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단 신

항균성을 가진 새로운 2-propyl-4(3H)-Quinazolinone유도체의 생물학적 평가와 합성

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Synthesis and Biological Evaluation of Some New2-propyl-4(3H)-Quinazolinone Derivatives as Anti-bacteria

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주제어: Benzoxazin-4(3H)one, Quinazolin-4(3H)one, Anthranil

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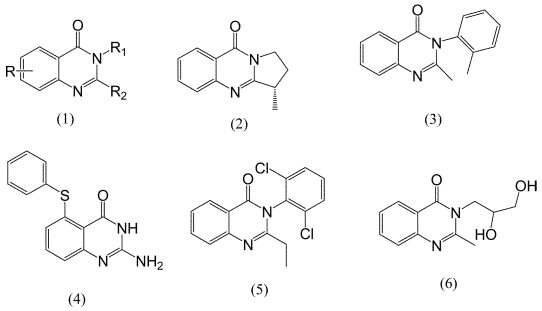
INTRODUCTION

Quinazolin-4-one is a frequently encountered unit in nature products such as L-vasicinone(1),[1] Chrysongine(2),[2] and drugs[3] such as methaqualone(3),[4] Nolatrexed(4),[5] Chloroqualone(5),[5] Diproqualone[5](6). This molecules which based on the quinazolin-4-one ring were reported as interesting pharmacological activities,[6] including anticonvulsant, antibacterial, anti tumor,[7] analgesic,[8] anti-inflammatory,[9] and anti-diabetic activity.[10,11] The most common synthetic method to quinazolin-4-one is based on acylation of anthranilic acid and ring closure with acetic anhydride to afford corresponding benzoxazinone[12] which was treated with hydrazine hydrate to give a new 3-aminoquinazolin-4-one derivatives. The current study also involves in vitro antimicrobial screening (neutriet agar) of synthesized quinazolinone derivatives by filter paper disc method.[13]



RESULT AND DISCUSSION

The key starting material 2-propyl-4H- 3,1-benzoxazin-4-one (2) has been synthesized via the interaction of butyroyl chloride with anthranilic acid in the presence of pyridine which yielded the corresponding anthranil 1. Treatment of anthranil 1 with acetic anhydride afforded the benzoxazinone 2. The structure of anthranil 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, υNH and υOH respectively. IR spectrum of the benzoxazinone 2 exhibits strong absorption bands at 1614, 1764 (cm^{-1}) due to υ_{max}.of C=N and C=O and lack of any band for NH and / or OH such IR data agreed well with the proposed structure.

The 3-amino-2- propylquinazolin-4(3H)-one (3) resulted via treatment of the Benzoxazinone 2 with hydrazine hydrate in boiling ethanol. The structure of compound 3 was confirmed based on its elemental and spectral analyses, thus IR spectrum of compound 3 reveals strong absorption band at 1596, 1673, 3309 and 3212 attributable to υ_{max} for C=N, C=O and NH_2. EIMS of compound 3 exhibits an ion peak at m/z (M^-,203). ^{1}HNMR spectrum of compound 3 exhibits δ(ppm) in $CDCl_3$ 1 (t,3H,CH_3), 1.8(m, 2H,CH_2Me), 2.8(t, 2H, CH_2Q), 7.2-8 (m, 4H, aromatic), 9.3(s, 2H, NH_2).

