Int. J. Chem. Sci.: 8(1), 2010, 367-377

SYNTHESIS OF SOME NOVEL QUINAZOLINONE DERIVATIVES

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ABSTRACT

In this work, an efficient two step synthesis for the preparation of some novel quinozolinones has been reported. In step I, various 2-substituted-3, 1-benzoxazin-4-ones are formed by the reaction of anthranilic acid and acetic anhydride / benzoyl chloride / propionic anhydride. In step II, 2-substituted-3, 1-benzoxazin-4-ones, which are formed in step I, are condensed with valdecoxib. The resulting quinazolinone derivatives were characterized by IR, NMR, ^{13}C NMR and mass spectral analysis.

Key words: 2-Substituted-3, 1-Benzoxazin-4-one, Valdecoxib, Quninazolinone derivatives, IR, NMR, Mass spectroscopy.

INTRODUCTION

Quinazolinone derivatives have been reported as antimalarial[1], diuretic[2], sedative and hypotenstion[3], monoaminooxidaseinhibitoractivity[4-6], antihypertensive[7], antitububer-cular[8], analgesic[9], antiinflammatory[10,] antifibrillatory[11], antihistamine[12], CNSdepresant[13,14], anticonvulsant[15,16], antiparkinsonisom[17,18], antibacterial[19,20], antiviral[21], antiallergy[22], anthelmintic[23], anticancer[24], antiHIV[25], antitubercular[26], CVS[27] and bronchodilator[28]. Valdecoxib is a potent COX-2inhibitor and also contain $–SO_2NH_2$ group. This group can be condensed with benzoxainone derivatives and the products are novel quinazolinones, which may show better or additional activities. 4-(4-Methyl-3-phenyl-4-isoxazolyl)benzene sulfonamide, empirical formula $C_{16}H_{14}N_2O_3S$, molecular weight 314.36, is a white crystalline powder, which is relatively insoluble in ethanol, methanol, but freely soluble in

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organic solvents and aqueous alkali. Valdecoxib is a nonsteroidal antiinflammatory drug that exibits antiinflammaoty, analgesic and antipyretic properties. The mechanism of action is believed to be due to inhibition of prostaglandin synthesis primarily through inhibition of cyclo-oxygenase-2 (COX-2). At therapeutic plasma concentrations in human, valdecoxib does not inhibit cyclo-oxygenase-1 (COX-1). It was found that when one biodynamic heterocyclic system was coupled with another heterocyclic system, an enhanced biological activity was produced.

EXPERIMENTAL

All the melting jpoints were taken in Veego-Vmp 1 melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer FT-IR spectrometer. NMR spectra were recorded on Bruker spectrospeir 200 MHz and the chemical shifts are referenced to TMS.

Synthesis of compounds[29-34]

Synthesis of 2-phenyl-3, 1-benzoxazin-4-one (PB-1)

To a solution of anthranilic acid **(1a-c)** (0.01 mol) in pyridine (30 mL), benzoylchloride (0.02 mol) was added, and the mixture was shaken for 5 min and then kept aside at room temperature for further 25 min with occasional shaking. The reaction mixture was treated with 5% $NaHCO_3$ solution (15 mL), filtered, washed with water, dried and the crude product was recrystallised from absolute ethanol.

Synthesis of 2-ethyl-3, 1-benzoxazin-4-one (PB-2)

A mixture of anthranilic acid (0.1 mol) and propionic anhydride (0.2 mol) was refluxed for 4 hr under anhydrous conditions. The excess of propionic anhydride was distilled off under reduced pressure and it was cooled to room temperature. The **PB-2** separated as solid mass. The crude drug thus obtained was recrystallized from absolute alcohol.

Synthesis of 6-bromo-2-methyl-3, 1-benzoxazin-4-one (PB-3)

A mixture of 5-bromoanthranilic acid (0.1 mol) and acetic anhydride (0.2 mol) was refluxed for 4 hr under anhydrous conditions. The excess of acetic anhydride was distilled off under reduced pressure and it was cooled to room temperature. The **PB-3** separated as solid mass. The crude drug thus obtained was recrystallized from absolute alcohol.

