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Synthesis and antimicrobial activity of some new isopropylquinazolin-4(3H)-one derivatives

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ABSTRACT

*Some new substituted 3-((4-(-phenyl) thiazol-2-yl) amino)-2-isopropylquinazolin-4(3H)-one (**III**) have been synthesised from different hydrazinyl thiazole derivatives (**I**) by condensing with 2-isopropyl-4H-benzo[d][1,3]oxazin-4-one (**II**). Their chemical structures have been confirmed by IR, 1H NMR, and MASS and by elemental analysis. Investigation of antimicrobial activity of compound was done by the disk diffusion technique. Among the compound with -F,-Cl and –NO_2 substitution showed the most favourable antimicrobial activity.*

Keywords: Quinazolinone, Hydrazinyl thiazole, antibacterial and antifungal activity.

INTRODUCTION

Quinazolinone and their derivatives constitute an important class of heterocyclic compounds. It is evident from literature that quinazolinone derivatives are known to be associated with broad spectrum of biological activity like antibacterial[1], anti-inflammatory[2], analgesic[3], anti viral[4], antifungal[5], antitubercular [6] and anti cancer activity[7].

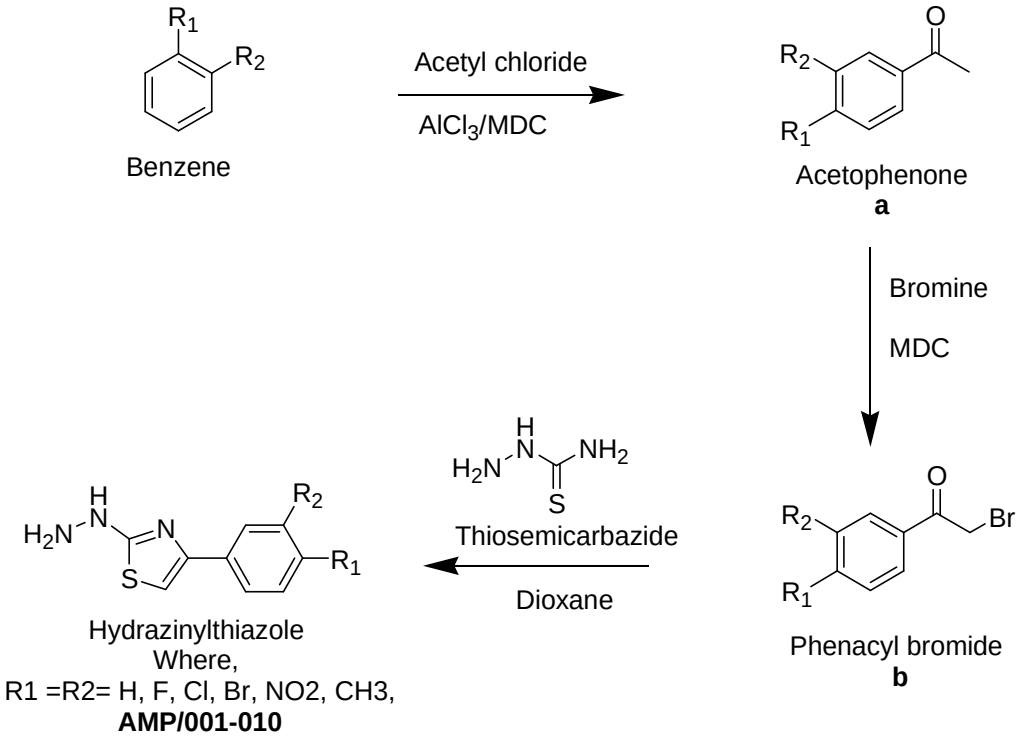
Hydrazinyl thiazole derivative shows anticancer activity[8]. Looking at the biological significance of quinazolinone and hydrazinyl thiazole nucleus it was thought to design and synthesize new quinazolinone derivatives and screen them for their antibacterial activity.