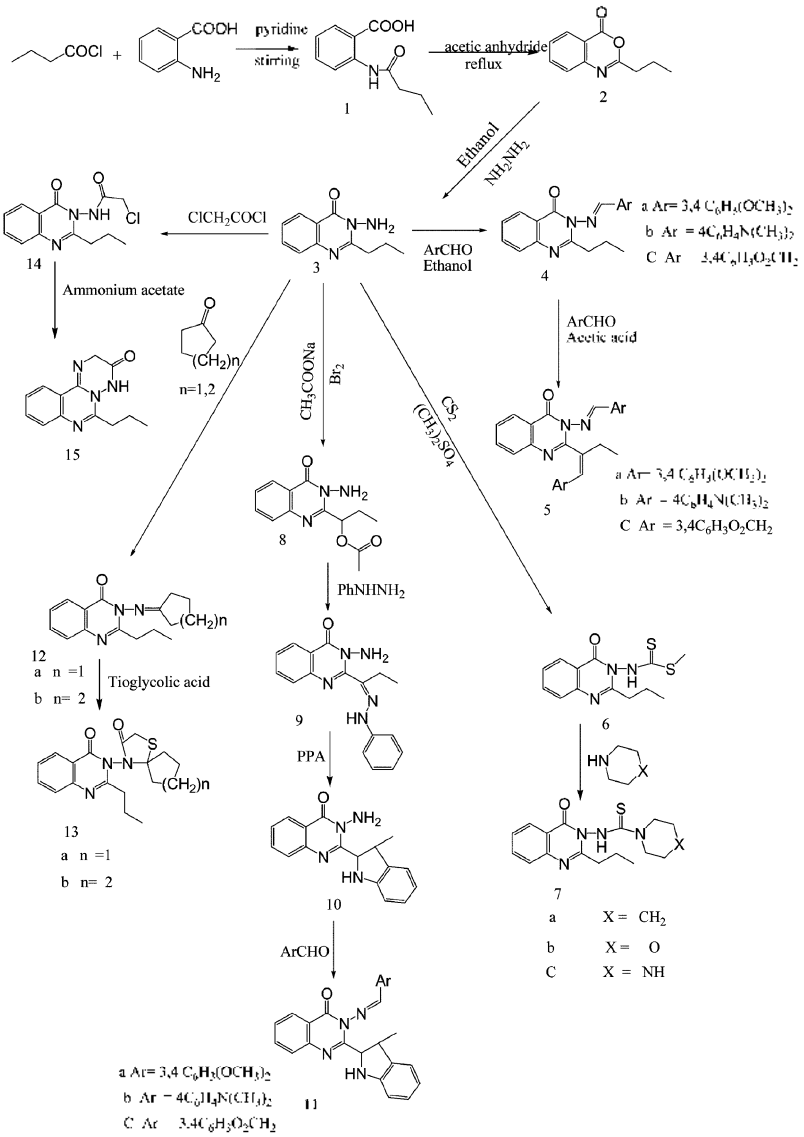
Stirring of 3-amino-2- propylquinazolin-4(3H)-one (3) with aromalic aldehydes namely, 3,4-dimethoxy benzaldehyde, 4-N,N-dimethylaminobenzaldehyde and 3,4-methylenedioxy benzaldehyde in ethanol at room temperature afforded 3-(arylidenamino)-2-propylquinazolin-4(3H)-ones (4a-c). The structure of compound 4 were confirmed on the basis of their elemental analyses. Thus IR spectra of compounds (4a-c) revealed strong absorption bands at 1600-1612, 1669-1676; attributable to υC=N and υC=O respectively, and lacked of any band due to NH_2. On treatment of compounds 4a-c with aromatic aldehyde namely, 3,4-dimethoxy benzaldehyde, 4-N,N-dimethylaminobenzaldehyde and 3,4-methylenedioxy benzaldehyde in refluxing glacial acetic acid the 3-(arylideneamino)-2-(1-phenylbut-1-en-2-yl)quinazolin-4(3H)-ones (5a-d) were obtained. The structure of compounds 5 were inferred from their IR spectra which exhibit strong absorption bands at the region 1600-1605 and 1670 -1676 attributable to υ_{max} C=N and C=O respectively. EIMS of compound 5b exhibited an ion peak at m/z (465; M^-).

when compound 3 was allowed to react with carbon disulfide and dimethylsulfate in the presence of sodium hydroxide it yielded methyl-4-oxo-2-propylquinazolin-3(4H)-ylcarbamodithioate (6), The structure of compounds 6 was inferred from elemental analyses, its IR spectrum revealed strong absorption bands at 1450 and 1673 attributable to υ_{max} C=S and C=O respectively and devoid the band of NH_2. The refluxing of compound 6 with secondary amine namely, piperidine, morpholine and piprazine in methanol yielded the corresponding carbothioamide 7a-c. IR spectra of compounds 7a-c exhibit absorption bands in the regions 1450-1470 and 1658-1670 cm^{-1} attributable to υ_{max} of C=S and C=O respectively, EIMS of compound 7c gave molecular ion peak at M^+ (332).

Bromination of compound 3 by treatment with bromine in glacial acetic acid in the presence of sodium acetate yielded 1-(3-amino-4-oxo-3,4-dihydroquinazolin-2yl)propyl acetate (8). Formation of compound 8 takes place via bromination of methylene group at position 2 followed by nucleophilic substitution by acetate ion. The structure of compound (8) was proved from its IR spectrum (cm^{-1}) which showed a strong absorption bands at 1612, 1645, 1725, 3214 and 3324 due to υ_{max} of C=N, C=O (amide), C=O (ester) and NH_2 respectively. EIMS of 8 exhibited a molecular ion peak at (M^+, 260). The reaction of ester 8 with phenylhydrazine involves nucleophilic substitution, with a subsequent oxidation process analogous to the formation of osazones[14] to afford 2-(1-phenylhydrazonopropyl)-3-amino-4(3H)-quinazolinone (9). IR Spectrum of compound (9) exhibits strong absorption bands at 1610, 1673 and 3200, 3300 and 3360 attributable to υ_{max} for C=N, C=O, NH and NH_2 respectively. On treatment of compound 9 with phosphoric acid under fisher indol synthesis condition yielded 3-amino-2-(-3-methylindolin-2-yl)quinazolin-4(3H)-one (10). IR spectrum of compound 10 revealed absorption bands at 1612, 1676, abroad band 3240-3400 due to υ_{max} for C=N, C=O, and NH, NH_2 respectively. When compound 10 was allowed to react with aromatic aldehydes namely, 3,4-dimethoxy benzaldehyde, 4-N,N-dimethylaminobenzaldehyde and 3,4-methylenedioxy benzaldehyde afforded schiffs bases 3-(arylideneamino)-2-(3-methylinolin-2-yl)quinazolin-4(H)-one (11a-c). the structure of compounds 11 were proved from

their IR spectra which showed absorption at regions 1600-1612, 1665-1675 attributable to υ_{max} for C=N and C=O and lack the band of NH_2. EIMS of 11b exhibited a molecular ion peak (M^+, 438).