Synthesis of 6-bromo-2-phenyl-3, 1-benzoxazin-4-one (PB-4)

To a solution of 5-bromoanthranilic acid (0.01 mol) in pyridine (30 mL), benzoylchloride (0.02 mol) was added, and the mixture was shaken for 5 min and then kept aside at room temperature for further 25 min with occasional shaking. The reaction mixture was treated with 5% $NaHCO_3$ solution (15 mL), filtered, washed with water, dried and the crude product was recrystallised from absolute ethanol.

Synthesis of 6-bromo-2-ethyl-3, 1-benzoxazin-4-one (PB-5)

A mixture of 5-bromoanthranilic acid (0. 1 mol) and propionicanhydride (0.2 mol) was refluxed for 4 hr under anhydrous conditions. The excess of acetic anhydride was distilled off under reduced pressure and cooled to room temperature. The **PB-5** separated as solid mass. The crude drug thus obtained was recrystallized from absolute alcohol.

Synthesis of 6-bromo-2-methyl-3, 1-benzoxazin-4-one (PB-6)

A mixture of 3,5-dibromoanthranilic acid (0.1 mol) and acetic anhydride (0.2 mol) was refluxed for 4 hr under anhydrous conditions. The excess of acetic anhydride was distilled off under reduced pressure and it was cooled to room temperature. The **PB-6** separated as solid mass. The crude drug thus obtained was recrystallized from absolute alcohol.

Synthesis of 6, 8-dibromo-2-phenyl-3, 1-benzoxazin-4-one (PB-7)

To a solution of 5-bromoanthranilic acid (0.01 mol) in pyridine (30 mL), benzoylchloride (0.02 mol) was added and the mixture was shaken for 5 min and then kept aside at room temperature for further 25 min with occasional shaking. The reaction mixture was treated with 5% $NaHCO_3$ solution (15 mL), filtered, washed with water, dried and the crude product was recrystallised from absolute ethanol.

Synthesis of 6, 8-dibromo-2-ethyl-3, 1-benzoxazin-4-one (PB-8)

A mixture of 3,5-dibromoanthranilic acid (0. 1 mol) and propionicanhydride (0.2 mol) was refluxed for 4 hr under anhydrous conditions. The excess of acetic anhydride was distilled off under reduced pressure and it was cooled to room temperature. The **PB-8** separated as solid mass. The crude drug thus obtained was recrystallized from absolute alcohol. The melting points molecular weights, R_f values and yields of the compounds **PB-1** to **PB-8** are given in Table 1.

Synthesis of 2-phenyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)-phenyl]sulfonyl}4-(3H) quinazolinone (PBV-1)

An equimolar (0.1 mol) mixture of 2-phenyl-3,1-benzoxazin-4-one and valdecoxib was refluxed for 6 hr with 10 mL of glacial acetic acid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol.

Synthesis of 2-ethyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)-phenyl] sulfonyl}4-(3H) quinazolinone (PBV-2)

An equimolar (0.1 mol) mixture of 2-ethyl-3,1-benzoxazin-4-one and valdecoxib was refluxed for 6 hr with 10 mL of glacial acetic acid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol.

Synthesis of 6-bromo-2-methyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)-phenyl] sulfonyl}-4-(3H) quinazolinone (PBV-3)

An equimolar (0.1 mol) mixture of 6-bromo-2-methyl-3,1-benzoxazin-4-one and valdecoxib was refluxed for 6 hr with 10 mL of glacial acetic acid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol.

Synthesis of 6-bromo-2-phenyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)-phenyl] sulfonyl}4-(3H) quinazolinone (PBV-4)

An equimolar (0.1 mol) mixture of 6-bromo-2-phenyl-3,1-benzoxazin-4-one and Valdecoxib was refluxed for 6 hr with 10 mL of glacial acetic acid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol.

