SYNTHESIS, CHARACTERISATION AND MECHANISTIC STUDY OF SOME BENZIMIDAZOLO / TETRAZOLO QUINAZOLINES

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ABSTRACT: Through the use of a simple and accessible method, substituted Benzimidazolo/ tetrazolo quinazolines have been synthesized. The characterization of Benzimidazolo/ tetrazolo quinazolines was the goals of this study. An excess of the synthetic chemicals was produced during this synthesis.

KEY WORDS: Benzimidazolo quinazolines , tetrazolo quinazolines.

INTRODUCTION: Quinazolones, as well as condensed quinazolones, exhibit a variety of pharmacological properties, with the main ones being anticancer[1-3],, antibacterial[4, 5], antifungal[6, 7], antiarrhythmic[8], antidiabetic[9-14], and antiinflammatory activity[15-18]. Some pyridoquinazole compounds are calcium antagonists and share the ability to prevent the calcium L channel [19] from allowing external calcium to enter the cell. Many academic institutions have also reported on the use of quinazolines and quinazolones as antimicrobial, anti-convulsant, and anti-diabetic medicines [20-22]. Quinazolines link with anticancer properties [23, 24]. has greatly stimulated interest in their chemistry. The tactic used was the creation of quinazolone compounds with folic acid-like properties [25, 26]. These substances were primarily tested for their ability to block the dihydrofolate reductase enzyme, and in human lukemia cells [27, 28] as well as EGFR-tyrosine kinase (anti-tumor))[29].

MATERIALS AND METHODS: All of the chemicals and solvents employed in this synthetic endeavour were of the laboratory grade and were purchased from SD fine chemicals and Sigma Aldrich India. Following reactions with various compounds, certain fresh Benzimidazolo/ tetrazolo quinazolines were created from anthranilic acid. By using FTIR, ^{1}H NMR, ^{13}C NMR, Mass spectrometry, and elemental analysis, the synthesised compounds were characterised. Compounds melting point were determined using the Toshniwal melting point equipment and recorded results are incorrect. A Perkin-Elmer 157 spectrophotometer was used to record IR spectra (vmax in cm-1), ^{13}C NMR spectra (Chemical shift in ppm), and ^{1}H NMR spectra in $CDCl_3$ using internal standards of TMS at 300 MHz and 40 MHz, respectively. On a Jeol SX-102 (FAB) mass spectrometer with m-nitrobenzylalcohol as matrix, the mass spectra were captured.

(1, 3- DIOXO- 1, 3- DIHYDRO- ISOINDOL- 2- YL)- ACETAMIDE/ N- BENZOYLAMINOACETAMIDE(18): 1, 3- Dioxo- 1, 3- dihydro- isoindol- 2- yl) acetyl chloride/ N- benzoyl- amino acetyl chloride (**16**) (0.05 mole) was allowed to cool at 0°C and to this an ice-cold solution of ammonia was added slowly with vigorous stirring. Temperature was not allowed to rise above 0°C. On completion of the process of addition of ammonia solution, the separated solid was treated with a solution of freshly prepared sodium bicarbonate (10%) in order to dissolve any carboxylic acid which was not converted into acid chloride. The solid was filtered off and washed with cold water. It was air dried and recrystallized from ethanol.

(1, 3- DIOXO- 1, 3- DIHYDRO- ISOINDOL- 2- YL) – ACETAMIDE: White needles; m. p. 209 – 210°C [210°C] [30]; yield 67%.

N- BENZOYL AMINO ACETAMIDE: White crystalline solid; m.p. 225 – 226°C [227°C] [30].