Compound (3) was converted to 3-(cyclopentylidine/hexylidineamino)-2-propylquinazolino-4(3H)-one(12a,b) by the reaction with cyclopentanone and cyclohexanone in ethanol, the structure of compound(12a,b)were proved from their IR spectra (cm^{-1}) which showed absorption bands at υ_{max} 1675, 1610 attributable to C=O and C=N and devoid any band for NH_2. EI.MS of 12a and 12b showed molecular ion peak at m/z (M^+ 269) and m/z (M^+ 283) respectively. When Compounds (12a,b) were submitted to react with thioglycolic acid gave spiro-componds (13a,b). IR spectra of compounds (13a,b) revealed strong absorption bands at υ_{max} 16141687, 1675 and attributable to C=N and two carbonyl group respectively. EI. MS of 13b exhibited a molecular ion peak m/z (M^+ 357).

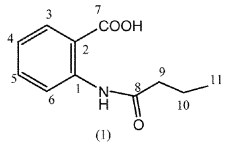
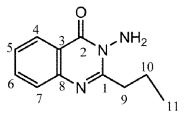
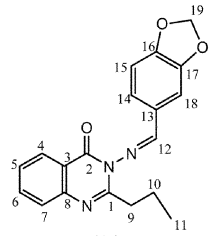
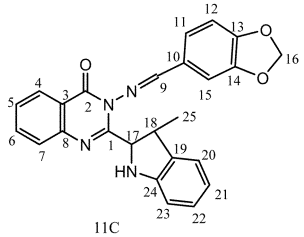
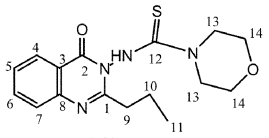
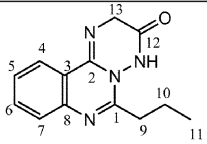


Schem I

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	C11H13NO3 207	63.76 63.62	6.28 6.18
2	59	Petroleum ether40-60	C11H11NO2 189	69.84 69.76`	5.82 5.92
3	85	Petroleum ether60-80	C11H13N3O 203	65.02 64.89	6.40 6.38
4a	143	Ethanol	C20H21N3O3 351	68.37 68.22	5.98 5.83
4b	175	Ethanol	C20H18N4O 330	72.72 72.55	5.45 5.32
4c	145	Ethanol	C19H17N3O3 335	68.05 68.12	5.07 4.87
5a	185	Ethanol	C29H29N3O5 499	69.73 69.67	5.81 5.68
5b	245	Ethanol	C29H31N5O 465	73.51 73.64	6.66 6.64
5c	175	Benzene	C27H21N3O5 467	69.37 69.38	4.49 4.52
6	160	benzene	C13H15N3OS2 293	53.24 52.96	5.11 5.20
7a	191	Methanol	C17H22N4OS 330	61.63 61.65	6.64 6.61
7b	145	Methanol	C16H20N4O2S 331	57.83 57.72	6.02 6.19
7c	180	Methanol	C16H21N5OS 331	64.00 63.96	7.00 6.78
8	165	Benzene	C13H14N3O3 260	60.00 60..13	5.38 5.41
9	222	Ethanol	C17H17N5O 307	66.44 66.32	5.53 5.58
10	<300	Ethanol	C17H13N4O 289	70.58 70.45	4.49 4.55
11a	255	Ethanol	C26H22N4O3 438	71.23 71.40	5.02 5.11
11b	280	Methanol	C26H23N5O 421	74.10 74.24	5.46 5.65
11c	247	Ethanol	C25H18N4O3 422	71.09 71.32	4.26 4.30
12a	129	Benzene	C17H21N3O 283	72.08 71.98	7.42 7.33
12b	125	Benzene	C16H19N3O 269	71.37 71.12	7.06 7.16
13a	175	benzene	C18H21N3O2S 343	62.97 63.10	6.12 5.98
13b	157	benzene	C19H23N3O2S 357	63.86 63.78	6.44 6.55
14	200	Methanol	C13H14N3O2Cl 279	55.91 56.21	5.01 4.97
15	185	Ethanol	C13H14N4O 242	64.46 64.56	5.78 5.74

Table (2) : ^{13}C-NMR of some synthesized compounds

Structure formula and compound No.	δ(ppm) carbon atom number
 (1)	143.3 (C-1), 115.15(C-2), 129.7 (C-3), 122.4(C-4), 132.98(C-5), 121.52 (C-6), 168.8 (C-7), 173.0 (C-8), 38.1 (C-9), 19.0 (C-10), 13.2 (C-11)
 (3)	155.2 (C-1), 161 (C-2), 120 (C-3), 128 (C-4), 127.4 (C-5), 133.5 (C-6), 122 (C-7), 147 (C-8), 25.1 (C-9), 14.6 (C-10), 13.9 (C-11)
 (4c)	164 (C-1), 160 (C-2), 120.9 (C-3), 128.8 (C-4), 127.4 (C-5), 133.5 (C-6), 122.4(C-7), 147.1(C-8), 25.6(C-9), 14.6(C-10), 13.9 (C-11), 143(C-12), 127 (C-13), 122(C-14), 115 (C-15), 151(C-16), 148 (C-17), 114(C-18), 101(C-19)
 11C	164 (C-1), 160 (C-2), 120.9 (C-3), 128.8 (C-4), 127.4 (C-5), 133.5 (C-6), 122.4(C-7), 147.1(C-8), 143(C-9), 127 (C-10), 122(C-11), 115 (C-12), 151(C-13), 148 (C-14), 114(C-15), 101(C-16), 56.1(C-17) ,32(C-18), 137(C-19),127(C-20), 116(C-21), 126(C-22),113(C-23), 149(C-24),15.9(C-25).
 (7b)	155.2 (C-1), 161 (C-2), 120 (C-3), 128 (C-4), 127.4 (C-5), 133.5 (C-6), 122 (C-7), 147 (C-8), 25.1 (C-9), 14.6 (C-10), 13.9 (C-11), 179.3 (C-12), 52.5 (C-13), 66.5(C-14)
 (15)	155.2 (C-1), 164 (C-2), 123 (C-3), 130.5 (C-4), 127.4 (C-5), 133.5 (C-6), 122 (C-7), 148.8 (C-8), 25.4 (C-9), 14.6 (C-10), 13.7 (C-11),165.7(C-12), 49.7(C-13)

