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Synthesis and Biological Evaluation of Some New 4(3h)-Quinazolinone Derivatives as Non-Classical Antifolate

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ALL living cell need tetrahydrofolate cofactor for the synthesis of purines, some amino acid and thymidine. Most bacteria and plant produce this folate cofactor by de novo biosynthesis. Compounds that interfere with this pathway, antifolate agents have found use as anticancer. Thus, the 2-propyl-4H-3,1-benzoxazin-4-one (2) was synthesized and allowed to interaction with Ammonium acetate or formamide afforded -2- propylquinazolin-4(3H)-one (3). Behaviour of quinazolinone towards carbon electrophiles namely, aromatic aldehyde, chloroacetylchloride, and ethylchloroacetate has been investigated and all the synthesized compounds were tested as anti-cancer in National Cancer Institute (NCI) in USA.

Keywords: Benzoxazin-4-one, Quinazolin-4(3H) one and Anthranil .

The synthesis of quinazolinone heterocycles has become the cornerstone for synthetic chemists and gained extensive importance in medicinal chemistry because of their diverse pharmacological activities including antimycobacterial[1,2], antimalarial[3], antihypertensive[4], antihistaminic[5-9], local anesthetic[10], anti-parkinson[11], cardiotonic[12], anticancer[13-16], antiviral[17] and thymidylate synthase inhibitory activities[18]. Several simple and condensed quinazolines are also known to exhibit potent CNS activities as analgesic[19,20], anti-inflammatory[21,22] and anti-convulsant activities[23,24]. Besides these, the quinazolinone skeleton is frequently encountered as building block for hundreds of naturally occurring alkaloids[25] and hence the exploration of this skeleton as privileged new chemical entities (NCEs) in drug discovery research is beyond doubt of paramount importance for the synthesis chemist. One of the most important features in 4H-3,1-benzoxazinones chemistry is their use as key starting materials for further transformations. With the aim of the extending information on the reactivity of 2-propyl-4H-3, 1-benzoxazinone and also synthesizing from them new quinazolin-4-ones systems, potentially with biological activity and in continuation of our work on the behavior of 3-propylquinazolin-4-one towards carbon nucleophiles, other derivatives were obtained via the interaction of hydrazide derivative 9 with acetic anhydride, acetylacetone, aromatic aldehydes, 3-nitrophthalic anhydride and ethyl acetoacetate.

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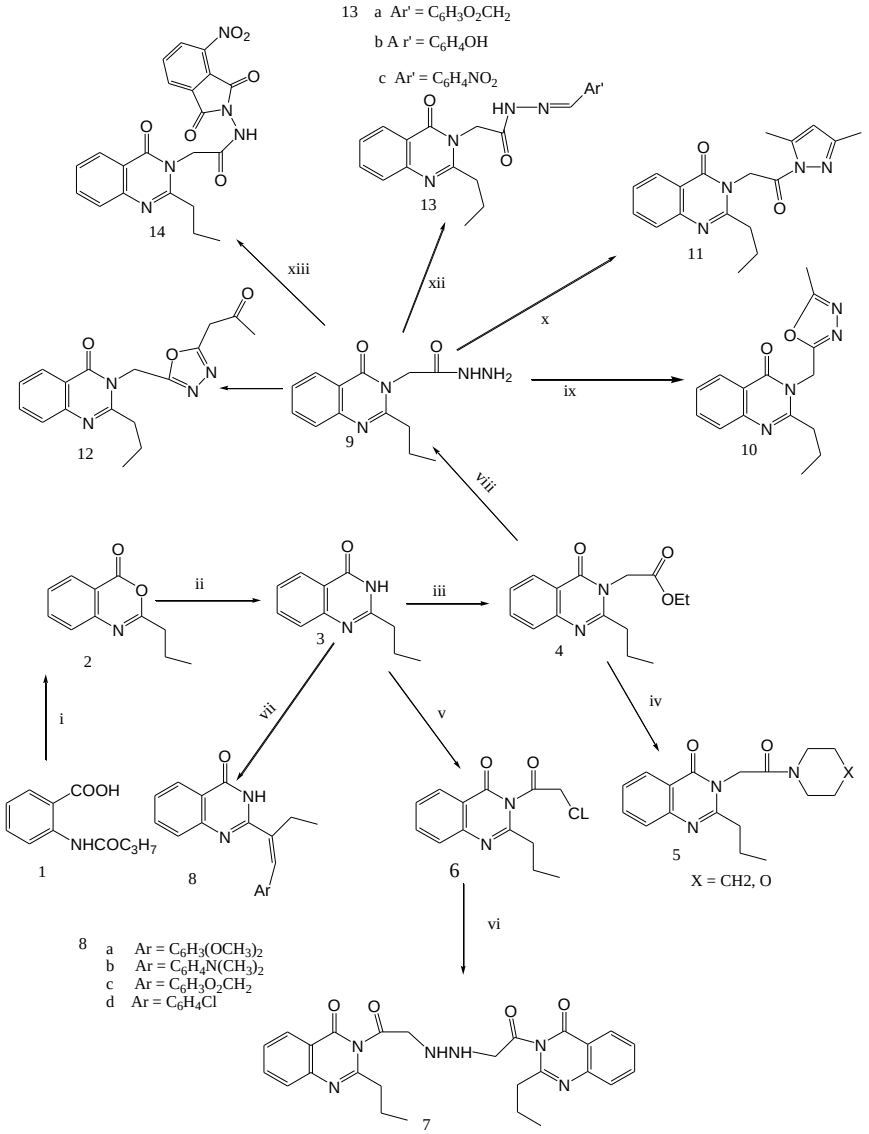
Results and Discussion