2- BENZAMIDOMETHYL/ PHTHALIMIDO- METHYL- QUINAZOLIN- 4(3H) ONE/ 2- BENZAMIDOMETHYL- QUINAZOLIN- 4- OL (19): A mixture of (1, 3- dioxo- 1, 3- dihydro- isoindol- 2- yl)- acetamide/ N- benzoyl amino acetamide (**18**) and anthranilic acid (equimolar quantity) was heated at 130 - 135°C for four hours. Subsequently, the hot melt was allowed to cool for half an hour at room-temperature. During this period the molten mass solidified. It was treated with an aqueous solution of sodium bicarbonate (10%) in order to dissolve any unreacted acid into the cyclized product. An additional quantity of sodium bicarbonate solution was added to ensure the complete dissolution of the acid (till there was no effervescence of carbon dioxide). The solid phase was filtered off and washed with water in order to remove any inorganic materials. It was dried under vacuum overnight and recrystallized from ethanol.

2- BENZAMIDOMETHYL- QUINAZOLIN- 4(3H) -ONE: White crystalline mass; m.p. 235 - 236°C; yield 62%.

Anal for $C_{16}H_{13}N_3O_2$: N Calcd. 15.05%, N Found. 14.75%.

PHTHALIMIDOETHYL- QUINAZOLIN- 4(3H)- ONE: White crystalline solid; m.p. 260 - 261°C; yield 65%.

Anal for $C_{17}H_{11}N_3O_3$: N calcd. 13.77%, N found 13.65%.

4- CHLORO- 2- BENZAMIDOMETHYL/ PHTHALIMIDOMETHYL- QUINAZOLINES (20): The imidol form of (**19**) i.e. 2- benzamidomethyl/ phthalimido- methyl quinazoline- 4- ol (0.02 mole) and phosphorus pentachloride (PCl_5) (0.02 mole) were taken in phosphorus oxychloride ($POCl_3$) (50 ml). The resultant reaction mixture was heated for five hours in such a manner that it was free from atmospheric moisture. Subsequently, the reaction mixture was allowed to cool till it attained the room-temperature. It was poured into ice-cold water (250 ml) in installments with stirring after each addition. Precipitation occurred

which was allowed to be completed by standing undisturbed for one hour. The solid phase was filtered off and washed repeatedly with cold water. It was dried *in vacuo* and recrystallized from rectified spirit.

4- CHLORO- 2- BENZAMIDOMETHYL- QUINAZOLINE: Light brown crystals; m.p. 261°C; yield 50%.

Anal for $C_{16}H_{12}N_3OCl$: N Calcd. 14.11%, N found 14.55%.

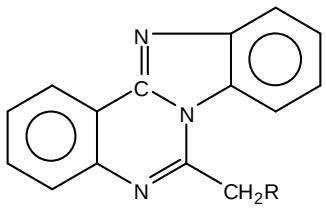
4- CHLORO- 2- BENZAMIDOMETHYL- QUINAZOLINE: Light brown crystalline mass; m.p.275 – 276°C; yield 55%.

Anal for $C_{17}H_{10}N_3O_2Cl$: N calcd. 12.94%, N found 12.75%.

2- BENZAMIDOMETHYL/ PHTHALIMIDO- METHYL- BENZIMIDAZOLO [2, 1- c] QUINAZOLINES (21): A mixture of 4- chloro- 2- benzamidomethyl/ phthalimidomethyl- quinazoline (0.01 mole) and o- phenylenediamine (0.01 mole) in dry pyridine (50 ml) was heated under reflux for six hours under anhydrous reaction conditions. Subsequently, the hot reaction mixture was allowed to cool at room temperature. It was poured into ice-cold water (250 ml) containing diluted hydrochloric acid (15 ml) slowly with constant stirring. A solid separated out on the complete addition of the reaction mixture. It was washed with cold water repeatedly till there was no smell of adhered pyridine. The crude compound was air-dried and recrystallized from diluted ethanol. The compounds thus synthesized are recorded in **Table IX** alongwith their characterization data.

2- BENZAMIDOMETHYL/PHTHALIMIDO- METHYL- TETRAZOLO [1, 5- c] QUINAZOLINES (22): To a solution of 4- chloro- 2- benzamidomethyl/ phthalimidomethyl quinazoline (0.01 mole) in Dimethyl Sulphoxide (DMSO) and glacial acetic acid (5 ml) a solution of sodium azide (0.02 mole) in water (10 ml) was added portion wise. The resultant reaction mixture was stirred at 40°Cfor four hours. Stirring was continued further for five days at ambient temperature. A precipitate was formed which was filtered off and washed with water and recrystallized from Dimethyl Formamide (DMF). The compounds of this category are presented in **Table X** alongwith their characterization data.

