pharmacophore. Quinazoline is a compound made up of two fused six member simple aromatic rings- benzene & pyrimidine ring. It is a yellow colored compound, found usually in crystalline form. Medicinally it is used as ant malarial agent. It was first prepared by Gabriel in 1903 and first isolated from the Chinese plant aseru. The development of research on biological activity of quinazolinecompounds started when the compound 2-methyl-1,3-aryl-4-quinazoline was synthesized. This compound has soporific & sedative action.[1-4] In last 10 to 15 years of research for medicinal has been characterized by significant advances. In 1968 only two derivatives were used, soporific & anticonvulsant-methaqualone and diuretic quinathiazone. By 1980, about 50 kinds of derivatives of this class includes medicinal with different biological actions like 'soporific, sedative, tranquilizing, analgesic, anticonvulsant, antitussive, myorelexant, anti rheumatic, hypotensive, antiallergic, bronchodilating, antidiabetic, cholagogue, diuretic, cystatic, antimalarial, spermicidal etc.

Quinazolinone scaffold has been considered as a magic moiety possessing myriad spectrum of medicinal activities. Diversity of biological response profile has attracted considerable interest of several researchers across the globe to explore this skeleton for its assorted

therapeutic significance. Various novel classes of structurally different quinazolinones have been designed and synthesized depicting potential interventions such as antibacterial, antifungal, antiviral, anticonvulsant, CNS depressant, anti-inflammatory, antihistaminic, anticancer and so on. Moreover, the nucleus constitutes an integral structural component in a number of drugs currently employed in several clinical therapies.[5-9]

Table 1: List of chemicals.

S.NO	CHEMICAL	GRADE	Mfd.COMPANY
1	Sodium hydroxide	LR	SdfiNE-CHEM LIMITED.MUMBAI-400 030
2	Bromine	LR	SdfiNE-CHEM LIMITED.MUMBAI-400 030
3	Phthalamide	LR	Spectrochem Pvt.Ltd.MUMBAI-400 018
4	Hydrochloric acid	LR	RFCL Limited NEW DELHI-110 020
5	Glacial acetic acid	LR	FINAR Chemicals.AHMEDABAD-180 006
6	Pyridine	LR	SdfiNE-CHEM LIMITED.MUMBAI-400 030
7	Benzoyl chlorid	LR	FINAR Chemicals.AHMEDABAD-180 006
8	Sodium bicarbonate	LR	Spectrum reagents chemicals Pvt Ltd-cochin
9	Hydrazine hydrate	LR	Merck specialitiesPvt Ltd-MUMBAI-400 018
10	Ethanal	AR	CHANGSHU YANGYUAN CHAMICAL CHINA
11	Aniline	LR	Chemport(India)Private LTD. MUMBAI-400 021
12	n-Veratraldehyde	LR	Sisco Research Laboratories PvtLtd.MUMBAI- 093
13	Vanillin	LR	Sisco Research Laboratories PvtLtd.MUMBAI- 093
14	P-hydroxyBenzoldehyde	LR	Sisco Research Laboratories PvtLtd.MUMBAI- 093
15	Formaldehyde	LR	SdfiNE-CHEM LIMITED.MUMBAI-400 030
16	Silica gel-G	-	Merck specialitiesPvt Ltd-MUMBAI-400 018

AIM AND OBJECTIVES

- Quinazolin-4(3H)-ones are attractive targets for designing of new bioactive agents of therapeutic intervention. Among the various quinazolines reported, C-2, N-3 substituted quinazolines exhibit interesting pharmacological activities.
- Our present work aims to synthesize simple derivatives of quinazoline by combining with aromatic primary amine, hydrazine hydrate and benzoxazine.
- The purity of the compounds are checked by thin layer chromatography and are characterized by melting point analysis. The structures of synthesized compounds are assigned by FT-IR analysis.

METHODOLOGY

Step- I

Synthesis of anthranilic acid

Prepare a solution of 30 gms of sodium hydroxide in 120 ml of water. Cool to 0^0c.add 0.16 ml of bromine and shake until all the bromine gets reacted. Cool to 0^0c. prepare a solution of 22 gms of NaOH in 80 ml of water. Add finely powdered phthalimide(0.163 mol) in one portion to the cold sodium hypobromite solution in the form of a thin paste. Shake vigorously until a clear yellow solution is obtained. Add the prepared NaOH rapidly, heat to 80^0c for 2 minutes. Cool in ice and add concentrated hydrochloric acid slowly with stirring until the solution is just neutral. Precipitate anthranilic acid completely by gradual addition of glacial acetic acid. Filter and recrystallise from hot water.

Step – II

Synthesis of 2-phenyl-1, 3-benzoxazin-4-one

Anthranilic acid (I) (0.1mol) was dissolved in 50 ml of pyridine. To this benzoyl chloride (IA) (0.2 mol) was added drop wise with constant stirring at low temperature. When the addition of benzoyl chloride was completed, mixture was treated with 10% sodium bicarbonate solution(15 ml). After the effervescence ceased, mixture was filtered and washed repeatedly with water to remove inorganic materials. The crude drug thus obtained was recrystallised from ethanol.