Synthesis of 6-bromo-2-ethyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)-phenyl] sulfonyl}-4-(3H) quinazolinone (PBV-5)

An equimolar (0.1 mol) mixture of 6-bromo-2-ethyl-3,1-benzoxazin-4-one and valdecoxib was refluxed for 6 hr with 10 mL of glacial acetic acid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol.

Synthesis of 6, 8-dibromo-2-methyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)-phenyl] sulfonyl}-4-(3H) quinazolinone (PBV-6)

An equimolar (0.1 mol) mixture of 6,8-dibromo-2-methyl-3,1-benzoxazin-4-one and valdecoxib was refluxed for 6 hr with 10 mL of glacial acetic acid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol.

Table 1: Physical data of synthezised compounds

Code	Molecular formula	Molecular weight	Melting point (^oC)	% yield	R_f value
PB-1	$C_{14}H_9NO_2$	223.233	120	89	0.75
PB-2	$C_{10}H_9NO_2$	175.188	104	74	0.86
PB-3	$C_9H_6BrO_2N$	240.57	123	55	0.68
PB-4	$C_{14}H_8BrNO_2$	302.129	180	58	0.87
PB-5	$C_{10}H_8BrNO_2$	254.084	190	69	0.97
PB-6	$C_9H_5Br_2NO_2$	318.953	176C	61	0.93
PB-7	$C_{14}H_7Br_2NO_2$	381.025	153	60	0.81
PB-8	$C_{10}H_7Br_2NO_2$	332.980	158	83	0.85
PBV-1	$C_{30}H_{21}N_3O_4S$	519.574	135	81	0.70
PBV-2	$C_{26}H_{21}N_3O_4S$	471.537	146	77	0.68
PBV-3	$C_{25}H_{18}BrN_3O_4S$	536.397	157	86	0.72
PBV-4	$C_{30}H_{20}BrN_3O_4S$	598.467	155	94	0.69
PBV-5	$C_{26}H_{20}BrN_3O_4S$	550.424	148	97	0.84
PBV-6	$C_{25}H_{17}Br_2N_3O_4S$	615.293	168	80	0.58
PBV-7	$C_{30}H_{19}Br_2N_3O_4S$	677.363	160	96	0.63
PBV-8	$C_{26}H_{19}Br_2N_3O_4S$	629.320	138	78	0.71

Synthesis of 6, 8-dibromo-2-phenyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)-phenyl] sulfonyl} 4-(3H) quinazolinone (PBV-7)

An equimolar (0.1 mol) mixture of 6,8-dibromo-2-phenyl-3,1-benzoxazin-4-one and valdecoxib was refluxed for 6 hr with 10 mL of glacial acetic acid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol.

Synthesis of 6, 8-dibromo-2-ethyl-3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)-phenyl] dulfonyl}-4-(3H) quinazolinone (PBV-8)

An equimolar (0.1 mol) mixture of 6,8-dibromo-2-ethyl-3,1-benzoxazin-4-one and valdecoxib was refluxed for 6 hr with 10 mL of glacial acetic acid. The mixture was cooled to room temperature and poured into crushed ice. Then it was filtered and dried. The solid thus obtained was recrystallised from absolute alcohol. The melting points, molecular weight, R_f values and yields of the compounds **PBV-1** to **PBV-8** are given in Table 1.

Spectral analysis of the compounds[33-35]

PB-1: IR (KBr): 1764 (C=O str), 1612 (C = Nstr) cm^{-1}

PMR (200MHz; $CDCl_3$): δ 7.63-8.34 (m, 9H, Ar-H)