2-Propyl-4H-benzo[d][1,3]ozazin- 4-one (2) has been synthesized from the interaction of butyroyl chloride with anthranilic acid in pyridine and yielded, 2-butyramidobenzoic acid (1), ring closure of the acid 1 by using acetic anhydride afforded the desired benzoxazinone derivative 2 the structure of acid (1) was proved from its microanalytical data and its IR spectra (cm^{-1}) which showed strong absorption bands at 1672, 1693, 3286 and 3422 attributable to υ_{max} of two carbonyl groups, NH and OH of acid. The structure of compound 2 was inferred from its IR spectrum which exhibits strong absorption bands at 1614, 1764 (cm^{-1}) due to υ_{max}.of C==N and C==O of benzoxazinone and lack of any band for NH and / or OH.

The key starting material 2-propylquinazolin-4(3H)-one (3)was synthesized by two methods; the first by heating compound 2 with ammonium acetate in an oil bath and the second method was carried by refluxing of compound 2 in formamide. The structure of compound 3 was inferred from its IR spectrum which exhibits strong absorption bands at 1614, 1670 and 3200, (cm^{-1}) due to υ_{max}. of C==N, C==O and NH and of quinazolinone and lack of any band for C=O of benzoxazinone.

2-Propylquinazolin-4 (3H) – one (3) reacts with ethylchlorocaetate in the presence of anhydrous K_2CO_3 in boiling acetone afforded ethyl 2-(4-oxo-2-propylquinazolin-3(4H)-yl)acetate (4). Treatment of ester 4 with secondary amine namely (piperidine and/or morpholine) gave 3-(2-piperidino or morpholino-2-oxoethyl)-2-propylquinazolin-4(3H)-one (5a-b). On the other hand, when compound 3 was allowed to react with chloroacetylchloride yielded 3-(2-chloroacetyl)-2-propylquinazolin-4(3H)-one (6) which on treatment with hydrazine hydrate afforded the bis compound 7. Interaction of the quinazolinone 3 with aldehydes in glacial acetic acid affording (E) 2-(1-aryl)but-1-en-2-yl)quinazolin-4(3H)-one (8a-d). On the other hand, the ester 4 was treated with hydrazine hydrate afforded the corresponding hydrazide derivatives (9). Compound (9) was used for the synthesis of diverse heterocyclic compound, thus when compound (9) was allowed to react with boiling acetic anhydride yielding 3 - ((5- methyl- 1, 3, 4 - oxadiazol-2 -yl) methyl)- 2-propylquinazolin-4(3H)-one (10). Acetylacetone reacts with hydrazide derivative 9 to give 3- (2- (3,5 – dimethyl - 1H – pyrazol -1-yl) -2-oxoethyl) -2-propylquinazolin-4(3H)-one (11), also when compound 9 was allowed to react with ethylacetoacetate in boiling ethanol yielded 3-(5-(2-oxopropyl)-1,3,4-oxadiazol-2-yl)-2-propylquinazolin-4(3H)-one (12). When compound 9 was stirred with aromatic aldehyde namely,pipronal, p-hydroxybenzaldehyde and p-nitrobenzaldehyde at 70 ^{o}C in ethanol affording the corresponding arylidene aminoquinazolinone (13a-c).N-(4-nitro-1,3-dioxoisoindolin-2-yl)-2-(4-oxo-2- propylquinazolin -3 (4H) -yl) acetamide (14) was obtaind by refluxing compound (9) with 3-nitrophthalic anhydride in ethanol.