MATERIALS AND METHODS

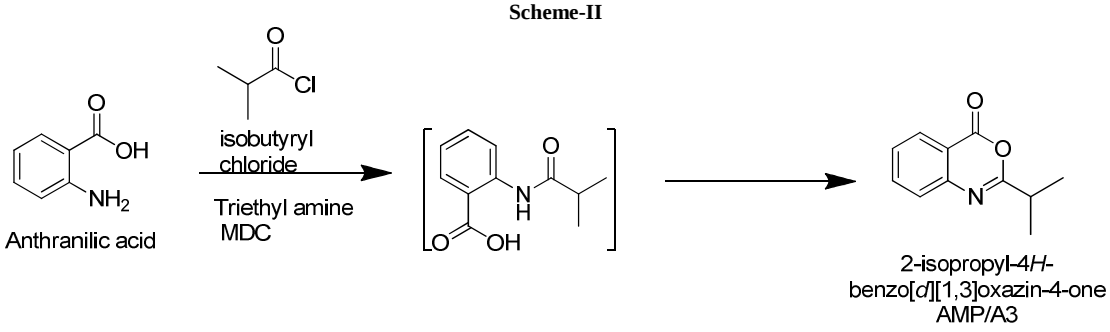
All the melting points were determined by open capillary using V-Scientific Melting Point apparatus and are uncorrected. Purity of compound was checked by TLC on silica Gel-coated plates. IR spectra were recorded in KBr on FTIR Prestige-211 Simadzu spectrophotometer.^{1}H NMR spectra were recorded on 500 MHz Bruker using $CDCl_3$/DMSO and Mass spectra were recorded on using EI-MS mode. Elemental analysis was performed on Perkin-Elmer Series 2400.

*Synthesis of Hydrazinyl thiazole :(**AMP/001-010**)*
As shown in scheme-I. As literature serve the synthesis of hydrazinyl thiazole derivatives synthesis by the process [8]. The different substituted benzene were reacted with acetyl chloride in presence of aluminium chloride by friedle craft acylation we get different substituted acetophenone (**a**) further more reaction of them with bromine gives substituted phenacyl bromide(**b**) each of phenacyl bromide subjected to a cyclization with thiosemicarbazide in presence of dioxane to yield corresponding substituted hydrazinyl thiazole(**AMP/001-010**).All these hydrazinyl thiazole derivatives were identified by IR, ^{1}H NMR and MASS.

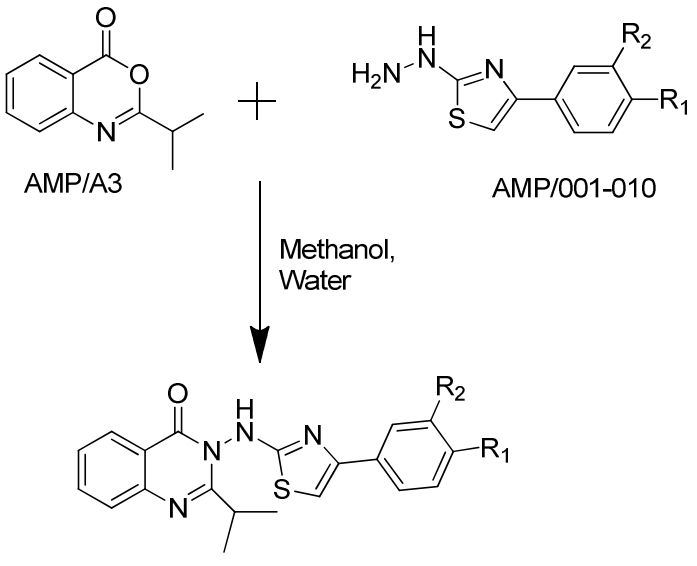
Scheme-I



Scheme-II



Scheme-III



Where, when 1) R_1= -F,-Cl,-Br,-NO_2,-CH_3 or -H then R_2= -H, 2) R_2= -NO_2 then R_1= -H and 3) R_1=R_2= -F,-Cl,-CH_3.

*Synthesis of Preparation of 2-isopropyl-4H-benzo[d][1,3]oxazin-4-one:(**AMP/A3**)*
Charge Anthranilic acid(1.0 mmol) in to methylene dichloride(10.0 ml) in to round bottom flask and cool down reaction mass up to 0-5°C temperature then add triethyl amine (2.5 mmol) and stir reaction mass for 30 minutes then slowly add isobutyryl chloride (1.5 mmol) in to reaction mass within 30 minutes at 0-5°C then raise temperature of reaction mass up to room temperature and maintain reaction mass for another 1 hour after that charge water (10.0 ml) in to reaction mass and stir for 15 minutes then separate lower organic layer and wash it with water (10.0 ml) and distille out solvent from organic layer under vacuum, get solid collect it (A3). As shown in scheme-II.