PB-2: IR (KBr): 1685 (C=O str), 1640 (C = N str) cm^{-1}

PB-3: IR (KBr): 1700 (C=O str), 1613 (C=N str), 530 (C-Br str) cm^{-1}

PB-4: IR (KBr): 1755(C=O str), 1578(C=N str), 560(C-Br str) cm^{-1}

PB-5: IR (KBr): 1700(C=O str), 1613(C=N str), 530(C-Br str) cm^{-1}

PB-6: IR (KBr): 1712(C=O str), 1598(C=N str), 532 (C-Br str) cm^{-1}

PB-7: IR (KBr): 1756(C=O str), 1614(C=N str), 583,537 (C-Br str) cm^{-1}

PB-8: IR (KBr): 1774(C=O str), 1579(C=N str), 530,554 (C-Br str) cm^{-1}

PBV-1: IR (KBr): 1643(C=O str), 1333 and 1150(S=O str), 1599 (C=N str) cm^{-1}

PMR (200MHz; DMSO): δ 1.54 (s, 3H, CH_3)7.63-8.34 (m, 18H, Ar-H)

PBV-2: IR (KBr): 1678 (C=O str), 1332 and 1150(S=O str), 1465 (C=N str) cm^{-1}

PMR (200MHz; DMSO): δ 0.69 (t, 3H, $CH_3.CH_2$) 1.39 (q, 2H,CH_2CH_3), 1.85 (s, 3H, CH_3), 6.80-6.95 (m, 13H, Ar-H)

PBV-3: IR (KBr): 1663 (C=O str), 1333 and 1150 (S=O str), 1578 (C=N str) cm^{-1}

PMR (200MHz; $CDCl_3$): δ 1.22 (s, 3H, CH_3) 1.56 (s, 3H, CH_3), 6.52-7.51 (m, 11H, Ar-H)

PBV-4: IR (KBr): 1664(C=O str), 1338 and 1156 (S=O str), 1597(C=N str) cm^{-1}

PMR (200MHz; DMSO): δ 1.56 (s, 3H, CH_3)6.47-7.77(m, 17H, Ar-H)

PBV-5: IR (KBr): 1656(C=O str), 1334 and 1150(S=O str), 1502 (C=N str) cm^{-1}

PMR (200MHz; DMSO): δ 0.68 (t, 3H, $CH_3.CH_2$)1.41 (q, 2H, $CH_2.CH_3$), 1.82 (s, 3H, CH_3), 6.62-6.92 (m, 12H, Ar-H)

PBV-6: IR (KBr): 1663(C=O str), 1333 and 1151(S=O str), 1598 (C=N str) cm^{-1}

PMR (200MHz; DMSO): δ 1.20 (s, 3H, CH_3)1.55 (s, 3H, CH_3), 6.46-7.51 (m, 11H, Ar-H)

PBV-7: IR (KBr): 1662(C=O str), 1332 and 1156(S=O str), 1578 (C=N str) cm^{-1}

PMR (200MHz; $CDCl_3$): δ 1.54 (s, 3H, CH_3), 7.63-8.34(m, 18H, Ar-H)