8 a Ar = $C_6H_3(OCH_3)_2$
b Ar = $C_6H_4N(CH_3)_2$
c Ar = $C_6H_3O_2CH_2$
d Ar = C_6H_4Cl

Scheme 1. Reagent and condition: (i) Ac_2O, 140 ^oC, (ii) CH_3COONH_4, 150 ^OC, (iii) ClCH2COOEt, anhydrous K_2CO_3, dry acetone, 56 ^oC, (iv) piperidine/ morpholine, C_2H_5OH, 78 ^oC, (v) ClCH2COCl, pyridine 115 ^oC, (vi) NH_2NH_2, C_2H_5OH, 78 ^oC, (vii) ArCHO, CH_3COOH/CH_3COONa (viii) NH_2NH_2, C_2H_5OH, 78 ^oC, (ix) Ac_2O, 140 ^oC, (x) Ac_2CH_2, C_2H_5OH, 78 ^oC, (xi) EAA, C_2H_5OH, 78 ^oC, (xii) Ar'CHO, C_2H_5OH, 65 ^oC, (xiii) 3-nitrophthalic anhydride, C_2H_5OH, 78 ^oC.

TABLE 1. Characterization and physical data of synthesized compounds.

Comp No.	M.P. C°	Solvent	Formula M. wt.	Analysis %calc/found C	H
1	125	benzene	$C_{11}H_{13}NO_3$ 207	63.76 63.62	6.28 5.05
2	59	Petroleum ether40-60	$C_{11}H_{11}NO_2$ 189	69.84 69.25	5.82 5.12
3	195	DMF	$C_{11}H_{12}N_2O$ 188	70.21 69.95	6.38 6.52
4	105	Petroleum ether60-80	$C_{15}H_{18}N_2O_3$ 274	65.69 65.60	6.56 6.49
5a	119	Methanol	$C_{18}H_{23}N_3O_2$ 313	69.00 69.11	7.34 7.23
5b	116	Ethanol	$C_{17}H_{21}N_3O_3$ 315	64.76 64.72	3.34 3.45
6	285	Ethanol	$C_{13}H_{13}N_2O_2Cl$ 264.5	58.97 58.52	4.9 4.86
7	202	Ethanol	$C_{26}H_{28}N_6O_4$ 488	63.93 63.87	5.73 5.72
8a	160	benzene	$C_{20}H_{20}N_2O_3$ 336	71.42 71.31	5.95 5.89
8b	150	Methanol	$C_{20}H_{21}N_3O$ 319	75.23 75.36	6.58 6.56
8c	145	Methanol	$C_{19}H_{16}N_2O_3$ 320	71.25 71.29	5.00 4.90
8d	151	Methanol	$C_{18}H_{15}N_2OCl$ 310.5	69.56 69.66	4.83 4.79
9	165	Ethanol	$C_{13}H_{16}N_4O_2$ 260	60.00 59.94	6.15 6.19
10	145	benzene	$C_{15}H_{16}N_4O_2$ 284	63.38 63.64	5.63 5.71
11	195	Ethanol	$C_{18}H_{20}N_4O_2$ 356	60.67 60..49	5.61 5.54
12	265	Ethanol	$C_{17}H_{18}N_4O_3$ 326	62.57 62.57	5.52 5.51
13a	245	Ethanol	$C_{21}H_{20}N_4O_4$ 392	64.28 64.31	5.10 5.21
13b	174	Ethanol	$C_{20}H_{20}N_4O_3$ 364	65.93 65.88	5.49 5.40
13c	260	Ethanol	$C_{20}H_{19}N_5O_4$ 393	61.06 61.10	4.83 4.81
14	250	Methanol	$C_{21}H_{17}N_5O_6$ 435	57.93 57.82	3.90 3.82

Biological Part

The 1960s saw the emergence of unique class of DHFR inhibitors. These quinazoline and pyrimidine analogues of folic acid are called nonclassical or lipophilic because they lack the glutamate residue found in classical DHFR inhibitors like Methotrexate (MTX)[26]. All compounds were evaluated in the National Cancer Institute (NCI), USA, Invitro preclinical antitumor screening program and inhibited the growth of tumor cells in cultcure micromoles to submicromoles concentrations.