Interaction of 3-amino-2-propylquinazolin-4(3H)-one (3) with chloroacetyl chloride in pyridine yielded 2-chloro-N-(4-oxo-2-propylquinazolin-3(4H)-yl)acetamide (14), IR spectrum of compound 14 was revealed strong absorption bands at 1614, 1672, 1710 and 3120 attributable to υ_{max} C=N , tow carbonyl groups and NH. Treatment of compound 14 with ammonium acetate in oil bath yielded 6-propyl-2H-[1,2,4]triazino[2,3-c]quinazolin-3(4H)-one (15). IR spectrum of 15 revealed strong absorption bands at υ_{max} 1615, 1680 and 3200 attributable to υ_{max} C=N,C=O, and NH respectively.

BIOLOGICAL PART

All the synthesized compound were screened for anti-bacteria activity using the following method. The neutrient agar was used as media and filter paper disc (0.7 mm diameter). The qunazolinone derivatives were prepared in ethanol at 3 X concentrations (200 μg/ml,100 μg/ml and 50 μg/ml) Two bacteria isolates (E.coli and Staph. Aureus) were used as a test organisms The compounds 3, 4a, 4b, 5a, 5b, 14 and 15 were highly active against (E. Coli and B.Sublet), whereas 1, 4c, 5c, 7b, 7c, 8, 9, 12a, 12b, 13a and 13b showed moderate activity this microorganism. No significant inhibitory activity of other synthesized derivatives was seen by any against (E. Coli and B.Sublet).

EXPERMINTAL PART

All melting point are uncorrected and determined by the open capillary method using Gallen Kamp melting point apparatus. Microanalysis 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.[15,16] Mass spectrometry were recorded were recorded Shomadzu, GC-MS (QP-1000EX).

2-butyramidobenzoic acid (1)

A stirred solution of 2-aminobenzoic acid 13.7 g (0.1 mol) in dry pyridine (150 ml) was treated drop wise with n-butyroyl chloride 10.5 g (0.11 mol) during 10 min. the mixture was stirred at room temperature (3 hours) and poured into a mixture of ice and hydrochloric acid gave crude 2-butyramidobenzoic acid crystallize from the proper solvent. 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- 3,1-benzoxazin-4-one(2)

A suspension of 2-butyramidobenzoic acid 2.07 g

Table 3. Inhibition zones in mm for the synthesized compound at deferent concentration

Comp. No.	E. Coli			B. Sublet		
	50 μg/ml	100 μg/ml	200 μg/ml	50 μg/ml	100 μg/ml	200 μg/ml
1	9	12	13	10	11	11
2	12	15	20	15	16	18
3	25	29	33	22	26	29
4a	28	29	30	14	25	30
4b	26	30	33	23	28	29
4c	10	15	16	13	14	14
5a	28	19	32	22	25	29
5b	27	28	28	29	29	33
5c	8	15	16	11	13	15
6	-	-	-	-	-	-
7a	-	-	-	-	-	-
7b	10	16	19	9	11	14
7c	8	11	12	6	12	13
8	5	11	13	14	15	17
9	11	15	19	15	18	20
10	-	-	-	-	-	-
11a	-	-	-	-	-	-
11b	-	-	-	-	-	-
11c	-	-	-	-	-	-
12a	5	11	16	8	12	16
12b	9	11	13	8	13	19
13a	17	19	19	15	16	18
13b	9	15	19	10	12	16
14	25	27	30	28	29	33
15	26	28	29	28	29	34

(-) Represent no inhibition of growth

(0.01 mol) in 50 ml acetic anhydride was heated under reflux (3hours) and then concentrated. The solid was obtained crystallized from petroleum ether 40-60 °C, giving 2-propyl-4H-3,1-benzoxazin-4-one as a colorless crystals melting point(59 °C). IR(KBr) cm^{-1}: 3055 (CH aromatic), 2965, 2935, 2875 (CH aliphatic),1764(C=O), 1614(C=N),1161 (C-O).

3-amino-2- propylquinazolin-4(3H)-one (3)

Compound (2) (1.89 g- 10 mmol) and 5 ml hydrazine hydrate were heated on water bath for 1/2 hour and then added 50 ml ethanol the mixture was refluxed 3hours, then concentrated and poured on cooled water, the precipitate formed was collected by filtration, dried and crystallization from petroleum ether 60- 80 °C to give (1.5g) 3-amino-2-propylquinazolin-4(3H)-one IR(KBr) cm^{-1}: 3309, 3212 (NH_2),3055 (CH aromatic), 2965, 2935, 2875 (CH aliphatic),1673(C=O), 1596(C=N); MS: m/z 203[M^+], 188, 174, 158, 145, 132, 104, 77; ^{1}HNMR ($CDCl_3$) : δ7.2-8 (m, 4H, aromatic),12 (s, 2H, NH_2). 1(t, 3H, CH_3), 1.8 (sextet,2H,CH_2Me), 2.8 (t,2H, CH_2Q).

