International Journal of Technical Research and Applications e-ISSN: 2320-8163,
www.ijtra.com Volume 2, Issue 6 (Nov-Dec 2014), PP. 89-90

AN INVESTIGATION LEADING TO THE DESIGN AND SYNTHESIS OF BENZIMIDAZOLO/ TETRAZOLO QUINAZOLINES

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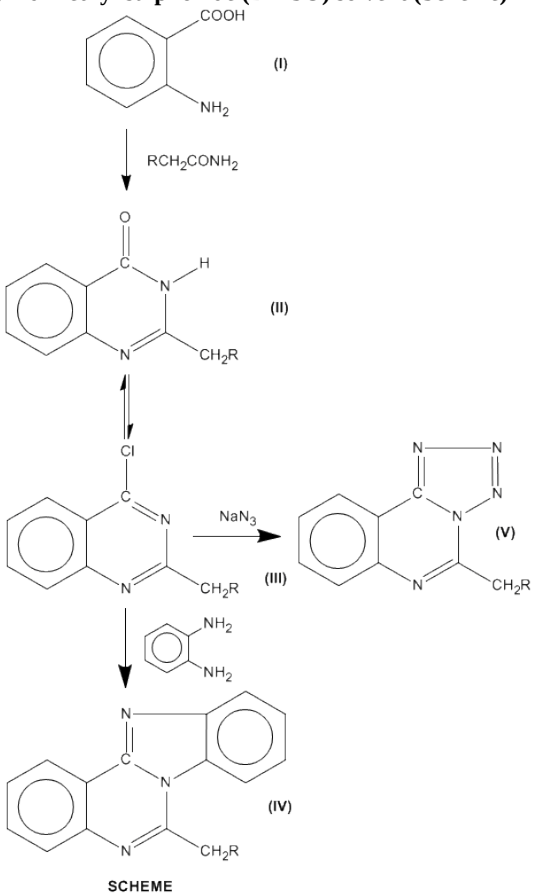
Abstract: Anthranilic acid on heating with a primary amide resulted in benzamidomethyl/ phthalimidomethyl-quinazolin 4 (3H) ones (II) which on treatment with phosphorus oxychloride ($POCl_3$) and phosphorus pentachloride (PCl_5) afforded 4-chloro-2-benzamidomethyl/phthalimidomethyl-quinazolines (III). Reaction of (III) with o-phenylenediamine in anhydrous pyridine furnished 2-benzamidomethyl/ phthalimido-methyl-benzimidazolo [2, 1-c] quinazolines (IV). A part of synthetic strategy was also adopted for the synthesis of 2-benzamidomethyl/ phthalimidomethyl-tetrazolo [1, 5-c] quinazolines (V) with the interaction of (III) with sodium azide (NaN_3) indimethyl sulphoxide (DMSO) solvent (Scheme)



SCHEME

I. INTRODUCTION

Quinazoline compounds are associated with diverse pharmacological properties. Several alkaloids have been investigated which contain quinazoline moiety in their molecular architectures. The most interesting quinazoline alkaloid is febrifugine, a substance of high antimalarial activity[1]. Some quinazoline alkaloids have been isolated from bacteria and fungi[2-4]. More importantly, quinazolines were evaluated for inhibition of the enzyme dihydrofolate reductase. Some of the analogs were found more potent than methotrexate as inhibitor of dihydrofolate in human leukemia cells[5, 6]. Baker and co-workers[7] on evaluation of several tetrahydroquinazolines reported the pronounced anticancer activity of such compounds. Recently, tetrahydroquinazolines were reported to possess remarkable antiviral activity against *Japanese encephalitis virus*, *Herpes Simplex virus* and *Influenza virus*[8]. These valid observations prompted the author to undertake the synthesis of some benzimidazolo/ tetrazolo quinazolines.

II. EXPERIMENTAL

Melting points were determined in open capillary tubes and are therefore incorrected. The IR spectra were recorded in cm^{-1} and were acquired as potassium bromide pellets on Perkin-Elmer 1800 and Shimadzu 8201 PC FTIR spectrophotometers. The ^{1}HNMR and CMR spectra were recorded on Bruker WM-400 spectrophotometer using tetramethylsilane as the internal standard and the chemical shift are expressed in δ (ppm). The mass spectra were recorded on Joel SX-102 (FAB) mass spectrometer in which p-nitrobenzyl alcohol was used as matrix. Purity of synthesized compound was checked by Thin Layer Chromatography (TLC) using silica gel-G and spots were visualized in iodine vapours.

2-Benzamidomethyl/2-Phthalimidomethyl-Quinazolin 4(3H) Ones (II)

A mixture of (1, 3-dioxo-1, 3-dihydroisoindol-2-yl) acetamide/ N-benzoylamino acetamido and anthranilic acid (equimolar amounts) was heated at 130-135° C for half an hour at room-temperature. 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. The solid phase was distilled off and washed with cold water. It was dried under vacuum and recrystallized from ethanol.

2-Benzamidoemethyl-quinazolin-4(3H)-one

White crystalline mass; m.p. 235-236°C; yield 6.2%
Anal for $C_{14}H_{13}N_3O_2$; N calcd 15.05%; N found 14.75%

2-Phthalimidomethyl-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% percent

4-Chloro-2-benzamidomethyl/ phthalimidomethyl quinazolines (III)

The imidol form of (II) (0.02 mole) and PCl_5 (0.02 mole) in $POCl_3$ (50 ml) were heated together for five hours under reflux under dry conditions. The resultant solution was poured into ice-cold water (250 ml) in installments with stirring after each addition. Precipitation occurred which was allowed to settle down. It was filtered at the pump and was recrystallized from ethanol.

