BEHAVIOUR OF 4-(4-ACETYLAMINOPHENYL)-4-OXO-BUT-2-ENOIC ACID TOWARDS NUCLEOPHILES AND SYNTHESIS OF VARIOUS N-HETEROCYCLES

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The present work deals with the reaction of 4-(4-acetylaminophenyl-4-oxobut-2-enoic acid (**1**) with sulfur reagents, e.g. thiophenol at different acidity of medium, phenol in the presence of concd. sulfuric acid, and phosphorous pentachloride to afford the corresponding adducts **2-6**. Reaction of the latter compounds with different electrophilic and nucleophilic reagents yields some important heterocyclic derivatives.

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Introduction

(E)-4-Aryl-4-oxo-2-butenoic acids have been shown that convenient polyelectrophilic reagents in the synthesis of heterocyclic rings for which the addition reaction of N-, S-, P- and C-nucleophiles[1-3] occur exclusively at the α-carbonyl electrophilic center of the molecules.

Also, they exhibit abroad spectrum of physiological activities,[4] Alzheimer,[5] their esters as intermediate in the field of medical science, agriculture, and perfume.[6] The substitution pattern on the aroyl moiety influences the antiproliferative activity against the human cervix carcinoma (Hela cells)[7] and they have activated double bond, half-wave reduction potentials ($E_{1/2}$)[8] display good correlations with Hammett sigma value, attempts to obtain good correlations using frontier orbitals of the molecules.

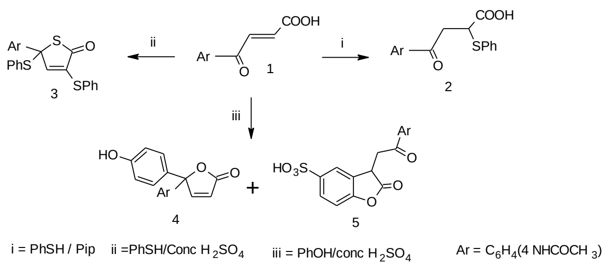
Also, they have emerged the most promising drug candidates[9] which are selective for integrase S-1360[10] and class of Human immunodeficiency virus type-1 (HIV-1) integrase inhibitors,[11] cytostatic activity used as an aid to study and determine factors affecting the human eye's UV filters,[12] as *Aspergillus* controller[13] and inhibitors of phospholipase[14a] and anticancer.[15]

They are used a key starting material due to their high electrophilicity, they react readily with nucleophiles including nitrogen and carbon nucleophiles afford either cyclic or normal Michael adducts.

Hence, keeping these reports in view we continue our researches[16] in the field of 4-(4-acetylaminophenyl)-4-oxo-2-butenoic acid derivatives.

Results and Discussion

The structure of adducts that produced *via* the reaction of 4-(4-acetylaminophenyl)-4-oxo-2-butenoic acid (**1**) and thiophenol was depended on acidity of the medium. So, when the acid **1** was allowed to react with thiophenol[14,16] in the presence of few drops of piperidine (under Michael reaction condition, alkaline medium) afforded the adduct, 4-(4-acetylaminophenyl)-4-oxo-2-phenylmercapto-butanoic acid (**2**). That to be differed from the behavior of the acid **1**, when it was allowed to react with thiophenol in the presence of concd. H_2SO_4 (acidic medium) afforded 2,4-diphenylmercapto-2-(4-acetylaminobenzoyl)thiophen-5-one (**3**), *via* the adduct **2** as outlined (Scheme1). Moreover, when 3-(4-acetylaminophenyl)-4-oxo-2-butenoic acid (**1**) with phenol in the presence of concd. H_2SO_4 yielded[14] a mixture of 2–(4-hydroxyphenyl-2-(4-acetylaminophenyl)-5-oxofuran (**4**) and 2-oxo-3-(2-oxo-2-(4-acetylamino-phenyl))ethyl-5-benzo[b]-furansulphonic acid (**5**)



Scheme 1

When 4-(4-acetylaminophenyl)-4-oxobut-2-enoic acid **(1)** was allowed to react with phosphorous pentachloride afforded 4-(4-acetylaminophenyl)-4-oxobut-2-enoyl chloride **(6)** as key starting material for synthesis some important heterocycles (Scheme 2) .