3-(3,4-dimethoxybenzylideneamino)-2-propylquinazolin-4(3H)-one (4a), 3-(4-(dimethylamino)-benzylideneamino)-2-propylquinazolin-4(3H)-one (4b) and 3-(benzo[d][1,3]dioxol-5-ylmethyleneamino)-2-propylquinazolin-4(3H)-one (4c)

a mixture of vetraldehyde (1.66 g., 10 mmol) or 4-N,N-dimethylaminobenz aldehyde (1.49 g., 10 mmol) or piperonal (1.5 g., 10 mmol) and compound 3 (2.03 g., 10 mmol) in 50 ml ethanol was stirred for 3 hr. the obtained solid was filtered off and recrystalization from the proper solvent to give 4a, 4b or 4c.

3-(3,4-dimethoxybenzylideneamino)-2-propylquinazolin-4(3H)-one (4a).

IR(KBr) cm^{-1}: 3076 (CH aromatic), 2962, 2919, 2870 (CH aliphatic), 1673(C=O), 1605(C=N); MS: m/z 351[M^+], 320, 289, 192, 179, 97; ^{1}HNMR ($CDCl_3$) : δ7.7-8.4 (m, 7H, aromatic), 6 (s, H, N=CH), 3.4 (s, 6H, $2OCH_3$), 1(t, 3H, CH_3), 1.5 (sextet,2H, CH_2Me), 1.3 (t,2H, CH_2Q).

3-(4-(dimethylamino)benzylideneamino)-2-propylquinazolin-4(3H)-one (4b).

IR(KBr) cm^{-1}: 3059 (CH aromatic), 2975, 2925, 2875 (CH aliphatic), 1675(C=O), 1600(C=N); MS: m/z 330[M^+], 315, 300, 286, 273, 259, 244, 216, 188, 174; ^{1}HNMR ($CDCl_3$) : δ7.7-8.3 (m, 8H, aromatic), 6 (s, H, N=CH), 3.3 (s, 6H, $N(CH_3)_2$), 1(t, 3H, CH_3), 1.9 (sextet, 2H, CH_2Me), 2.9 (t, 2H, CH_2Q).

3-(benzo[d][1,3]dioxol-5-ylmethyleneamino)-2-propylquinazolin-4(3H)-one (4c).

IR(KBr) cm^{-1}: 3076 (CH aromatic), 2962, 2919, 2870 (CH aliphatic), 1671(C=O), 1601(C=N), 1255 (C-O-C); MS: m/z 235[M^-], 320, 289, 274, 259, 254, 145; ^{1}HNMR ($CDCl_3$) : δ7.2-8.1 (m, 7H, aromatic), 6.1 (s, 2H, O-CH2-O), 6 (s, H, N=CH) 1(t, 3H, CH_3), 1.8 (sextet, 2H, CH_2Me), 2.8 (t, 2H, CH_2Q).

3,4-dimethoxybenzylideneamino)-2-(3,4-dimethoxyphenyl)but-1-en-2-yl) quinazolin-4(3H)-one(5a)

4-(dimethylamino)benzylideneamino)-2-(4-dimethylamino)phenyl)but-1-en-2-yl) quinazolin-4(3H)-one (5b)

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

A solution of compound 4a (3.51 g 10 mmol) or 4b (3.3 g., 10 mmol) or 4c (3.35 g., 10 mmol) and vetraldehyde (1.66 g., 10 mmol) or 4-N,N-dimethylaminobenz aldehyde (1.49 g., 10 mmol) or piperonal (1.5 g., 10 mmol) respectively in 10 ml glacial acetic acid and the mixtures were refluxed for 12 hours and then allowed to cool and the obtained solids were filtered and recrystallization from proper solvent yielded (5a-c).

3,4-dimethoxybenzylideneamino)-2-(3,4-dimethoxyphenyl)but-1-en-2-yl)quinazolin-4(3H)-one(5a).

IR(KBr) cm^{-1}: 3076 (CH aromatic), 2962, 2919, 2870 (CH aliphatic), 1673(C=O), 1605(C=N); MS: m/z 499[M^-], 468, 437, 406, 375, 300, 225; ^{1}HNMR (DMSO-d_6) : δ7.7-8.4 (m, 7H, aromatic), 6 (s, H, N=CH), 5.5 (s, 1H, C=CH) 3.4 (s, 12H, $2OCH_3$), 1(t, 3H, CH_3), 2.2 (q,2H,CH_2Me).

4-(dimethylamino)benzylideneamino)-2-(4-dimethylamino)phenyl)but-1-en-2-yl) quinazolin-4(3H)-one (5b).

IR(KBr) cm^{-1}: 3059 (CH aromatic), 2975, 2925,

2875 (CH aliphatic), 1675(C=O), 1600(C=N); MS: m/z 465[M⁻], 421, 377, 315, 303, 228; ^{1}HNMR (DMSO-d_6) : δ7.7-8.3 (m, 8H, aromatic), 6 (s, H, N=CH), 5.8 (s, 1H, C=CH), 3.3 (s, 12H, N(CH_3)$_2$), 1(t, 3H, CH_3), 2.2 (q, 2H, CH_2Me).