Synthesis of substituted 3-((4-(-phenyl) thiazol-2-yl) amino)-2-isopropylquinazolin-4(3H)-one:
(AMP/A301-310)
General Procedure
A mixture of equimolar quantity of different hydrazinyl thiazole derivatives (0.01 mol) **AMP/001-010** and *2-isopropyl-4H-benzo[d][1,3]oxazin-4-one* (0.01 mol) in 10 ml of methanol stir for 12 hours at room temperature then charge 50 ml water in to reaction mass then stir for another 1 hour and filter solid mass and wash with water and dry material at 50-60°C.As shown in **scheme-III**.

Spectral Data
1. *3-((4-(4-fluorophenyl) thiazol-2-yl) amino)-2-isopropyl quinazolin-4(3H)-one* **(AMP/A301)**:
IR (KBr); 3435.34(-N-H stretching), 3086.21(Aromatic –C-H stretching), 1502.60(Aromatic -C=C- stretching), 2966.62(Aliphatic -C-H stretching), 1375.29(Aliphatic –C-H bending), 1579.75(-C=O stretching of carbonyl), 1159.26(-C-F stretching); 1 H NMR (DMSO) ppm: 1.23-1.24(6H,d,$(-CH_3)_2$), 3.51-3.6(1H,m,-CH), 6.602-6.996(1H,m,ArH), 7.079(1H,s,ArH), 7.153-7.257(2H,m,ArH), 7.584-7.627(1H,m,ArH), 7.793-7.998(2H,m,ArH), 8.002-8.059(1H,m,ArH), 8.756-8.807(1H,d,ArH), 10.636(1H,s,-NH) ; MS m/z: 399 [$M+NH_4$]

2. *3-[4-(4-Chloro-phenyl)-thiazol-2-ylamino]-2-isopropyl-3H-quinazolin-4-one* **(AMP/A302)**:
IR (KBr); 3456.55(-N-H stretching), 3066.92(Aromatic –C-H stretching), 1487.17(Aromatic –C=C- stretching), 2964.69(Aliphatic –C-H stretching), 1400.37(Aliphatic –C-H bending), 1577.82(-C=O stretching of carbonyl), 754.19(C-Cl stretching); 1 H NMR (DMSO) ppm: 1.247-1.279(6H,d,$(-CH_3)_2$), 3.518-3.586(1H,m,-CH), 6.932-6.996(1H,m,ArH), 7.252(1H,s,ArH), 7.401-7.472(2H,m,ArH), 7.583-7.626(1H,m,ArH), 7.802-7.831(2H,m,ArH), 7.996-8.020(1H,dd,ArH), 8.775-8.796 (1H,d,ArH), 10.643 (1H, s, -NH) ; MS m/z: 415 [$M+NH_4$]

3. *2-Isopropyl-3-[4-(4-nitro-phenyl)-thiazol-2-ylamino]-3H-quinazolin-4-one* **(AMP/A303)**:
IR (KBr); 3439.19(-N-H stretching), 3117.07(Aromatic –C-H stretching), 1410.01(Aromatic –C=C- stretching), 2972.40(Aliphatic –C-H stretching), 1342.50(Aliphatic -C-H bending), 1595.19(-C=O stretching of carbonyl), 1504.53(-N-O stretching); 1 H NMR (DMSO) ppm: 1.249-1.281(6H,d,$(-CH_3)_2$), 3.529-3.595(1H,m,-CH), 6.969-7.006(1H,m,ArH), 7.480(1H,s,ArH), 7.577-7.629(2H,m,ArH), 7.920-7.939(2H,m,ArH), 8.205-8.348(2H,m,ArH), 8.779-8.801(1H,d,ArH), 10.570(1H,s,-NH) ; MS m/z:426 [$M+NH_4$]