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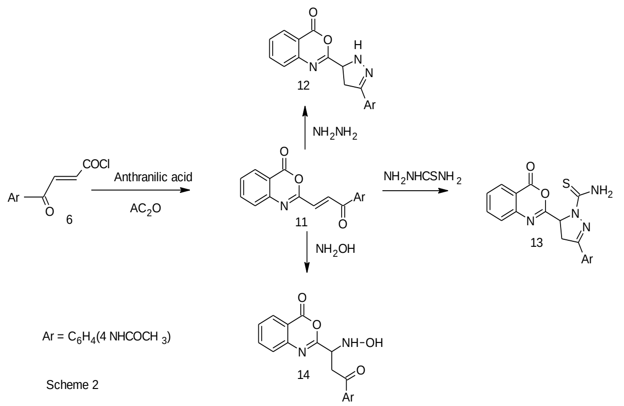
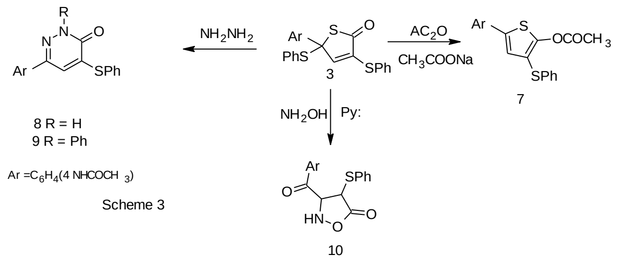
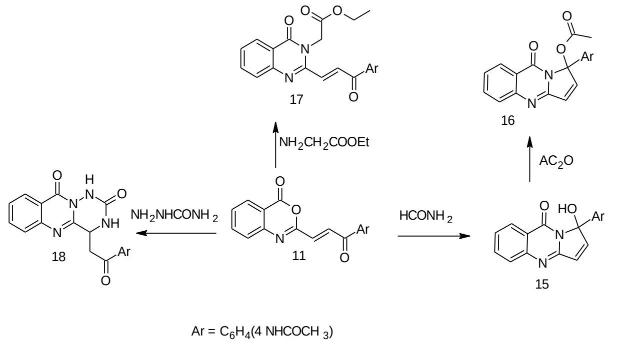


Scheme 2



Scheme 3



Scheme 4

The thiophenone **3** can be allowed to react with some electrophilic and nucleophilic reagents. Thus, it was treated with acetic anhydride in the presence of sodium acetate, hydrazine hydrate and hydroxylamine in boiling pyridine, which afforded thiophene ester **7**, pyridazinone derivatives **8** and **9** and isoxazolone derivative **10.** (Scheme 3).

The present work has succeeded in the synthesis of a series of some important heterocycles from 4-acetamido phenyl-4-oxo-2-butenoic acid and in the synthesis of benzoxazinone derivative bearing α,β-unsaturated ketone moiety on aromatic substituents in the position 2, that enhances the reactivity of benzoxazinone moiety towards nitrogen nucleophiles.[16e] Thus, when acid chloride **6** was allowed to react with anthranilic acid in the presence of acetic anhydride, it afforded benzoxazinone **11**. Reaction of the latter compound with hydrazine hydrate, thiosemicarbazide and hydroxylamine afforded 3-benzoxazinyl pyrazole derivatives **12, 13** and hydroxylamino benzoxazinone **14** (Scheme 2).

Another aspect was the synthesis of novel quinazoline derivatives. When the benzoxazinone **11** was allowed to react with formamide, it yielded pyrrolo[1,2-b]quinazolinone **15** that was confirmed chemically by its reaction with acetic anhydride to give compound **16**. Moreover, reaction of benzoxazone **11** with ethyl glycinate and semicarbazide afforded quinazolinone **17** and 1,2,4-triazine **18,** respectively (Scheme 4).