Evaluation of cytotoxicity of Quinazolin-4-ones derivatives

In-vitro

The Development Therapeutics Program (DTP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) USA has used an Invitro model consisting of 60 human tumor cell lines as the primary anti-cancer screen. An analysis of the data indicated that approximately 95% of the actives from the 60-cell line screen could be identified using only three cell lines. For this reason, the DTP has begun using, as its primary anti-cancer assay, a 3-cell lines panel consisting of NCI-H 460(Lung), MCF7 (Breast), and SF-268 (CNS). The NCI protocol has been described previously briefly. Cell lines were inoculated onto a series of 96-well plates. Seeding densities varied depending upon growth characteristics. After a 24hr – drug - free incubation, test compounds were added routinely at five ten fold dilutions starting at maximum 10-4M. After incubation periods of 48hr or 6 days, cell growth or viability was assayed using the sulphorhodamine B procedure. From the results of antineoplastic evaluation of the tested compounds it is evident that compounds (8a-d) , namely compound (8a) showed cytotoxic effects and high selectivity against Malanoma (SK-MEL-2), Renal cancer (TK-10) and Ovarian cancer (IGROV1). Compound (8b) showed cytotoxic effects and high selectivity against Prostate cancer(PC-3) and Renal cancer (TK-10), compounds (8c) showed cytotoxic effects and high selectivity against Renal cancer (TK-10) and Colon cancer (HCC-2998) and Compound (8d) showed cytotoxic effects and high selectivity against Renal cancer (TK-10), Prostate cancer (PC-3) and CNS cancer (SF-295).Compound 10 showed cytotoxic effects and high selectivity against Breast cancer (MCF7) and Leukemia (SR), also compound 11 showed cytotoxic effects and high selectivity against Colon cancer (HT29) and CNS cancer (SF-268). Evaluation of cytotoxicity of some synthesized compounds against human cancer cell line (*In-vitro*) is shown in Table 2.

TABLE 2. Evaluation of cytotoxicity of some synthesized compound against human cancer cell line (*In-vitro*).

Comp. No.	NSC	Cancer cell line activity againest	LogGI 50
8a	746764	Malanoma (SK-MEL-2), Renal cancer (TK-10) and Ovarian cancer (IGROV1)	4.91 -5.23 -4.86
Mean value			-4.86
8b	746765	Prostate cancer (PC-3), Renal cancer (TK-10)	4.88 -5.08
8c	746855	Renal cancer (TK-10), Colon cancer (HCC-2998)	-5.00 -4.91
Mean value			-4.96
8d	746856	Renal cancer (TK-10), Prostate cancer (PC-3) CNS cancer (SF-295)	-4.73 -4.68 -4.56
Mean value			-4.66
10	746857	Breast cancer (MCF7) Leukemia (SR)	-4.55 -4.54
Mean value			-4.55
11	746858	Colon cancer (HT29) CNS cancer (SF-268)	-5.01 -5.01
Mean value			-5.01

Log GI_{50}: growth inhibition effect of fifty percent.

Experimental Part

All melting points are uncorrected and determined by the open capillary method using Gallen Kamp melting point apparatus. Microanalyses were carried out by the Micro Analytical Unit at Cairo University. IR spectra (KBr disk) were recorded on FT/IR-300E Jasco spectrophotometer. HNMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution on a Varian EM 390-90 MHz. Mass spectrometry were recorded on Shomadzu, GC – MS (QP – 1000EX.

Butyramidobenzoic acid (1)

A stirred solution of 2-aminobenzoic acid 13.7g (0.1 mol) in dry pyridine (150 ml) was treated drop wise with n-butyroyl chloride 10.5g (0.11 mol) during 10 min the mixture was stirred at room temperature (3hr) and poured into a mixture of ice and hydrochloric acid to give . 2-butyramidobenzoic acid IR (KBr) cm^{-1}: 3422 (OH), 3286(NH), 3055 (CH aromatic), 2957, 2927, 2869 (CH aliphatic), 1693 (c=o, acid), 1672 (c=o, amide).

2-Propyl-4H- benzo[d][1,3]oxazin-4-one (2)

A suspension of 2-butyramidobenzoic acid 2.07g (0.01mol) in 50 ml acetic anhydride was heated under reflux (3hr) and then concentrated. The residue was crystallized from petroleum ether 40-60^{o}C, giving 2-propyl-4H-

benzo[d][1,3]oxazin-4-one as a colorless crystals melting point(59 ^{o}C). IR (KBr) cm^{-1}: 3055 (CH aromatic), 2965, 2935, 2875 (CH aliphatic), 1764 (c=o), 1614(C=N),1161 (C-O).

2-Propylquinazolin-4(3H)-one (3)

Method A

2-Propyl-4H- benzo[d][1,3]oxazin-4-one(2) (1 mmol) was heated with ammonium acetate (4 mmol) in an oil bath at 150^{o}C for 2 hr, the reaction mixture was cooled and poured in cold water. The precipitated solid was filtered off , washed with water and recrystallization from the proper solvent to give (3) IR(KBr) cm^{-1} : 3215 (NH), 3024 (CH aromatic), 2969, 2935, 2905, 2877 (CH aliphatic),1675 (C=O), 1597(C=N) ; MS: m/z 189 [M^{+}], 187, 172, 158, 144, 130; ^{1}HNMR ($CHCl_3$) : δ 7.21 – 8.23 (m, 4H, aromatic), 1.14(t, 3H, $\underline{CH_3}$), 1.92 (sextet,2H,$\underline{CH_2}$Me), 2.72 (t,2H, $\underline{CH_2}$Q).