4-Chloro-2-benzamidomethyl-quinazoline

Light brown crystals; m.p. 261°C; yield 50%

Anal for $C_{14}H_{12}N_3OCl$; 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/ phthalimidomethyl-benzimidazolo [2, 1-c] quinazolines (IV)

A mixture of (III) (0.01mole) and o-phenylenediamine (0.01 mole) in dry pyridine was heated under reflux for 6 hrs under anhydrous reaction conditions. Subsequently the hot reaction mixture after cooling at room-temperature was poured into cold-water (250 ml) containing diluted HCl (15ml) slowly with constant stirring. A solid separated out which was filtered off and recrystallized from diluted ethanol.

2-Benzamidomethyl benzimidazolo [2, 1-c] quinazoline (IVa)

Brown crystalline solid, m.p. 165-166°C, IR (KBr, in cm^{-1}) 1665 (sec. amide C=O), 1635(C=N), 2935 (C-H), ^{1}HNMR ($CDCl_3$, δppm), 6.70-7.55(m, 13H, ArH), 4.25(s, 2H, CH_3), 8.55(brs, 1H, CONH), ^{13}CNMR ($CDCl_3$,δppm), 175.65 (C=O), 165.40 (C=N), 45.50 (CH_2NH), 111.50-137.68 (Ar carbons).

MS (FAB): m/z (%) 352 $[M]^+$, (16), 105 (100), 77 (50), 51 (16).

Anal for $C_{22}H_{14}N_4O$; N calcd. 15.90%; N found 15.55%

2-Phthalimidomethyl, benzimidazolo [2, c]-quinazoline (IVb)

Melting point 180-181°C, brown crystalline mass, IR (KBr in cm^{-1}), 1705 (ter. Amido C=O), 1640(C=N), 2930 (CH); ^{1}HNMR ($CDCl_3$; δppm) 6.80 – 7.75 (m,12H, ArH), 4.20 (s, 2H, NCH_2), ^{13}CNMR (δ, $CDCl_3$), 177.25 (C=O), 168.50 (C=N), 45.00 (CH_2), 112.00-139.55 (Ar carbons), MS (FAB), m/z %; 378 $[M]^+$(20), 160 [100], 146 (16), 125 (25), 77 [35], 51 (15)

Anal for $C_{22}H_{14}N_4O_2$; N calcd. 14.78%; N found 14.80%

2-Benzamidomethyl-tetrazolo [1, 5-c] quinazolines (Va)

Melting point 201-202°C, light grey crystals, IR (KBr in cm^{-1}) 1675.20 (sec. amide C=O), 1637.50 (C=N), 1591.34 (N=N), 2915.00 (C-H), ^{1}HNMR ($CDCl_3$, δppm) 6.76-7.85 (m, 9H, ArH), 4.15 (s, 2H, CH_2), 9.20 (brs, 1H, CONH), ^{13}CNMR ($CDCl_3$, δppm) 175.45 (C=O), 163.55 (C=N), 42.50 (CH_2), 115.25-141.78 (Ar carbons) Mass (FAB) m/z %; 304 $[M^+]$ (16), 227 (12), 170 (35), 134 (20), 105 (100), 77 (50)

Anal for $C_{16}H_{12}N_6O$; N calcd. 27.63%; N found 27.55%

2-Phthalimidomethyl tetrazolo [1, 5-c] quinazoline (Vb)

Melting point 225-226°C, light grey, crystalline solid, IR (KBr in cm^{-1}) 1710(ter. amido C=O), 1636.00 (C=N), 1592.50 (N=N), 2905.15 (C-H), ^{1}HNMR ($CDCl_3$, δppm), 7.15-7.75 (m, 8H, ArH), 4.52 (s, 2H, NCH_2), ^{13}CNMR ($CDCl_3$, δppm), 177.25 (C=O),169.00(C=N), 43.25 (CH_2), 112.50-139.67 (Ar carbons), Mass (FAB) m/z % 330 $[M]^+$ (15), 105 (100), 77 (50) [51] (16).

Anal for $C_{17}H_{10}N_6O_2$; N calcd. 25.43%; N found 26.60%

III. BIOEVALUATION

All the four target compounds (Iva, IVb, Va and Vb) were evaluated for their antihyperglycemic activity in sucrose loaded rat models[9]. Male albino rats of Wistar strain were selected for the study. Fasting blood glucose level of each animal was checked by glucometer using glucostrips after an overnight starvation. Two groups of animals were selected viz; experimental group and control group. Rats of experimental group were administered the suspension of test sample orally prepared in 1% gum acacia (vehicle) at desired dose levels i.e. 100mg/kg body weight in case of standard antidiabetic drug, i.e. metformin. Animals of control group were given an equal amount of 1% gum acacia and termed as sham control. Quantitative glucose profile of each rat was calculated by Area Under Control (AUC) method using prism software. Comparing of AUC of experimental and control groups determined the percentage antihypertensive activity.

Benzimidazolo-quinazolines showed comparatively better antihyperglycemic activity than tetrazolo-quinazolines. However, all the four target compounds exhibited quite low order of antihyperglycemic activity in comparison to the standard drug.

IV. ACKNOWLEDGEMENT

The authors express their sincere thanks to The Head, Department of Chemistry, Lucknow University, Lucknow for providing necessary laboratory facilities and to the Director CDRI, Lucknow for elemental, spectral and biological activity data.

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