Experimental

All melting points are uncorrected and were determined on a Stuart electric melting point apparatus. Elemental analyses were carried out at the Microanalytical Center, National Research Center, Cairo, Egypt by Elementar Viro El Microanalysis. IR spectra (KBr) were recorded on infrared spectrometer FT-IR 400D using OMNIC program and are reported in terms of cm^{-1}. ^1H-NMR spectra were recorded on a Bruker spectrophotometer at 400 MHz using TMS as internal standard and with residual signals of the deuterated solvent δ=7.26 ppm for $CDCl_3$ and δ=2.51 ppm for DMSO-d_6. ^{13}C-NMR spectra were recorded on the same spectrometer at 100 MHz and referenced to solvent signals δ=77 ppm for $CDCl_3$ and δ 39.50 ppm for DMSO-d_6. DEPT 135 NMR spectroscopy were used where appropriate to aid the assignment of signals in the ^1H spectrum. The mass spectra were recorded on Shimadzu GCMS-QP-1000 EX mass spectrometer at 70 eV using the electron ionization technique. Homogeneity of all compounds synthesized was checked by TLC.

General Procedure for the Preparation of Compounds 3

An equimolar mixture of compound **1** (2.35 g; 0.01 mol) and thiophenol (1 mL, 0.01 mol) in the presence of few drops piperidine in 30 mL benzene. The reaction mixture was refluxed for 3 h. The solid that separated after cool was filtered off, washed by petroleum ether (b.p 40-60 ºC), dried and then, crystallized from ethanol .

*2,4-Bis(phenylmercapto)-2-(4-acetylaminobenzoyl)thio-phen-5-one (**3**)*

Yield 74%. M.p. 150-152 °C. IR(KBr) 1613 (C=N), 1650, 1670, 1689 (CO). ^1H NMR (DMSO): δ 2.5(s, 3H, CH3), 6.65 (s, 1H, proton of thiophene moiety), multiplet at 7.47–8.05 assigned for 14 ArH aromatic protons, acidic proton 13.1 a OH=NH proton exchanged in D_2O and Anal.: calcd. for $C_{24}H_{19}NO_2S_3$: C 66.82 , H 4.40 N 3.24; found: C 66.75 , H 4.33 N 3.10. MS: m/z 434, 431 [M], 373 [M-($NHCOCH_3$)], 236 [373-($PhSCH=CH_2$)].

General Procedure for the Preparation of Compounds 4 and 5

An equimolar mixture of compound **1** (2.35 g; 0.01 mol) and phenol (1g, 0.01 mol) in the presence of concd. H_2SO_4 (2 mL) in 30 mL methanol. The reaction mixture was refluxed for 3 h. The solid that separated after cool was filtered off, washed by petroleum ether (b.p. 40-60 ºC), dried and then, crystallized from benzene afford **4** and ethanol afford **5**.

2–(4-Hydroxyphenyl-2-(4-acetylaminophenyl)-5-oxo-furan (**4**)

Yield 70%. M.p. 180-182 °C. IR(KBr) 1600 (C=C), 1650, 1720 (CO), 3314 (NH), 3427 (OH). ^{1}H NMR (DMSO): δ 2.5(s, 3H, CH_3), multiplet at 7.35 – 7.92 assigned for 10 ArH aromatic and olefinic protons, acidic protons at 13.1 OH and NH protons exchanged in D_2O and aAnal: calcd. for $C_{18}H_{15}NO_4$: C 69.90, H 4.85; found: C 69.75, H 4.67. MS: m/z 309 [M], 265 [M-CO_2], 248 [M-(CH_3CO+H_2O)], 175

2-Oxo-3-(2-oxo-2-(4-acetylaminophenyl))ethyl-5-benzo[b]furan-sulphonic acid (**5**)

Yield 35 %. M.p. 150-152 ºC, IR(KBr) 3354 υNH, 2212 υCN, 1655, 1678, (cyclic amide and carboxyl group), and υC=N 1628. The EI-MS shows the molecular ion peak at m/e 392 and 389 corresponding to $(M+2)^{\cdot+}$ $(M^{\cdot+})$, respectively. Anal. for $C_{18}H_{15}NO_7S$: calcd: C 55.52,H 3.85; found: C 55.44, H3.80.

3-(4-Acetylaminophenyl)-4-oxobut-2-enoyl chloride (6)

A solution of 3-(4-acetamidobenzoyl)-prop-2-enoic acid (2.35 g; 0.01 mol) in phosphorous oxychloride (15 mL) was treated with PCl_5 (3 g; 0.015 mol). The reaction mixture was refluxed for 2 h. The solid that separated out on cooling was filtered off, washed with petroleum ether (b.p. 40-60 ºC) and dried. Yield: 70 %; M.p. 110-112 ºC; IR (KBr) 1645, 1690, 1790 (CO); Anal.: calcd. for $C_{12}H_{10}NO_3Cl$: C 57.37, H 3.89; found: C 57.25, H 3.80.