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

IR(KBr) cm^{-1}: 3076 (CH aromatic), 2962, 2919, 2870 (CH aliphatic), 1671(C=O), 1601(C=N), 1255 (C-O-C); MS: m/z 467[M$^+$], 421, 375, 300, 225,210, 196; ^{1}HNMR (DMSO-d_6) : δ7.2 -8.1 (m, 7H, aromatic), 6 (s, H, N=CH), 5.8 (s, 1H, C=CH),4 (s, 4H, 2O-CH_2-O), 1(t, 3H, CH_3), 2.2 (q, 2H, CH_2Me).

methyl 4-oxo-2-propylquinazolin-3(4H)-ylcarbamodithioate (6)

A solution of 3-aminoquinazolinone 3 (4.06 g., 0.02 mol) in dimethyl sulphoxide (10 ml) was stirred vigorously. then added carbon disulphide (1.6 ml) and aqueous sodium hydroxide 1.2 ml (20 mol solution) dropwise during 30 min with stirring . Dimethyl sulphate (0.02 mol) was added gradually keeping the reaction mixture stirring in freezing mixture for 2 hr. The solid obtained was filtered, washed with water, dried and recrystallized from proper solvent gave (6). IR(KBr) cm^{-1}: 3250 (NH), 3066 (CH aromatic), 2979, 2906, 2867 (CH aliphatic), 1673(C=O), 1600(C=N), 1450 (C=S); MS: m/z 293[M$^+$], 278, 246, 214, 202, 187, 172, 152, 142; ^{1}HNMR ($CDCl_3$) : δ 11 (s, 1H, NH), 7.4-8 (m, 4H, aromatic), 2.6 (s, 3H, SCH_3), 1(t, 3H, CH_3), 1.9 (sextet, 2H, CH_2Me), 2.8 (t, 2H, CH_2Q).

N-(4-oxo-2-propylquinazolin-3(4H)-yl)piperidine-4-carbothioamide (7a)

N-(4-oxo-2-propylquinazolin-3(4H)-yl)morpholine-4-carbothioamide (7b)

N-(4-oxo-2-propylquinazolin-3(4H)-yl)piperazine-4-carbothioamide (7c)

A mixture of (2.93 g, 0.01 mol) and of piperidine or morpholine or piperazine (10 ml) was refluxed for 3 hr. the produced mixture was cooled triturated with methanol and the solid obtained was filtered off and re crystallization from proper solvent yielded (7a-c).

N-(4-oxo-2-propylquinazolin-3(4H)-yl)piperidine-4-carbothioamide (7a)

IR(KBr) cm^{-1}: 3225 (NH), 3045 (CH aromatic), 2963, 2900, 2862 (CH aliphatic), 2270 (C=S), 1645(C=O), 1600(C=N); MS: m/z 331 [M$^+$], 330, 252, 220, 208, 193, 162, 120; ^{1}HNMR (DMSO-d_6) : δ 10.8 (s, 1H, NH), 7.2-87.7 (m, 4H, aromatic), 3.2 (s, 4H, N(CH_2)$_2$piperidine), 1.8 (pentet, 6H, piperidine), 1(t, 3H, CH_3), 1.8 (sextet, 2H, CH_2Me), 2.8 (t, 2H, CH_2Q).

N-(4-oxo-2-propylquinazolin-3(4H)-yl)morpholine-4-carbothioamide (7b)

IR(KBr) cm^{-1}: 3225 (NH), 3045 (CH aromatic), 2963, 2900, 2862 (CH aliphatic), 2270 (C=S), 1645(C=O), 1600(C=N), 1110 (c-o-c); MS: m/z 331 [M$^+$], 330, 303, 205, 186, 162, 145, 120, 90. 77; ^{1}HNMR (DMSO-d_6) : δ 11 (s, 1H, NH), 7.2-7.7 (m, 4H, aromatic), 3.8 (t,4H,O(CH_2)$_2$ morphiline), 3.2 (t, 4H, N(CH_2)$_2$ morpholine), 1(t, 3H, CH_3), 1.9(sextet, 2H, CH_2Me), 2.8 (t, 2H, CH_2Q).

N-(4-oxo-2-propylquinazolin-3(4H)-yl)piperazine-4-carbothioamide (7c)

IR(KBr) cm^{-1}: 3225 (NH), 3045 (CH aromatic), 2963, 2900, 2862 (CH aliphatic), 2270 (C=S), 1645(C=O), 1600(C=N); MS: m/z 331 [M$^+$], 330, 303, 205, 186, 162, 145, 120, 90. 77.

1-(3-amino-4-oxo-3,4-dihydroquinazolin-2-yl)-propyl acetate (8)

A mixture of 3 (2.03 g, 10 mmol) and sodium acetate (10 mmol) in glacial acetic acid (20 ml) was added bromine (10 mmol) in glacial acetic acid (10 ml) drop wise at 40-50 °C the reaction mixture was stirred for 3 hr, and it was then left to stand in refrigerator overnight the crystals were filtered off, washed with water and recrystallization from proper solvent to give (8). IR(KBr) cm^{-1}: 3324, 3249 (NH_2), 3025 (CH aromatic), 2963, 2923, 2849 (CH aliphatic), 1725 (C=O ester), 1645(C=O quinazolinone), 1612(C=N), 1265 (C-O); MS: m/z 260 [M⁻], 259, 244, 200, 184, 169, 155, 141; ^{1}HNMR (DMSO-d_6) : δ 12 (s, 2H, NH_2), 7.9 (s, 3H, COCH_3), 7.2-7.7 (m, 4H, aromatic), 5.5 (t, 1H, CHOCOMe), 1.2(t, 3H, CH_3), 2.2 (p, 2H, CH_2Me).