4. *2-Isopropyl-3-(4-phenyl-thiazol-2-ylamino)-3H-quinazolin-4-one* **(AMP/A304)**:
IR (KBr) 3433.41(-N-H stretching), 3063.06(Aromatic –C-H Stretching), 1450.52(Aromatic-C=C- stretching), 2968.55(Aliphatic –C-H stretching), 1377.22(Aliphatic –C-H bending), 1579.75(-C=O stretching of carbonyl); 1 H NMR (DMSO) ppm: 1.232-1.249(6H,d,$(-CH_3)_2$), 3.551-3.619(1H,m,-CH), 6.912-6.995(1H,m,ArH), 7.161(1H,s,ArH), 7.239-7.313(1H,m,ArH), 7.348-7.474(2H,m,ArH), 7.583-7.627(1H,m,ArH), 7.844-7.911(2H,m,ArH), 7.931-8.021(1H,m,ArH), 8.797-8.818(1H,d,ArH), 10.635(1H,s,-NH); MS m/z:381 [$M+NH_4$]

5. *3-[4-(4-Bromo-phenyl)-thiazol-2-ylamino]-2-isopropyl-3H-quinazolin-4-one* **(AMP/A305)**:
IR (KBr) 3308.03(-N-H stretching), 3068.85(Aromatic –C-H stretching), 1533.46(Aromatic –C=C- stretching), 2966.62(Aliphatic –C-H stretching), 1375.29(Aliphatic –C-H bending), 1577.82(-C=O stretching of carbonyl), 673.18(-C-Br stretching); 1 H NMR (DMSO) ppm: 1.125-1.233(6H,d,$(-CH_3)_2$), 3.501-3.651(1H,m,-CH), 6.958-6.998(1H,m,ArH), 7.173(1H,s,ArH), 7.436-7.516(2H,m,ArH), 7.586-7.735(1H,m,ArH), 7.758-7.931(2H,m,ArH), 8.001-8.662(1H,m,ArH), 8.777-8.798(1H,d,ArH), 10.670(1H,s,-NH) ; MS m/z: 460 [$M+NH_4$]

6. *2-Isopropyl-3-(4-p-tolyl-thiazol-2-ylamino)-3H-quinazolin-4-one* **(AMP/A306)**:
IR (KBr) 3441.12(-N-H stretching), 3113.21(Aromatic –C-H stretching), 1492.95(Aromatic –C=C-stretching), 2972.40(Aliphatic –C-H stretching), 1369.50(Aliphatic –C-H bending), 1579.75(-C=O stretching of carbonyl); 1 H NMR (DMSO) ppm: 1.244-1.262(6H,d,$(-CH_3)_2$), 2.297(3H,s,$-CH_3$), 3.552-3.646(1H,m,-CH), 6.906-7.015(1H,m,ArH), 7.061(1H,s,ArH), 7.146-7.217(2H,m,ArH), 7.517-7.620(1H,m,ArH), 7.681-7.963(2H,m,ArH), 7.994-8.018(1H,m,ArH), 8.796-8.817(1H,d,ArH), 10.631(1H,s,-NH); MS m/z: 395 [$M+NH_4$]

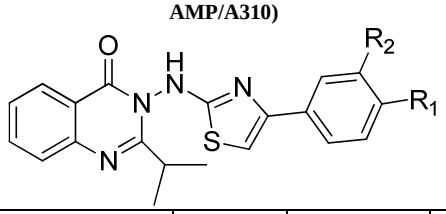
7. *2-Isopropyl-3-[4-(3-nitro-phenyl)-thiazol-2-ylamino]-3H-quinazolin-4-one* **(AMP/A307)**:
IR (KBr) 3365.90(-N-H stretching), 3126.71(Aromatic –C-H stretching), 1514.17(Aromatic –C=C- stretching), 2956.97(Aliphatic –C-H stretching), 1342.50(Aliphatic –C-H bending), 1579.75(-C=O stretching of carbonyl), 1514.17(-N-O stretching); 1 H NMR (DMSO) ppm: 1.239-1.252(6H,d,$(-CH_3)_2$), 3.558-3.651(1H,m,-CH), 6.721-6.762(1H,m,ArH), 6.979-7.312(1H,m,ArH), 7.429(1H,s,ArH), 7.601-7.738(2H,m,ArH), 8.012-8.345(1H,m,ArH), 8.213-8.556(1H,m,ArH), 10.912(1H,s,-NH); MS m/z: 426 [M+NH_4]