Methyl-5-(4-acetylaminophenyl)-2-thiophenate ester (**7**)

A mixture of **3** (0.01 mol), acetic anhydride (9.4 mL, 0.1 mol) , and anhydrous sodium acetate (2 g) was refluxed on water bath for 2 h. The excess acetic anhydride was removed by distillation and the reaction mixture was poured onto ice/H_2O. The separated product was filtered, dried and were recrystallized from mixture of toluene-ethanol. Yield 75 %. M.p. 130-132 °C. IR(KBr) 1640, 1762, 1843 (CO). ^{1}H NMR (DMSO-d$_6$*)*: δ 2.1 (s, 6H, 2CH_3), 7.46-7.71 (m, 10H, Ar-H), 12.40 (brs, 1H, NH of acetamido moiety). Anal. calcd. for $C_{20}H_{17}NS_2O_3$: C 62.66, H 4.43, S 16.71; found: C 62.30, H 4.25, S 16.60 MS: m/z 325 [M-NH(O)$COCH_3$].

General Procedure for the Preparation of Compounds 8 and 9

A mixture of **3** (0.01 mol) and hydrazine hydrate and/or phenyl hydrazine (0.01 mol) in ethanol (40 mL) and was heated under reflux for 5 h. The reaction mixture was allowed to cool and the separated product was filtered, dried and were recrystallized from ethanol.

4-(Phenylmercapto)-6-(4-acetylaminophenyl)-2,3-dihydro-pyridazin-3(2H)-one (**8**)

Yield: 70 %. M.p. 230-232 °C. IR(KBr) 1640, 1687 (CO), 3285 (NH). ^{1}H NMR (DMSO-*d6)*: δ 2.5(s, 3H, CH_3), 7.35-8.00 (m, 10H, Ar-H and pyridazine), 11.90 (brs, 2H, NH of acetamido and pyridazinone moieties). Anal: calcd. for $C_{18}H_{15}N_3SO_2$: C 64.09, H 4.45, N 12.46, S 9.49; found: C 63.70, H 4.20, N 12.36, S 9.32. MS: m/z 337 [M], 307 [M-CH_2O], 262 [M-Ph group].

2-Pheny-4-(phenylmercapto)-6-(4-acetylaminophenyl)-2,3-dihydropyridazin-3(2H)-one (**9**)

Yield: 60 %. M.p. 212-214 °C. IR(KBr) 1640, 1700 (CO), 3279 (NH). ^{1}H NMR (DMSO-d$_6$*)*: δ 2.1 (s, 3H, CH_3), 7.23-8.11 (m, 15H, Ar-H and pyridazine), 12.80 (brs, 1H, NH of acetamido moiety). Anal.: calcd. for $C_{24}H_{19}N_3SO_2$: C 69.73, H 4.60, N 10.16, S 7.74; found: C 69.50, H 4.30, N 9.86, S 7.52

3-(4-Acetylaminobenzoyl)-4-phenylmercapto-5-oxo-2,3,4,5-tetrahydro-1,2-oxazole (**10**)

A mixture of **3** (0.01 mol) and hydroxyl amine hydrochloride (1.03 g; 0.015 mol) in boiling pyridine (50 mL) and was heated under reflux for 6 h. The reaction mixture was allowed to cool, pour into ice/HCl and the product was filtered, dried, and were recrystallized from toluene. Yield 80 %. M.p. 300 °C. IR(KBr) 1650, 1707, 1786 (CO), 3142 (NH). ^{1}H NMR (DMSO): δ 2.51 (s, 3H, CH_3), 4.87 (m, 2H, CH-CH oxazole system), multiplet at 7.63–8.00 assigned for 9 ArH aromatic protons, acidic protons 9.80 (s, 1H, NH of oxazole moiety) and 12.85 (s, 1H, NH of acetamido group), all acidic NH protons that exchanged in D_2O. Anal.: Calcd. for $C_{18}H_{16}N_2SO_4$: C 60.67, H 4.49, N 7.86, S 8.98; found: C 60.40, H 4.20, N 7.50, S 8.66.