Step - III

Synthesis-of 3-amino-2-phenyl quinazolin-4-(3h)-one

An equimolar (0.01 mol) mixture of benzoxazine and hydrazine hydrate was refluxed for 6hrs with 10ml of ethanol. The mixture was cooled to room temperature and poured into crushed ice, filter and then washed with water. The solid thus obtained was recrystallised from ethanol.

Step – IV

Synthesis of 2-phenyl-3-substituted quinazolin-4-(3h)-one derivatives

An equimolar (0.01 mol) mixture of quinazoline, aniline (aromatic primary amine) and aldehyde was refluxed for 6hrs with 10ml of ethanol in acidic condition. The mixture was cooled to room temperature and poured into crushed ice, filter and then washed with water. The solid thus obtained was recrystallised from ethanol.

Table 2: Chemical compounds IUPAC names.

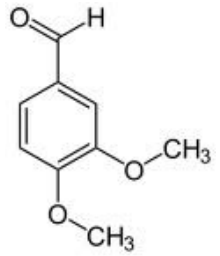
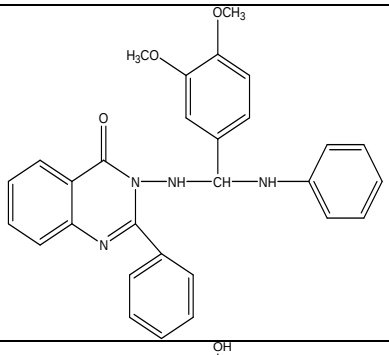
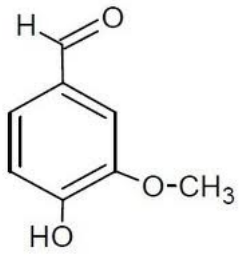
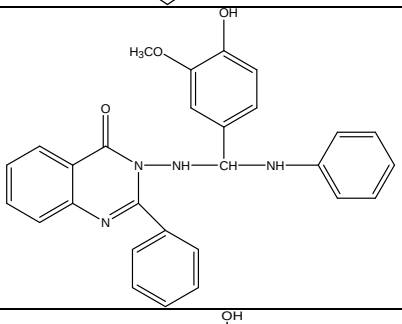
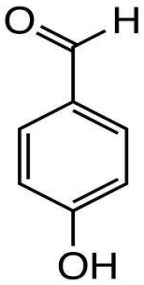
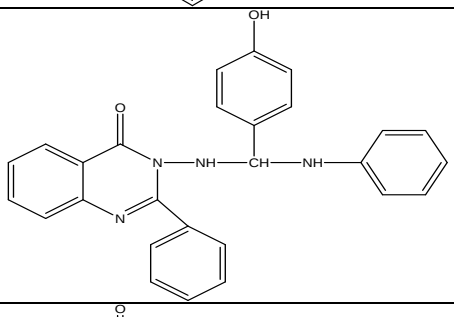
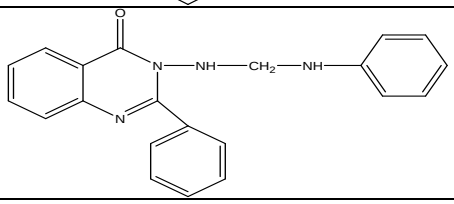
COMPOUND CODE	R	COMPOUND	IUPAC NAME
III A			3-{[(3,4-Dimethoxy-phenyl)-phenylamino-methyl]-amino}-2-phenyl-3H-quinazolin-4-one
IIIB			3-{[(4-Hydroxy-3-methoxy-phenyl)-phenylamino-methyl]-amino}-2-phenyl-3H-quinazolin-4-one
III C			3-{[(4-Hydroxy-phenyl)-phenylamino-methyl]-amino}-2-phenyl-3H-quinazolin-4-one
III D	**HCHO**		2-Phenyl-3-(phenylamino methyl-amino)-3H-quinazolin-4-one

Table 3: Chemical compounds molecular formula.

COMPOUND CODE	MOLECULAR FORMULA	% YIELD (%W/W)
I	$C_7H_7NO_2$	61.91
II	$C_{14}H_9NO_2$	59.30
III	$C_{14}H_{11}N_3O$	95.15
IIIA	$C_{29}H_{26}N_4O_3$	70.06
IIIB	$C_{28}H_{24}N_4O_3$	61.81
IIIC	$C_{27}H_{22}N_4O_2$	69.09
IIID	$C_{21}H_{18}N_4O$	64.56

Characterization

Determination of melting point

The **normal melting point** of a solid is defined as the temperature at which the solid and liquid are in equilibrium at a total pressure of 1 atmosphere. There are several methods by which melting points can be determined, and the choice of method depends mainly upon how much material is available.

Capillary Melting Points

Capillary melting points, either in an oil bath or a melting-point apparatus, are most often used for the determination of the melting point of a solid. A few crystals of the compound are placed in a thin walled capillary tube 10-15 cm long, about 1 mm in inside diameter, and closed at one end. The capillary, which contains the sample, and a thermometer are then suspended so they can be heated slowly and evenly.[10-12]

The temperature range over which the sample is observed to melt is taken as the melting point.