Method B

2-Propyl-4H- benzo[d][1,3]oxazin-4-one(2) (1 mmol) in formamide (20 ml) was refluxed for 3 hr, the reaction mixture was cooled and poured in cold water. The obtained solid was filtered off and recrystalized from the proper solvent IR(KBr) cm^{-1} : 3215 (NH), 3024 (CH aromatic), 2969, 2935, 2905, 2877 (CH aliphatic),1675 (C=O), 1597(C=N) ; MS: m/z 189 [M^{+}], 187, 172, 158, 144, 130; ^{1}HNMR ($CHCl_3$) : δ 7.21 – 8.23 (m, 4H, aromatic), 1.14(t, 3H, $\underline{CH_3}$), 1.92 (sextet,2H,$\underline{CH_2}$Me), 2.72 (t,2H, $\underline{CH_2}$Q).

Ethyl 2-(4-oxo-2-propylquinazolin-3(4H)-yl) acetate (4)

A suspension of 2-propylquinazolin-4(3H)-one (0.01mol) in 50 ml dry acetone was stirred and potassium carbonate (0.04 mol) was added after the mixture was stirred at room temperature 20 min, the ethylcloroacetate (0.02 mol) was added, and the mixture was refluxed 24hr. The solvent was evaporated under reduced pressure, water was added to the residue and the produced solid was filtered off and recrystallized from petroleum ether 60 – 80 ^{o}C yield (4) m. p. 105^{o}C. IR(KBr) cm^{-1} : 3024 (CH aromatic), 2969, 2935, 2905, 2877 (CH aliphatic), 1735 (C=O ester),1675 (C=O), 1597(C=N), 1232 (C-O ester); MS: m/z 275 [M^{+}], 273, 258, 244, 229, 215, 172, 158, 142 ; ^{1}HNMR ($CHCl_3$) : δ 7.21 – 8.23 (m, 4H, aromatic), 4.92 (s, 2H, Q$\underline{CH_2}$CO), 4.32 (q, 2H, O$\underline{CH_2}$)1.33 (t, 3H, OCH$_2\underline{CH_3}$) 1.14(t, 3H, $\underline{CH_3}$), 1.92 (sextet,2H,$\underline{CH_2}$Me), 2.72 (t,2H, $\underline{CH_2}$Q).

3-(2-Piperidino or morpholino-2-oxoethyl)-2-propylquinazolin-4(3H)-one (5a- b)

A mixture of 4 (0.01mol) and of piperidine or morpholine (10ml) was refluxed for 8hr. The produced mixture was cooled, evaporated under reduced pressure and water was added to the residue and the produced solid was filtered off and recrystallized from the proper solvent.

3-(2-Oxo-2-piperidin-1-yl)ethyl)-2-oxoethyl)-2-propylquinazolin-4(3H)-one (5a)

IR(KBr) cm^{-1} : 3040 (CH aromatic), 2956, 2906, 2868, (CH aliphatic), 1700, 1675 (2C=O), 1610(C=N) ; MS: m/z 313 ,311, 296,281, 269, 244, 229, 215, 172,

158, 171, 142 ; ^{1}HNMR ($CHCl_3$) : δ 7.2 – 8.23 (m, 4H, aromatic), 3.22 (s, 4H, $N(CH_2)_2$piperidine), 1.84 (pentet, 6H, piperidine) 1.14(t, 3H, $\underline{CH_3}$), 1.92 (sextet,2H,$\underline{CH_2}$Me), 2.72 (t,2H, $\underline{CH_2}$Q).

3-(2-Morpholino-2-oxoethyl)-2-propylquinazolin-4(3H)-one (5b)

IR(KBr) cm^{-1} : 3040 (CH aromatic), 2956, 2906, 2868, (CH aliphatic), 1695, 1672 (2C=O), 1605 (C=N); MS: m/z 316 [M$^+$], 314 299, 285, 271, 257, 171, 142; ^{1}HNMR (DMSO-d_6) : δ 8.14 (s, 1H, NH), 7.22 – 7.73 (m, 4H, aromatic), 3.81 (t,4H,$O(CH_2)_2$ morphiline), 3.22 (t, 4H, $N(CH_2)_2$ morphiline), 1.14(t, 3H, $\underline{CH_3}$), 1.92 (sextet,2H,$\underline{CH_2}$Me), 2.72 (t,2H, $\underline{CH_2}$Q).