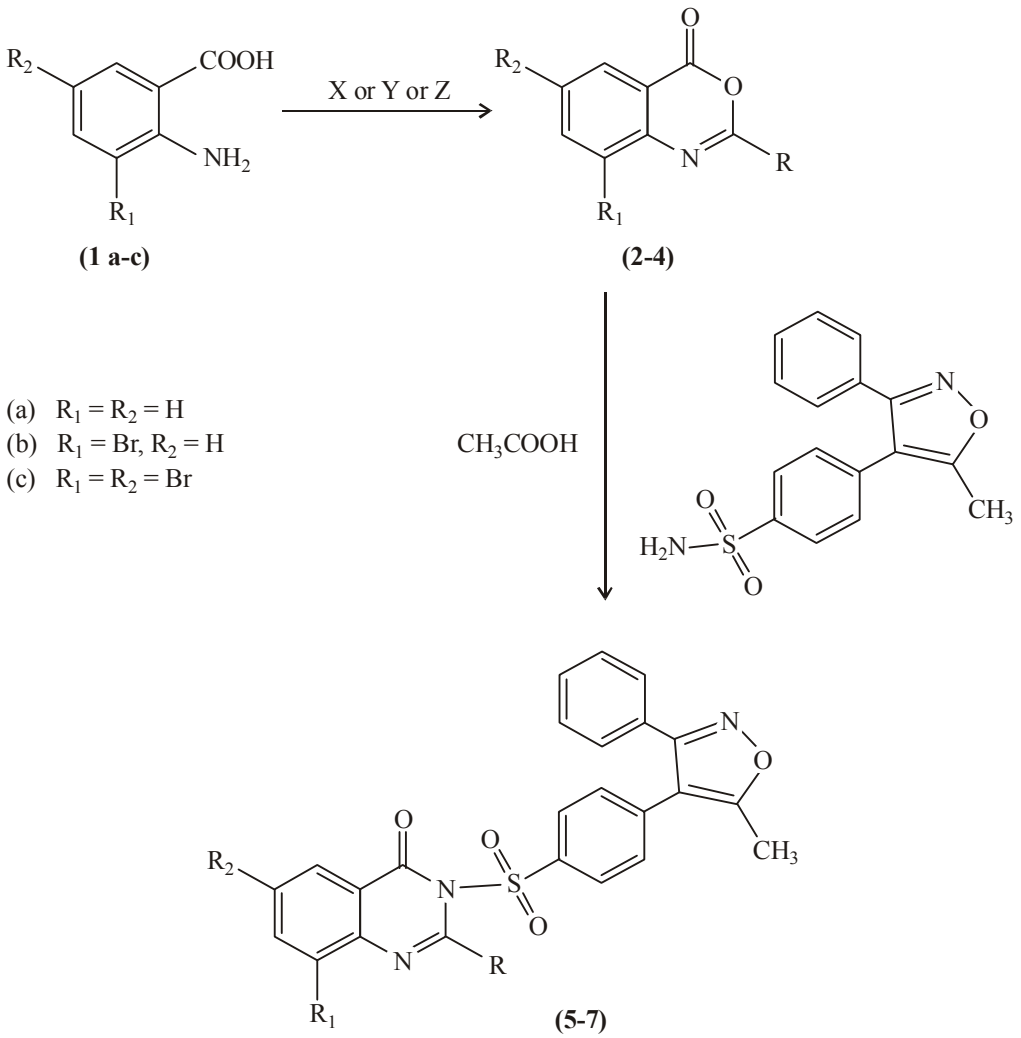
PBV-8: IR (KBr): 1656(C=O str), 1334 and 1150 (S=O str), 1502 (C=N str) cm^{-1}

PMR (200MHz; DMSO): δ 0.68 (t, 3H, $CH_3.CH_2$) 1.41 (q, 2H, $CH_2.CH_3$), 1.82 (s, 3H, CH_3), 6.62-6.92 (m, 12H, Ar-H).

RESULTS AND DISCUSSION

Eight novel quinazolinone derivatives were synthesized and characterized by spectral analysis. 2-Phenyl/ethyl,6-bromo-2-methyl/6-bromo-2-phenyl/6-bromo2-ethyl and 6,8-dibromo-2-methyl/6,8-dibromo-2-phenyl/6,8-dibromo-2-ethyl3-{[4-(5-methyl-3-phenyl-4-isoxazolyl)phenyl]sulfonyl}-4-(3H)quinozolinone were synthesized by refluxing equimolar amounts of 2-substituted-3,1-benzoxazin-4-one and valdecoxib in the presence of glacial acetic acid. The melting point of the synthesized compounds was found out by open capillary tube method and the results are uncorrected. The purity of the compounds was checked by TLC using silica gel G as an adsorbent, ethyl acetate and chloroform (9.8 : 0.2) were used as mobile phase. The spot was visualized by iodine vapor or dinitrophenyl-hydrazine solution. The structure of the synthesized compounds was characterized by its IR and ^1H NMR spectral analysis, where it complies with the normal values.

Scheme 1



X = C_6H_5COCl 2 & 5 R = C_6H_5

Y = $(CH_3CH_2CO)_2$ O/heat/4 hr 3 & 6 R = C_2H_5

Z = $(CH_3CO)_2$ O/heat/4 hr 4 & 7 R = CH_3

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Accepted : 07.10.2009