Filling a Capillary Tube

Usually, the melting point capillary can be filled by pressing the open end into a small heap of the crystals of the substance, turning the capillary open end up, and vibrating it by drawing a file across the side to rattle the crystals down into the bottom. If filing does not work, drop the tube, open end up, down a length of glass tubing about 1 cm in diameter (or a long condenser) onto a hard surface such as a porcelain sink, stone desk top, or the iron base of a ring stand. The solid should be tightly packed to a depth of 2-3mm. A variety of oil baths can be used in a melting point determination, as well as in a boiling point determination.

Arrangement of sample and thermometer for melting point determination

If a compound begins to decompose near the melting point, the capillary with the sample should be placed in the bath after the temperature has been raised to within 6 or 10 degrees of the expected melting point, so as to minimize the length of time that the sample is heated.

Table 4: Chemical compounds melting point.

S.NO	COMPOUND CODE	MOLECULAR FORMULA	MELTING POINT (^{O}C)
1	IIIA	$C_{29}H_{26}N_4O_3$	62
2	IIIB	$C_{28}H_{24}N_4O_3$	92
3	IIIC	$C_{27}H_{22}N_4O_2$	102
4	IIID	$C_{21}H_{18}N_4O$	96

Thin layer chromatography

Thin layer chromatography was carried out over plates (20cm×5cm) coated with silica gel – G 13% containing calcium sulphate as binder.

Principle

When a mixture of compounds is spotted on a TLC plate and development with a suitable solvent system the compound which are not strongly adsorbed move up along with a solvent. Those which are more strongly adsorbed more or less rapidly get separated due to different rates of migration on the layer.

Preparation of thin layer chromatography plates

50gms of silica gel-G was weighed out and shaken to a homogenous suspension with 100 ml of distilled water for 90 seconds. This suspension was poured in to a TLC applicator which was adjusted to 0.25mm thickness. Twenty carrier plates (20cm×5mm) were laid together in a row on a template and coated with a silica gel-G by drawing the applicator. The plates were allowed to dry at room temperature and then dried at 110^{0}c for 30min, in hot air oven for activation. The dry plates were stored in a dessicator and used whenever required.[9]

Application of the substance, mixture for separation

The substance mixture was dissolved in a suitable solvent was spotted on TLC plates 20cm above from its bottom. All the solutions for application were equally sized as far as possible and had a diameter ranging from 2mm – 5mm. These spots were visualized by exposing to Iodine vapors.

The elution technique

The fractions are collected at different time subject to TLC and resolved compounds are identified by using appropriate reagent.

Mobile Phase: Ethyl acetate: chloroform (1:1)

Table 5: Detecting agent: Iodine chamber.

S.NO	COMPOUND CODE	MOLECULAR FORMULA	MOLECULAR WEIGHT	Rf VALUE
1	IIIA	$C_{29}H_{26}N_4O_3$	478.55	0.83
2	IIIB	$C_{28}H_{24}N_4O_3$	464.52	0.80
3	IIIC	$C_{27}H_{22}N_4O_2$	434.49	0.70
4	IIID	$C_{21}H_{18}N_4O$	341.15	0.78

Table 6: Elemental analysis.

S.NO	COMPOUND CODE	MOL.FORMULA	MOL.WT	%C	%H	%N	%O
1	IIIA	$C_{29}H_{26}N_4O_3$	478.55	46.74	41.93	6.5	4.83
2	IIIB	$C_{28}H_{24}N_4O_3$	464.52	47.45	40.67	6.77	5.08
3	IIIC	$C_{27}H_{22}N_4O_2$	434.49	49.09	40.06	7.20	3.64
4	IIID	$C_{21}H_{18}N_4O$	341.15	47.72	40.90	9.09	2.27

Infra- red spectral analysis

Infra- red spectroscopy gives a unique 'chemical overview' of a sample with all the chemicals present contributing to the spectrum produced. The interpretation of infrared spectra involves the correlation of absorption bands in the spectrum of an unknown compound with the known absorption frequencies for types of bonds.[13-14] The peaks in IR spectrum gave an idea about the probable structure of the compound. IR region ranges from 4000- 666 cm^{-1}. Quanta of radiation from this region of spectrum correspond to the differences between different vibrational levels of molecules. The peaks showed similar correlation with the standard.

RESULTS AND DISCUSSION

2- Phenyl- 3- substituted quinazolinone derivatives were synthesized using different aldehydes. The purity of the compounds was checked by thin layer chromatography and Rf values were noted.[15-19] The synthesized compounds were characterized by melting point analysis. Melting point was recorded and compared with the standard references. The structures of synthesized compounds were analyzed by FT-IR analysis in the range of 4000-400 cm^{-1}.

CONCLUSION

The characterization of compounds provided further scope in the research towards the discovery of new derivatives for several ailments. Biological evaluation could be beneficial for future studies.

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