3-(2-Chloroacetyl)-2-propylquinazolin-4(3H)-one (6)

Compound 3 (0.01 mol) was dissolved in pyridine 30 ml and the mixture was stirred, chloroacetyl chloride was added dropwise at room temperature, and the mixture was continued in stirring for 3 hr. Then the mixture was poured on ice and HCl, the precipitate was collected by filtration and recrystallization from proper solvent. M.p.285. IR(KBr) cm^{-1} : 3040 (CH aromatic), 2956, 2906, 2868, (CH aliphatic), 1710, 1668 (2C=O), 1605 (C=N) ; MS: m/z 264.5 , 230, 215 201, 187, 153, 142 ; ^{1}HNMR (DMSO-d_6) : δ 7.22 – 7.73 (m, 4H, aromatic), 6.21 (s, 2H, CO$\underline{CH_2}$Cl), 1.14(t, 3H, $\underline{CH_3}$), 1.92 (sextet,2H,$\underline{CH_2}$Me), 2.72 (t,2H, $\underline{CH_2}$Q).

N,N'di(2-(4-oxo-2-propylquinazolin-3(4H)-yl)aceto)hydrazide(7)

A solution of compound 6 (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol 50 ml was heated under reflux for 3 hr. The reaction mixture was allowed to cool, filtered off and recrystallized from proper solvent to give (7) m.p. 202^{o}C. IR(KBr) cm^{-1} : 3271, 3285 (2NH), 3040 (CH aromatic), 2956, 2906, 2868, (CH aliphatic), 1685-1665 (4C=O), 1605 (C=N) ; MS: m/z 489 [M$^+$], 485,470, 456, 335, 299 260, 151, 71.

(E)-2-(1-aryl)but-1-en-2-yl) quinazolin-4(3H)-one (8a-d)

A solution of compound 3 (1.5 mmol), appropriate aldehyde (2 mmol) and sodium acetate (0.2 g) were dissolved in a mixture of 5 ml of glacial acetic acid and 1ml of acetic anhydride and the mixture was heated at reflux overnight, the acetic acid mixture solvent was removed under reduce pressure and the residues were partitioned between aqueous sodium bicarbonate and chloroform. The organic phase was extracted and excess solvent was evaporated to give compounds (8a-d) which were recrystallized from proper solvent.

(E)2-(1-(3,4-dimethoxyphenyl)but-1-en-2-yl)quinazolin-4(3H)-one (8a)

IR(KBr) cm^{-1}:2200 (NH), 3076 (CH aromatic), 2962, 2919, 2870 (CH aliphatic),1670(c=o), 1607(C=N); MS: m/z 337 [M$^+$], 335, 320, 306, 291, 277,262, 249, 158, 71; ^{1}HNMR (DMSO-d_6) : δ 12.12 (s, H, NH), 7.71 -8.12 (m, 7H, aromatic), 5.69 (s, 1H, C=$\underline{CH}$) 3.41 (s, 6H, $2OCH_3$), 1.22 (t, 3H, $\underline{CH_3}$), 2.31 (q,2H,$\underline{CH_2}$Me).

(E)-2-(1-(4-(dimethylamino) phenyl)but-1-en-2-yl)quinazolin-4(3H)-one (8b)

IR(KBr) cm^{-1}: 3210 (NH), 3063 (CH aromatic), 2975, 2925, 2875 (CH aliphatic),1671(C=O), 1606 (C=N); MS: m/z 319,318, 303, 278, 263, 247, 158;

^{1}HNMR (DMSO-d_6) : δ 12.12 (s, H, NH), 7.73 – 8.32 (m, 8H, aromatic), 5.69 (s, 1H, C=CH) , 3.34 (s, 6H, N(CH_3)$_2$), 1.3 2(t, 3H, CH_3), 2.31 (q,2H,CH_2Me).

(E)-2-(1-(benzo[d][1,3]dioxol-5-yl)but-1-en-2-yl)quinazolin-4(3H)-one (8c)

IR(KBr) cm^{-1}: 3210 (NH), 3076 (CH aromatic), 2962, 2919, 2870 (CH) aliphatic),1673(C=O), 1601(C=N), 1255 (C-O-C); MS: m/z 320 ,319, 304, 377, 262,232, 216, 128; ^{1}HNMR (DMSO-d_6) : δ 12.12 (s, H, NH), 7.71 – 8.12 (m, 7H, aromatic), 6.11 (s, 1H, C=CH) ,4.21(s,2H,O-CH_2-O), 1.22 (t, 3H, CH_3), 2.31 (q,2H,CH_2Me).

(E)-2-(1-(4-chlorophenyl) but-1-en-2-yl)quinazolin-4(3H)-one (8d)

IR(KBr) cm^{-1}: 3200 (NH), 3066 (CH aromatic), 2976, 2925, 2888 (CH) aliphatic),1672(C=O), 1607(C=N); ^{1}HNMR (DMSO-d_6) : δ 12.12 (s, H, NH), 7.73 – 8.32 (m, 8H, aromatic), 6.11 (s, 1H, C=CH) , 1.33 (t, 3H, CH_3), 2.41 (q,2H,CH_2Me).