2-(1-phenylhydrazonopropyl)-3-amino-4(3H)-quinazolinone (9)

To a solution of 8 (2.6 g, 0.01 mol) in ethanol (5 ml) was added phenyl hydrazine 1.81 ml, 2 g, 0.02 mol) the reaction mixture was refluxed for 4 hr. after cooling of mixture, the crystallized product was filtered off, washed with cooled ethanol, dried and recrystallization from proper solvent produced (9). IR(KBr) cm^{-1}: 3360, 3300 (NH_2), 3200 (NH) 3025 (CH aromatic), 2963, 2923, 2849 (CH aliphatic), 1673 (C=O), 1610 (C=N); MS: m/z 307 [M^+], 306, 292, 278, 201, 187, 170, 77; ^{1}HNMR (DMSO-d_6) : δ 11.3 (s, 2H, $\underline{NH_2}$), 7.2-7.7 (m, 9H, aromatic), 4.5 (s, 1H, $\underline{NH}$), 2.1(q, 2H, $\underline{CH_2}$Me), 1.2 (t, 2H, $\underline{CH_3}$).

3-amino-2-(3-methylindolin-2-yl)quinazolin-4 (3H)-one (10)

Compound 9 (3.07 g 0.1 mol)was added to 85% phosphoric acid (25 ml) at 180 °C. the reaction mixture was heated for 30 min then cooled and diluted with water 100 ml the solid was filtered and recrystallization from the proper solvent gave (10). IR(KBr) cm^{-1}: 3400-3324 (abroad NH_2 and NH), 3060 (CH aromatic), 2940 (CH aliphatic), 1676 (C=O), 1612(C=N); MS: m/z 289 [M^-], 288, 274, 258, 144, 114; ^{1}HNMR (DMSO-d_6) : δ 11.2 (s, 2H, $\underline{NH_2}$), 7.2-7.7 (m, 9H, aromaticand indole NH), 2.8 (s,3H, $\underline{CH_3}$).

3-(3,4-dimethoxybenzylideneamino)-2-(3-methylindolin-2-yl)quinazolin-4(3H)-one (11a), 3-(4-(dimethylamino)benzylideneamino)-2-(3-methylindolin-2-yl)quinazolin-4(3H)-one (11b), 3-(benzo[d][1,3]dioxol-5-ylmethyleneamino)-2-(3-methylindolin-2-yl)quinazolin-4(3H)-one (11c).

To asolution of 10 (2.89 g, 0.01 mol) in DMF (20 ml) and vetraldehyde (1.66 g., 10 mmol) or 4-N,N-dimethylaminobenzaldehyde (1.49 g, 10 mmol) or piperonal (1.5 g., 10 mmol) the mixture was stirred at 50 °C for 3 hr following pouring the reaction mixture in cooled water and recrystallization the solid produced from the proper solvent yielded (11a-c).

3-(3,4-dimethoxybenzylideneamino)-2-(3-methylindolin-2-yl)quinazolin-4(3H)-one (11a).

IR(KBr) cm^{-1} : 3180 (NH), 3055 (CH aromatic), 2967 (CH aliphatic), 1675 (C=O), 1610(C=N); MS: m/z438 [M^+], 437, 407, 376, 361, 284, 271, 257, 144, 113; ^{1}HNMR (DMSO-d_6) : δ 7.2-7.9 (m, 12H, aromaticand indole NH), 6 (s, H, N=$\underline{CH}$), 3.8(s, 6H, $\underline{2OCH_3}$), 2.8 (s, 3H, $\underline{CH_3}$).

3-(4-(dimethylamino)benzylideneamino)-2-(3-methylindolin-2-yl)quinazolin-4(3H)-one (11b).

IR(KBr) cm^{-1}: 3195 (NH), 3065 (CH aromatic), 2957 (CH aliphatic), 1675 (C=O), 1607(C=N); MS: m/z 421 [M^-], 377, 362, 349, 335, 191, 144, 77; ^{1}HNMR (DMSO-d_6) : δ7.2-7.9 (m, 13H, aromatic and indole NH), 6 (s, H, N=$\underline{CH}$), 3.2(s, 6H, N($\underline{CH_3}$)$_2$), 2.8 (s, 3H, $\underline{CH_3}$).

3-(benzo[d][1,3]dioxol-5-ylmethyleneamino)-2-(3-methylindolin-2-yl)quinazolin-4(3H)-one (11c).

IR(KBr) cm^{-1}: 3193 (NH), 3045 (CH aromatic), 2957 (CH aliphatic), 1675 (C=O), 1603(C=N); MS: m/z 422 [M^-], 407, 377, 361, 286, 273, 259, 144, 115; ^{1}HNMR (DMSO-d_6) : δ8.8 (s, H, N=$\underline{CH}$), 7.2-7.7 (m, 12H, aromaticand indole NH), 6 (s, 2H, $\underline{OCH_2O}$), 2.8 (s, 3H, $\underline{CH_3}$).

3-(cyclohexylideneamino)-2-propylquinazolin-4(3H)-one (12a), 3-(cyclopenty lidene amino)-2-propylquinazolin-4(3H)-one (12b).