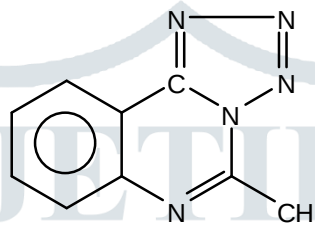
Table-IX



Characterization Data of 2- Benzamido- Methyl/ Phthalimido- Methyl- Benzimidazolo [2, 1- c] Quinazolines (21)

Compound No.	R	m.p. (°C)	Yield (%)	Colour	Molecular Formula	Molecular Weight	Analysis Nitrogen %	
							Calcd.	Found
(21a)	Benzamidomethyl	165 – 166	55	Brown	$C_{22}H_{16}N_4O$	352	15.90	15.55
(21b)	Phthalimidomethyl	180 – 181	60	Brown	$C_{23}H_{14}N_4O_2$	378	14.78	14.80

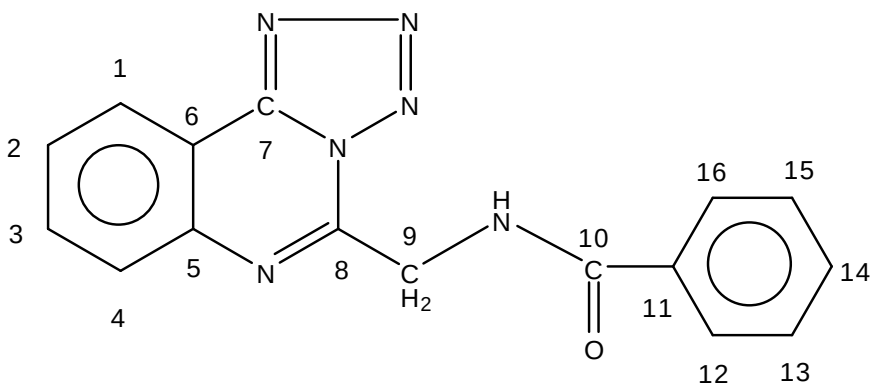
Table-X



Characterization Data of 2- Benzamidomethyl/ Phthalimidomethyl- Tetrazolo- [1, 5- c] Quinazolines (22)

Compound No.	R	m.p. (°C)	Yield (%)	Colour	Molecular Formula	Molecular Weight	Analysis Nitrogen %	
							Calcd.	Found
(22a)	Benzamidomethyl	201 – 202	50	Grey	$C_{16}H_{12}N_6O$	304	27.63	27.55
(22b)	Phthalimidomethyl	225 – 226	54	Grey	$C_{17}H_{10}N_6O_2$	330	25.45	25.60

Spectral Data of 2- Benzamidomethyl- Tetrazolo [1, 5- c] Quinazoline (22a)

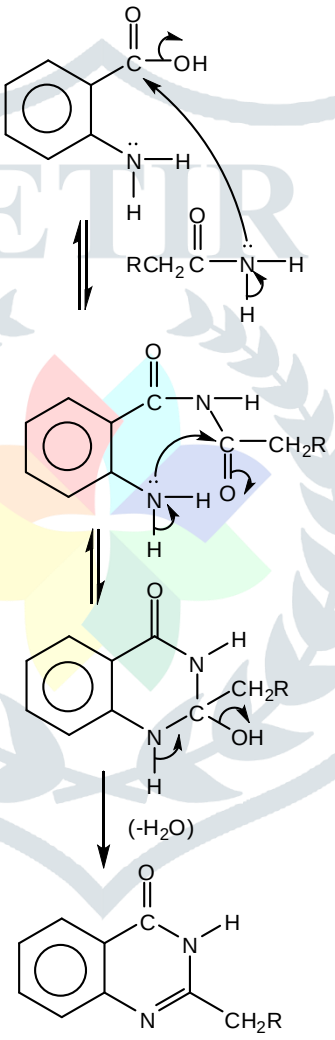


IR (KBr) (√ in cm^{-1}): 1675.20 (sec. amide, C=O), 1635.50 (C=N), 1591.34 (N=N)