2-(4-Oxo-2-propylquinazolin-3(4H)-yl) acetohydrazide (9)

A solution of ester 4 (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (50 ml) was refluxed for 3 hr, the reaction mixture was concentrated and then allowed to cool. The obtained solid was filtered off and recrystallization from ethanol yield compound (9) m.p.165^{o}C. IR (KBr) cm^{-1}:3312, 3271 (NH2), 3171 (NH), 3055 (CH aromatic), 2962, 2931, 2870, (CH aliphatic), 1685 (C=O), 1675 (C=O Quinazolinone), 1597(C=N); MS: m/z 260, 259, 244, 230, 216, 185, 157, 143,144; 1HNMR (DMSO-d6): δ 10.5 (s, H, NH_2), 7.22 – 7.71 (m, 4H, aromatic), 4.51 (s,H, NH), 2.83 (t,2H, CH_2Q)1.52 (sextet,2H,CH_2Me), , 1.11(t, 3H, CH_3).

3-((5-Methyl-1,3,4-oxadiazol-2-yl)methyl)-2-propylquinazolin-4(3H)-one (10)

A solution of compound 9 (0.01 mol) and acetic anhydride 30ml was refluxed for 3 hr, the reaction mixture was allowed to cool and the obtained solid was filtered off and recrystallized from proper solvent to yield compound 10 m.p. 145^{o}C IR(KBr) cm^{-1} : 3055 (CH aromatic), 2962, 2931, 2870, (CH aliphatic), 1675 (C=O Quinazolinone), 1597, 1605 (C=N) ; MS: m/z 284, 286, 271, 257, 233, 201, 185, 157, 143,144. ; 1HNMR (DMSO-d6): δ 7.22-7.71 (m, 4H, aromatic), 2.83 (t,2H, CH_2Q 1.52 (sextet,2H,CH_2Me), , 1.11(t, 3H, CH_3).

3-(2-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-oxoethyl)-2-propylquinazolin-4(3H)-one (11)

A solution of compound 9 (0.01 mol) and acetylacetone (0.01 mol) in ethanol 50 ml was heated under reflux for 3 hr. The reaction mixture was allowed to cool, filtered off and recrystallized from proper solvent to give 11 m.p .195. IR (KBr) cm^{-1}: 3055 (CH aromatic), 2962, 2931, 2870, (CH aliphatic), 1675 (C=O Quinazolinone), 1597, 1605 (C=N); MS: m/z 357 [M+], 324, 244, 309, 285, 271, 157, 143,144. ; 1HNMR (DMSO-d6) : δ , 7.22 – 7.71 (m, 4H, aromatic), 6.25 (s, 2H, CH_2CO),4.51 (s, H, C=CH) 2.94 (s,6H, CH_3pyrazol), 2.83 (t,2H, CH_2Q)1.52 (sextet,2H,CH_2Me) , 1.11(t, 3H, CH_3).

3-((5-(2-Oxopropyl)-1,3,4-oxadiazol-2-yl)methyl)-2-propylquinazolin-4(3H)-one(12)

A solution of compound 9 (0.01 mol) and ethylacetoacetate (0.01 mol) in ethanol 50 ml was heated under reflux for 3 hr. The reaction mixture was allowed to cool, filtered off and recrystallized from proper solvent to give (12) m.p. 265. IR(KBr) cm^{-1} : 3055 (CH aromatic), 2962, 2931, 2870, (CH aliphatic),1682 (CH_2C=O), 1700 (C=O pyrazol), 1675 (C=O Quinazolinone), 1597, 1605 (C=N); MS: m/z 327 [M+], 325, 243, 308, 284, 270, 157, 143,144, 99. ; 1HNMR (DMSO-d6) : δ, 7.22 – 7.71 (m, 4H, aromatic), 6.25 (s, 2H, CH_2CO), 5.41 (s, H, CHCOpyrazol),2.94 (s,3H, CH_3pyrazol), 2.83 (t,2H, CH_2Q)1.52 (sextet, 2H,CH_2 Me) , 1.11(t, 3H, CH_3).

(E)-N'-aryl-2-(4-oxo-2-propylquinazolin-3(4H)-yl)acetohydrazide (13 a-c)

A solution of hydrazide 9 (0.01 mol) and aldehyde namely, pipronal, p-hydroxybenzaldehyde and p-nitrobenzaldehyde (0.01 mol) in ethanol was stirred 3hr at 60°C. The obtained solid was filtered off and recrystallized from proper solvent.