2-[3-(4-Acetylaminophenyl)-3-oxopropen-1-yl]-3,1-benzoxa-zin-4-one (**11**)

A solution of 3-(4-acetamidobenzoyl)-prop-2-enoic acid chloride **5** (2. 5 g; 0.01 mol) and anthranilic acid (1.5 g; 0.01 mol) in 40 mL dry pyridine was refluxed for 3 h. The reaction mixture poured into ice/HCl, the solid that separated was filtered off, dried and recrystallized from ethanol. The anthranil product was refluxed with Ac_2O (5mL) for 1 h to afford **16**. Yield 75 %; m.p. 130-152 ºC; IR (KBr) 1660, 1683 (CO anthranil), 1780 (CO), 3220 (NH); ^{1}H NMR (DMSO-d$_6$*)*: δ 2.5 (s, 3H, CH_3), 7.46-8.11 (m, 10H, Ar-H and olefinic), 12.40 (brs, 1H, NH of acetamido moiety) and Anal.: calcd. for $C_{19}H_{14}N_2O_4$: C 68.26, H 4.19, N 8.38; found: C 68.00 , H 4.13, N 8.00.

2-[5-(4-Acetylaminophenyl)-2,3,4-trihydropyrazol-3-yl]-3,1-benzoxazin-4-one (**12**)

A mixture of **11** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (50 mL) was heated under reflux for 5 h. The reaction mixture was allowed to cool and the product was filtered off, dried and recrystallized from ethanol. Yield 70 %; m.p. 150-152 ºC; IR(KBr) 1709, 1731 (CO), 3319 (NH); ^{1}H NMR (DMSO-d$_6$*)* : δ 2.5 (s, 3H, CH_3), 3.2 (m, 4H, CH2-CH-NH), 7.46-8.11 (m, 8H, Ar-H), 12.40 (brs, 1H,NH of acetamido moiety). Anal.: calcd. for $C_{19}H_{16}N_4O_3$: C 65.51, H 4.60, N 16.09; found: C 65.38, H 4.50, N 16.30.

2-[5-(4-Acetylaminophenyl)-2-thiocarbamido-2,3,4-trihydro-pyrazol-3-yl]-3.1-benzoxazin-4-one (**13**)

A mixture of **11** (0.01 mol) and thiosemicarbazide (0.01mol) in ethanol (50 mL) was heated under reflux for 5 h.

The reaction mixture was allowed to cool and the product was filtered off, dried and recrystallized from ethanol. Yield 70%; m.p. 112-114 °C; IR (KBr) 1709, 1735 (CO), 3423 (NH). ^{1}H NMR (DMSO-d$_6$) : δ 2.5 (s, 3H, CH_3), 3.4 (m, 3H, CH_2-CH), 7.46-8.11 (m, 8H, Ar-H), 12.40 (brs, 3H, NH of acetamido and thioamide moieties) and Anal.: calcd. for $C_{20}H_{17}N_5SO_3$: C 58.96, H 4.17, N 17.19; found: C 58.70, H 4.00, N 17.00.

2-[3-(4-Acetylaminophenyl)-3-oxo-1-hydroxyaminopropan-1-yl]-3,1-benzoxazin-4-on (**14**)

A mixture of **11** (0.01 mol) and hydroxylamine hydrochloride (1.03 g; 0.015mol) was dissolved in boiling pyridine (50 mL) and heated under reflux for 6 h. The reaction mixture was allowed to cool, pour into ice/HCl, the product was filtered off, dried and recrystallized from dioxane. Yield: 70 %; M.p. 155-158 °C; IR (KBr) 1645, 1722 (CO), 3439 (NH) and (OH); ^{1}H NMR (DMSO-d$_6$): δ 2.1 (s, 3H, CH_3), 3.2 (m, 5H, CH_2CH-NHOH), 7.46-8.11 (m, 8H, Ar-H), 12.40 (brs, 1H, NH of acetamido moiety). Anal.: calcd. for $C_{19}H_{17}N_3O_5$: C 62.12, H 4.63, N 11.44; found: C 62.00, H4.43, N 11.26 .