^{1}HNMR (MeOD) (in δppm): 6.76 – 7.85 (m, 9H, ArH), 3.50 (s, 2H, CH_2), 9.20 (brs, 1H, CONH)

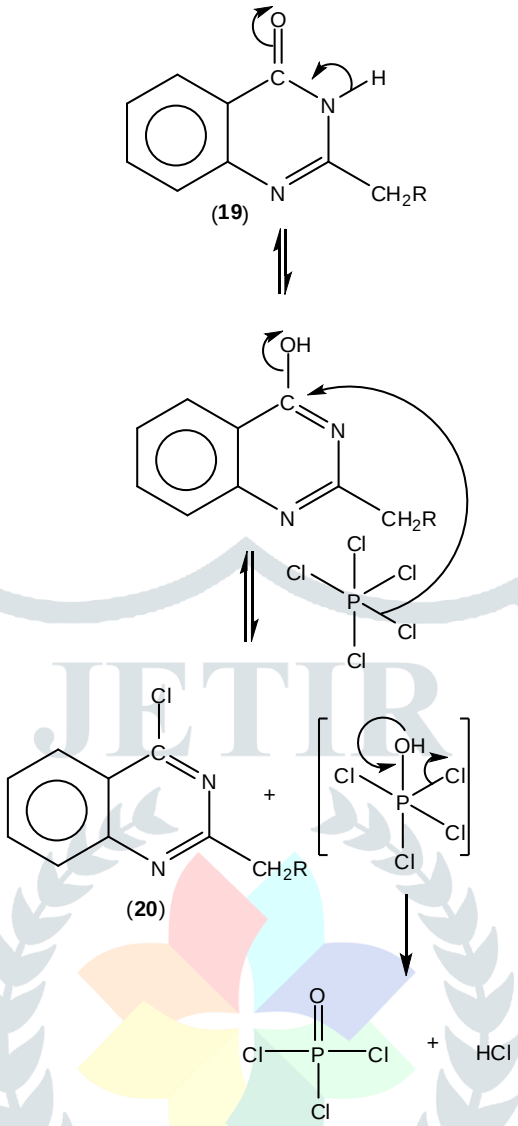
^{13}CNMR ($CDCl_3$) (in δppm): 42.50 (C-9), 115.25, 117.34, 121.25, 125.40, 131.68, 137.36, 137.90, 141.25, 141.78 (C-1 to C-6, C-11 to C-16), 163.55 (C-7, C-8), 175.45 (C-10)

Formation of (**19**) with the interaction of anthranilic acid and an amide has been explained on the basis of the following mechanism.

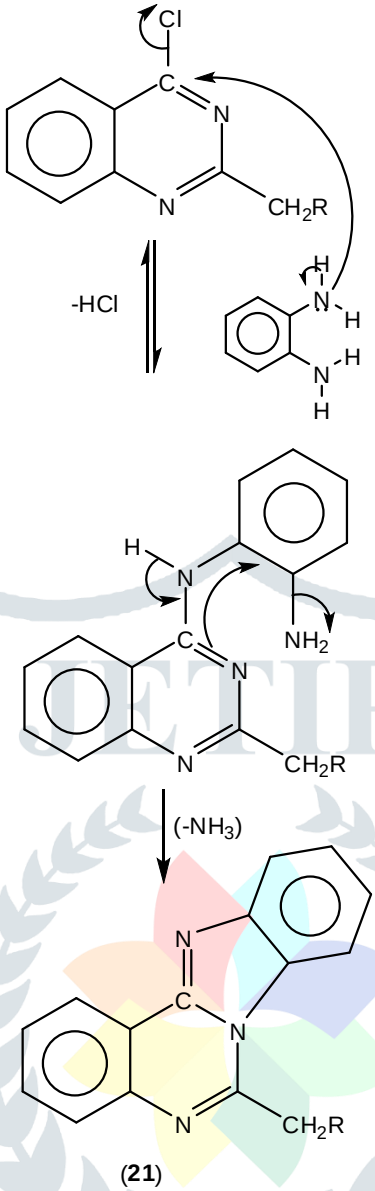


(**19**)