(E)-N'-(benzo[d][1,3] dioxol-5- ylmethylene)-2-(4-oxo-2- propylquinazolin-3 (4H) -yl) acetohydrazide (13a)

IR(KBr) cm^{-1}: 3200 (NH),3055 (CH aromatic), 2962, 2931, 2870, (CH aliphatic),1682 (CH_2C=O), 1675 (C=O) Quinazolinone), 1597, 1605 (C=N) ; MS: m/z 392 ,391, 377, 363, 349, 243, 308, 284, 270, 157, 143,144, 99. ; 1HNMR (DMSO-d6) : δ 9.21 (s, H, N=CH), 7.21 – 8.12 (m, 7H, aromatic), 6.33(s, 2H, CH_2CO), 6.25 (s, 2H, O-CH2-O),4.82 (s, H, NH), 2.83 (t,2H, CH_2Q) 1.52 (sextet,2H,CH_2Me) , 1.11(t, 3H, CH_3).

(E)-N'-(4-hydroxybenzylidene)-2-(4-oxo-2-propylquinazolin-3(4H)-yl) acetohydrazide (13b)

IR(KBr) cm^{-1}: 4400 (OH), 3200 (NH),3055 (CH aromatic), 2962, 2931, 2870, (CH aliphatic),1682 (CH_2C=O), 1675 (C=O) Quinazolinone), 1597, 1605 (C=N); MS: m/z 365 [M+], 363, 347, 332, 314, 300, 243, 308, 284, 270, 157, 143,144, 99.

(E)-N'-(4-nitrobenzylidene)-2-(4-oxo-2-propylquinazolin-3(4H)-yl) acetohydrazide (13c)

IR(KBr) cm^{-1}: 3200 (NH),3055 (CH aromatic), 2962, 2931, 2870, (CH aliphatic),1682 (CH_2C=O), 1675 (C=O) Quinazolinone), 1597, 1605 (C=N) ; MS: m/z 394 [M+] , 377, 363, 349, 308, 284, 270, 157, 143,144, 99 ; 1HNMR (DMSO-d6) : δ 9.21 (s, H, N=CH), 7.21 – 8.12 (m, 8H, aromatic), 6.33 (s, 2H, CH_2CO), 4.82 (s, H, NH), 2.83 (t,2H, CH_2Q)1.52 (sextet,2H,CH_2Me), 1.11(t, 3H, CH_3).

N-(4-nitro-1,3-dioxoisoindolin-yl)-2-(4-oxo-2-propylquinazolin-3(4H)-yl) acetamide (14)

A solution of hydrazide 9 (0.01 mol) and 3-nitrophthalic anhydride (0.01 mol) in ethanol was heated under reflux (3hr) the reaction mixture was allowed to cool and the obtained solid was filtered off and recrystallized from proper solvent. m.p. 250°C. 3271 (NH), 3055 (CH aromatic), 2962, 2931, 2870, (CH

aliphatic),1760, 1730, 1680, 1675 (4C=O), 1597, 1605 (C=N) ; MS: m/z 436 [M+],432, 317, 303, 189, 308, 284, 270, 157, 143, 144, 99.; 1HNMR (DMSO-d6) : δ 7.21 – 8.12 (m, 7H, aromatic), 6.33 (s, 2H, $\underline{CH_2}CO$), 4.82 (s, H, $\underline{NH}$), 2.83 (t,2H, $\underline{CH_2}Q$)1.52 (sextet,2H, $\underline{CH_2}Me$) , 1.11(t, 3H, $\underline{CH_3}$).

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التشييد والتقييم البيولوجي لبعض مشتقات ٤ (٣ يد) كينازولينون التي لها تاثير على انزيم التتراهيدرو فولات

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كل الكائنات الحية تحتاج الى انزيم التتراهيدروفولات اللازم لتخليق البيورين وبعض الاحماض الامينية والثيمدين حيث ان معظم البكتريا والنباتات تنتج هذا الانزيم بواسطة العمليات الحيوية ومن المركبات التي تتدخل في مراحل تكوين الانزيم ووجد انها تستخدم كمضادات للسرطان مركبات الكينازولينون.

وقد تم استخدام مركب ٢-بروبيل- ٤ (٣يد) كينازولينون (٢) كمفتاح لتشييد كثير من مشتقات الكينازولينون مثل تفاعله مع اسيتات الامونيوم او الفورماميد ليعطي مركب ٢-بروبيل كينازولين ٤(٣يد) اون (٣) ودرس تفاعل الكينازولينون مع الكربون الكتروفيلز مثل الالدهيدات الاروماتية وكلورو خلات الكلوريد والايثيل كلورو اسيتات. وجميع المركبات المحضرة اختبرت كمضادات للسرطان في معهد السرطان الامريكي ووجد ان بعض من هذه المركبات لها تاثير على الخلايا السرطانية.