8. *3-[4-(3,4-Difluoro-phenyl)-thiazol-2-ylamino]-2-isopropyl-3H-quinazolin-4-one* **(AMP/A308)**:
IR (KBr) 3455.62(-N-H stretching), 3115.75(Aromatic –C-H stretching), 1521.64(Aromatic –C=C- stretching), 2975.21(Aliphatic –C-H stretching), 1335.25(Aliphatic –C-H bending), 1589.24(-C=O stretching of carbonyl); 1 H NMR (DMSO) ppm: 1.224-1.259(6H,d,$(-CH_3)_2$), 3.458-3.598(1H,m,-CH), 7.103(1H,s,ArH), 7.213(1H,d,ArH), 7.264-7.281(1H,d,ArH), 7.345-7.473(1H,m,ArH), 7.512-7.627(1H,m,ArH), 8.137-8.235(1H,m,ArH), 8.687-8.721(1H,m,ArH), 10.632(1H,s,-NH); MS m/z: 417 [M+NH_4]

9. *3-[4-(3,4-Dichloro-phenyl)-thiazol-2-ylamino]-2-isopropyl-3H-quinazolin-4-one* **(AMP/A309)**:
IR (KBr) 3462.25(-N-H stretching), 3013.62(Aromatic –C-H stretching), 1562.25(Aromatic –C=C- stretching), 2969.64(Aliphatic –C-H Stretching), 1365.24(Aliphatic –C-H bending), 1592.64(-C=O stretching of carbonyl); 1 H NMR (DMSO) ppm: 1.224-1.259(6H,d,$(-CH_3)_2$), 3.452-3.512(1H,m,-CH), 6.634(1H,s,ArH), 7.282-7.299(1H,d,ArH), 7.512-7.589(1H,m,ArH), 7.623-7.625(1H,d,ArH), 8.125-8.345(2H,m,ArH), 8.415-8.527(1H,m,ArH), 8.734-8.740(1H,m,ArH), 10.62(1H,s,-NH); MS m/z: 450 [M+NH_4]

10. *3-[4-(3,4-Dimethyl-phenyl)-thiazol-2-ylamino]-2-isopropyl-3H-quinazolin-4-one* **(AMP/A310)**:
IR (KBr) 3465.54(-N-H stretching), 3142.25(Aromatic –C-H stretching), 1528.72(Aromatic –C=C- stretching), 2932.24(Aliphatic –C-H stretching), 1374.85(Aliphatic –C-H bending), 1592.87(-C=O stretching of carbonyl); 1 H NMR (DMSO) ppm: 1.227-1.259(6H,d,$(-CH_3)_2$), 1.925(6H,s,$-CH_3$), 3.543-3.668(1H,m,-CH), 6.957(1H,m,ArH), 7.135(1H,s,ArH), 7.177(1H,d,ArH), 7.21(1H,d,ArH), 7.322(1H,m,ArH), 7.413-7.418(2H,m,ArH), 7.751-7.73(1H,m,ArH), 10.66(1H,s,-NH); MS m/z: 409 [M+NH_4]

Table: 1 Physical property of synthesized substituted 3-((4-(-phenyl) thiazol-2-yl) amino)-2-isopropylquinazolin-4(3H)-one (AMP/A301-AMP/A310)



Sr. No.	R_1	R_2	Molecular Formula	M.P. (^{0}C)	Mol. Weight	Yield (%)	Elemental analysis Found (Calculated)		
							% C	% H	% N
AMP/A301	-F	-H	$C_{20}H_{17}FN_4OS$	175-177	380.44	87	63.01 (63.14)	4.27 (4.50)	14.59 (14.73)
AMP/A302	-Cl	-H	$C_{20}H_{17}ClN_4OS$	203-205	396.89	69	60.58 (60.52)	4.12 (4.32)	14.10 (14.12)
AMP/A303	- NO_2	-H	$C_{20}H_{17}N_5O_3S$	225-227	407.45	74	58.81 (58.96)	4.19 (4.21)	17.12 (17.19)
AMP/A304	-H	-H	$C_{20}H_{18}N_4OS$	168-170	362.45	86	66.17 (66.28)	4.98 (5.01)	15.38 (15.46)
AMP/A305	-Br	-H	$C_{20}H_{17}BrN_4OS$	212-214	441.34	71	54.33 (54.43)	3.87 (3.88)	12.58 (12.69)
AMP/A306	- CH_3	-H	$C_{21}H_{20}N_4OS$	197-199	376.47	93	66.95 (67.00)	5.31 (5.35)	14.75 (14.88)
AMP/A307	-H	- NO_2	$C_{20}H_{17}N_5O_3S$	187-189	407.45	59	58.94 (58.96)	4.19 (4.21)	17.17 (17.19)
AMP/A308	-F	-F	$C_{20}H_{16}F_2N_4OS$	211-213	398.43	68	60.15 (60.29)	3.95 (4.05)	14.03 (14.06)
AMP/A309	-Cl	-Cl	$C_{20}H_{16}Cl_2N_4OS$	237-239	431.34	76	55.65 (55.69)	3.65 (3.74)	12.80 (12.99)
AMP/A310	-CH_3	-CH_3	$C_{22}H_{22}N_4OS$	205-207	390.50	65	67.65 (67.67)	5.59 (5.68)	14.27 (14.35)