1-Hydroxy-1-(4-acetylaminophenyl)-9-oxo-1,9-dihydropyr-rolo[2,1-b]quinazoline (**15**)

A mixture of **11** (0.01 mol) and formamide (30 mL) and was heated under reflux for 3h. The reaction mixture was allowed to cool and pour into iced water. The product was filtered off, dried and recrystallized from ethanol. Yield 65 %; M.p. 185-187 °C; IR (KBr) 1660, 1716 (CO), 3438 (NH and OH); ^{1}H NMR (DMSO-d$_6$): δ 2.5 (s, 3H, CH_3) 5.5 (s, 1H, OH), 7.55-8.11 (m, 10H, Ar-H and pyrrole), 12.40 (brs, 1H, NH of acetamido group). Anal.: calcd. for $C_{19}H_{15}N_3O_3$: C 68.46, H 4.50, N 12.61; found: C 68.60, H 4.60, N 12.70.

1-Acetoxy-1-(4-acetylaminophenyl)-9-oxo-1,9-dihydropyr-rolo[2,1-b]quinazoline (**16**)

A mixture of **15** (0.01 mol) and acetic anhydride (30 mL) was heated under reflux for 3 h. The reaction mixture was allowed to cool and pour into iced water. The product was filtered off, dried and recrystallized from ethanol. Yield 70%; m.p. 165-167 °C; IR (KBr) 1660, 1744, 1771 (CO) , 3202 (NH). ^{1}H NMR (DMSO-d$_6$) : δ 2.5 (s, 6H, 2CH_3) 7.55-8.11 (m, 10H, Ar-H and pyrrole), 12.40 (brs, 1H, NH of acetamido group) and Anal. Calc. for $C_{21}H_{17}N_3O_4$: C 67.20, H 4.53, N 11.20; found: C 67.30 , H 4.60, N 11.30.

Ethyl 2-(2-(3-(4-acetylaminophenyl)-3-oxopropen-1-yl]-4-oxoquinazolin-3(4H)-yl)acetate (**17**)

A mixture of **11** (0.01 mol) and ethyl glycinate (1.03 g ; 0.015 mol) was dissolved in boiling pyridine (50 mL)and heated under reflux for 6 h. The reaction mixture was allowed to cool, pour into ice/HCl, the product was filtered off, dried, and recrystallized from dioxane. Yield 75 %; M.p. 110-112 °C; IR (KBr) 1645, 1720, 1745 (CO), 3474 (NH); ^{1}HNMR (DMSO-*d6*) : δ 1.32 (t, 3H, CH_3), 2.1 (s, 3H, CH_3), 4.2 (q, 2H, CH_2), 5.1 (s, 2H, NCH_2CO), 7.46-8.11 (m, 10H, Ar-H and olefinic), 12.40 (brs, 1H, NH of acetamido moiety). Anal.: calcd. for $C_{19}H_{17}N_3O_5$: C 65.87, H 5.01, N 10.02; found: C 65.60, H 4.83, N 10.26.

1-(4-Acetylaminophenyl)acetyl-3,4-dioxo-1,3,4-triazino[4,5-b]quinazoline (**18**)

A mixture of **11** (0.01 mol) and semicarbazide (1.03 g; 0.015 mol) was dissolved in boiling pyridine (50 mL) and heated under reflux for 6 h. The reaction mixture was allowed to cool, pour into ice/HCl, the product was filtered off, dried and were recrystallized from dioxane. Yield 80 %, M.p. 215-217 °C; IR (KBr) 1645, 1688 (CO), 3397, 3207 (NH); ^{1}H NMR (DMSO-d$_6$): δ 2.1 (s, 3H, CH_3), 7.46-8.00 (m, 10H, Ar-H and olefinic), 12.40 (brs, 4H, NH of acetamido and urea precursors). Anal.: calcd. for $C_{20}H_{17}N_5O_4$: C 61.38, H 4.34, N 17.90; found: C 61.40, H 4.43, N 17.70.

Conclusion

The present work studied the effect of the pH on the behavior of 4-(4-acetylaminophenyl)-4-oxo-but-2-enoic acid towards sulphur, carbon and nitrogen nucleophiles, producing a series of some important heterocycles, pyridazinone, benzoxazinone and quinazolinone derivatives bearing hetaryl moiety that enhances the biological effect many-fold as compared to their parent nuclei.

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