The quinazolone compound shows the amide-imidol tautomerism and the imidol form then reacts with PCl_5 in the presence of $POCl_3$ to give the 4- chloro derivative of the quinazoline.

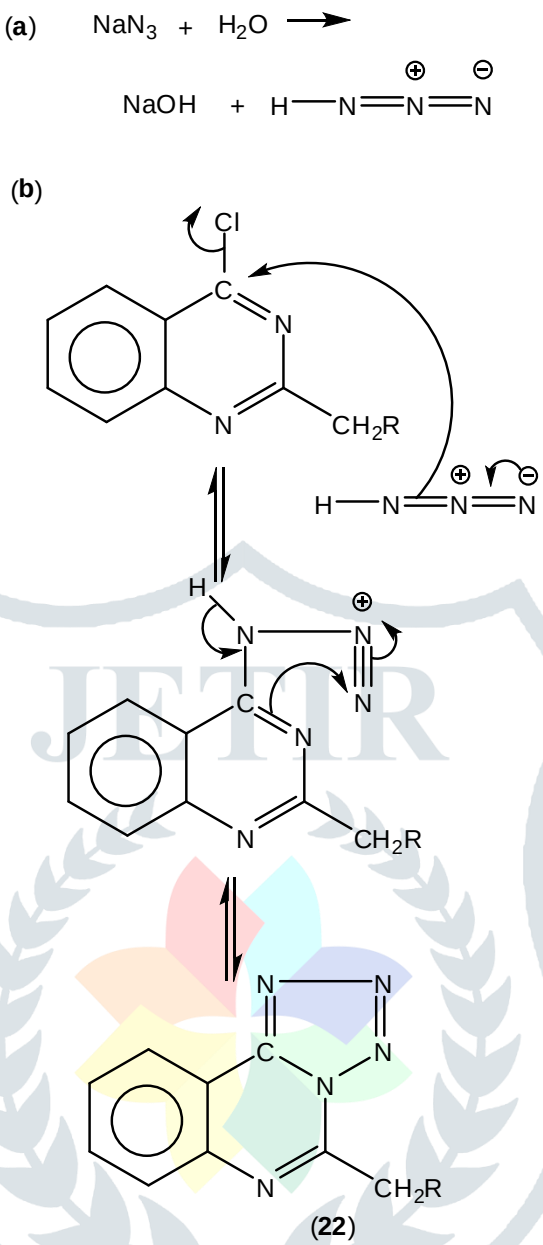


Reaction of (**20**) with o- phenylene diamine gives a benzimidazole derivative (**21**) with the expulsion of ammonia as is shown here with a plausible mechanism. Initially, the nucleophilic attack by the amine nitrogen takes place and HCl is removed from the system followed by the removal of ammonia.



(**21**)

Reaction of (**20**) with sodium azide in the presence of glacial acetic acid and water in Dimethyl Sulphoxide (DMSO) solvent has been explained on the basis of the following mechanism.



(**22**)

RESULTS AND DISCUSSION: Substituted Benzimidazolo/Tetrazolo Quinazolines have been synthesised using an easy and accessible approach. Compounds melting point were determined using the Toshniwal melting point equipment and recorded results are incorrect. A Perkin-Elmer 157 spectrophotometer was used to record IR spectra (vmax in cm-1), ^{13}C NMR spectra (Chemical shift in ppm), and ^{1}H NMR spectra in $CDCl_3$ using internal standards of TMS at 300 MHz and 40 MHz, respectively. On a Jeol SX-102 (FAB) mass spectrometer with m-nitrobenzylalcohol as matrix, the mass spectra were captured.

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