In Vitro Antimicrobial Activity
Evaluation of antibacterial and antifungal activities was done by the disk diffusion techniqu[9]. The tested compound solution were prepared in dimethylformamide (DMF) and evaluated them for their in vitro antibacterial and antifungal activity against *Bacillus subtillis* NCIM 2250, *Staphylococcus aureus* NCIM 2079, *Escherichia coli* NCIM 2109, *Aspergillus niger* NICM 501 and *Candida albicans* NICM 7431, respectively.

Table: 2 In Vitro antimicrobial activity of substituted 3-((4-(-phenyl) thiazol-2-yl) amino)-2-isopropylquinazolin-4(3H)-one (AMP/A301-AMP/A310)

Sr. No.	R_1	R_2	*E-coli*	*B-Subtillis*	*S-Aureus*	*S-Cerevisiae*	*A-niger*
AMP/A301	-F	-H	++	+++	+	+	++
AMP/A302	-Cl	-H	+++	++	+++	+	+
AMP/A303	- NO_2	-H	+	+	+	++	+
AMP/A304	-H	-H	+	+	+	+++	+
AMP/A305	-Br	-H	+	+++	+++	+	+++
AMP/A306	- CH_3	-H	+	+	+	+	+
AMP/A307	-H	- NO_2	+	+	+	++	+
AMP/A308	-F	-F	+++	+++	++	+++	+++
AMP/A309	-Cl	-Cl	+	+	+	+	+++
AMP/A310	$-CH_3$	$-CH_3$	+	+	+	+	+

**Effectively was classified in to three zones on the bases of the diameter of zone of inhibition*

+++ : Most effective
++ : Moderate effective
+ : Slightly effective
- : Non effective

All bacteria were grown on Mueller-Hinton agar (Hi media) plates (37°C, 24 h) and fungi were grown on subouraud dextrose agar (Hi media) plates (26°C, 48-72h). The results were established by the presence of clear zone of inhibition around the activity compound.

RESULTS AND DISCUSSION

As many as new ten compounds were synthesized by adopting similar above procedure and then characterized by their physical, analytical and spectral data. The detail of some of the representative compounds are given in the experimental section. Their physical and elemental analysis data are presented in **Table 1**.

The entire synthesized compounds were tested for in vitro antimicrobial activity by the disk diffusion technique. The results are summarized in **Table 2** that includes the activity of reference compound Ampicillin.

The tested compound exhibited mild to moderate antibacterial activity against all three strains of bacteria. The compound AMP/A 301, AMP/A302, AMP/A304, AMP/A305, AMP/A208, AMP/A309 shows highest activity

The antifungal activity of the compound was studied for the two pathogenic fungi. Amphotericin B was used as reference for inhibitory activity against fungi.it was observed that compound AMP/A303, AMP/A304, AMP/A307, AMP/A308 had highest activity against *S-Cerevisiae* and AMP/A301, AMP/A302, AMP/A305,AMP/A308 AMP/A309 tested against *E-coli* and showed good activity against *A-Niger*. It has also observed that compound AMP/A301, AMP/A302, AMP/A305, AMP/A308 against *B-Subtillis* and compound AMP/A302, AMP/A305 and AMP/A308 against *S-Aureus.*

CONCLUSION

The antimicrobial study revealed that substitution in the 3rd position of quinazolinone with methyl and 4th position of hydrazinyl thiazole with Fluorine, bromine chlorine or Nitro produced more active compound in a series.

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