Cyclohexanone (0.01 mol) or cyclopentanone (0.01 mol) was added to solution of 3 (0.01 mol) in 50 ml ethanol. The reaction mixture was heated under reflux for 3 hr and then poured in cooled water and stirring the mixture for 5 min. the solid that separated was filtered and washed with water and recrystallized from the proper solvent giving (12a,b).

3-(cyclopenty lidene amino)-2-propylquinazolin-4(3H)-one (12a).

IR(KBr) cm^{-1}: 3035 (CH aromatic), 2967, 2906, 2876, 2789 (CH aliphatic), 1675 (C=O), 1609(C=N); MS: m/z 283 [M^-], 363, 239, 180, 146, 120, 92, 65.

3-(cyclohexylideneamino)-2-propylquinazolin-4(3H)-one (12b).

3035 (CH aromatic), 2967, 2906, 2876, 2789 (CH aliphatic), 1675 (C=O), 1609(C=N) ; MS: m/z 269 [M^-], 254, 240, 226, 158, 144, 120, 77.

2-(1-(4-oxo-2-propylquinazolin-3(4H)-ylamino)-cyclohexylthio)acetic acid (13a) or 2-(1-(4-oxo-2-propylquinazolin-3(4H)-ylamino)cyclopentylthio)-acetic acid (13b).

A mixture of compound 12a (2.83 g,. 0.01 mol) or 12 b (2.69 g, 0.01 mol) and thioglycolic acid (0.01 mol) in benzene (50 ml) were refluxed for 3 hr and the solvent was evaporated under reduced pressure. The residue was crystallization from the proper solvent gave (13a,b).

2-(1-(4-oxo-2-propylquinazolin-3(4H)-ylamino)-cyclopentylthio)acetic acid (13a).

IR(KBr) cm^{-1}: 3035 (CH aromatic), 2967, 2906, 2876, 2789 (CH aliphatic), 1685 (C=O thiazole), 1675 (C=O Quinazolinone), 1609(C=N); MS: m/z 357 [M^-], 358, 343, 269, 254, 240, 226,144, 120; ^{1}HNMR (DMSO-d_6) : δ7.2-7.7 (m, 9H, aromatic), 5.8 (s, 2H, CH_2 thiazole ring), 2.1 (t, 4H, cyclopentane), 1.8 (pentet, 6H, cyclopentane) 1.8 (sextet, 2H, CH_2Me), 2.7 (t, 2H, $\underline{CH_2}$Q), 1(t, 3H, CH_3).

2-(1-(4-oxo-2-propylquinazolin-3(4H)-ylamino)-cyclohexylthio)acetic acid (13b).

IR(KBr) cm^{-1}: 3035 (CH aromatic), 2967, 2906, 2876, 2789 (CH aliphatic), 1687 (C=O thiazole), 1675 (C=O Quinazolinone), 1609(C=N); MS: m/z 343 [M^+], 328, 314, 300, 269, 254, 240, 226, 144, 120; ^{1}HNMR (DMSO-d_6) : δ7.2-7.7 (m, 9H, aromatic), 5.8 (2H, CH_2 thiazole ring), 2.1 (t, 4H, cyclopentane), 1.8 (pentet, 4H, cyclopentane) 1.5 (sextet, 2H, $\underline{CH_2}$Me), 2.8 (t, 2H, $\underline{CH_2}$Q), 1(t, 3H, $\underline{CH_3}$).

2-chloro-N-(4-oxo-2-propylquinazolin-3(4H)-yl)acetamide (14).

Compound 3 (2.03 g, 0.01 mol)was dissolved in dry pyridine (25 ml) was stirred at room temperature, chloroacetyl chloride was added drop by drop during 20 min the stirring was continued for 3 hr the produced mixture was poured on ice and HCl, the resulting precipitate was collected and washed with water and recrystallization from the proper solvent gave (14). IR(KBr) cm^{-1}: 3120 (NH), 3068 (CH aromatic), 2967, 2906, 2876, 2789 (CH aliphatic), 1710 (C=O), 1672 (C=O Quinazolinone), 1610(C=N); MS: m/z 279 [M^+], 244, 230, 202, 187, 158; ^{1}HNMR (DMSO-d_6) : δ10.9 (s, 1H, $\underline{NH}$), 7.2-7.7 (m, 4H, aromatic), 6.6 (s,2H, CO$\underline{CH_2}$Cl), 1(t, 3H, $\underline{CH_3}$), 1.8 (sextet, 2H, $\underline{CH_2}$Me), 2.8 (t, 2H, $\underline{CH_2}$Q).

6-propyl-2H-[1,2,4]triazino[2,3-c]quinazolin-3-(4H)-one (15)

Compound (14) (2.79, 0.01 mol) and ammonium acetate (5 g) was heated in oil bath for 3 hr. The reaction mixture was allowed to cool and treated with water the obtained solid was filtered off and recrystallized from the proper solvent gave (15). IR(KBr) cm^{-1}: 3200 (NH), 3068 (CH aromatic), 2967, 2906, 2876, 2789 (CH aliphatic), 1680 (C=O), 1615(C=N); MS: m/z 242 [M^-], 227, 213, 199, 171, 157, 142; ^{1}HNMR (DMSO-d_6) : δ 11.5 (s, 1H, $\underline{NH}$), 7.2-7.7 (m, 4H, aromatic), 5.1 (s, 2H, CO$\underline{CH_2}$), 1(t, 3H, CH_3), 1.8 (sextet, 2H, CH_2Me), 2.8 (t, 2H, CH_2Q).

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