AMERICAN JOURNAL OF PHARMTECH RESEARCH

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Synthesis, Characterization and Bio Evaluation of N-(substituted)-2-[4-oxo-2-Phenylquinazolin-3*(4H)*-yl] Acetohydrazide Derivatives

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ABSTRACT

A series of novel N-(substituted)-2-[4-oxo-2-phenylquinazolin-3*(4H)*-yl] acetohydrazide derivatives were designed and synthesized, and their structures were characterized by ^{1}H, ^{13}C NMR, IR and Mass Spectral analysis. Their antimicrobial activity against bacterial strains and *unicellular* and *multicellular* pathogenic fungal strains were evaluated, and the results of *in vitro* antimicrobial evaluations of all newly synthesized compounds revealed that compounds **4(a-g)** found to possess varied degree of antibacterial and antifungal activities Therefore, it can be inferred that presence of Schiff base nucleus in newly synthesized compounds can act as better system for antimicrobial activity. Lipinski rule were evident that all synthesized compounds have a good potential for development as an oral agent and can be potentially active drug candidate.

Keyword: Quinazolinone, Schiff base, NMR, IR, Mass spectra, antimicrobial evaluation and Lipinski rule

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Received 07 July 2018, Accepted 04 August 2018

Please cite this article as: Kant P *et al*., Synthesis, Characterization and Bio Evaluation of N-(substituted)-2-[4-oxo-2-Phenylquinazolin-3(4H)-yl] Acetohydrazide Derivatives. American Journal of PharmTech Research 2018.

INTRODUCTION

Drugs are the versatile molecules used as medicines or as components in medicines to diagnose, cure, mitigate, treat, or prevent diseases. Not only the designing but its synthesis, its isolation from natural sources, its method of administration and the development of tests and procedures to establish how it operates in the body and its safety assessment are also very important factors. In last decade, different types of treatments were developed for various diseases but they had several drawbacks *viz.* difficulty in administration, length of treatment, toxicity, cost and increasing parasitic resistance. In view of the above facts, the discovery of new drugs from natural sources as well as synthetic pathway is very essential. Quinazolinone motifs are building blocks of several known naturally as well as synthetic heterocyclic compounds, which show various diverse pharmacological as well as biological activities. The discovery of innovative quinazolinone based drugs on new molecular scaffolds that target the specific metabolic route of the harmful pathogen, should be highly prioritized, which in turn requires new medicinal chemistry approaches to search novel lead compounds that might populate a pipeline of new therapeutics. Quinazolinone based compounds were exhibited a broad spectrum of diverse biological and pharmacological activities *viz*. antioxidant [1] antifungal [2], antimicrobial [3-8], anticonvulsant [9], anti-inflammatory [10], anti-hyperlipidemic [11], antimalarial [12], anticancer [13], anti-hypertension [14] antiplasmodial [15] analgesic [16], antiviral [17], antitubercular [18], antidiabetic [19], anti-asthmatic [20] and anti-Leishmanial [21] activities. The aforementioned biological activity of quinazolinone motif indicates that it is a valuable pharmacophore for the development of a new drug. In the guest for new biological heterocycles, we sought an unexplored, synthetically available heterocyclic template (quinazolinone) capable of bearing some potential pharmacophore to elicit and improve inherent biological activity.

Hugo Schiff first time reported Schiff bases in1864 which is product of condensation of primary amines with carbonyl compounds [22-23]. Now a days literature survey revealed that Schiff base play a significant role in research perspective of coordination chemistry, bioinorganic chemistry, biomedical applications, supramolecular chemistry, catalysis and material science, separation and encapsulation processes.[24-25] Schiff bases are characterized by the -N=CH- (imine) group which involve in interpreting the mechanism of transamination and rasemination reaction in biological system.[26-30] It is used as corrosion inhibitor because its ability to form a monolayer spontaneously on the surface to be protected. Various types of Schiff bases are known today, Isatin as well as others Schiff base possess diverse biological activities *viz*. antiviral [31], anti-HIV, [32-

34] anticonvulsant, [35] antiprotozoal, [36] anthelmintic, [37-38] anti-inflammatory [39-40] and antibacterial [41-42] activities. Schiff bases are active against several microorganisms such as *Candida Albicans, Escherichia coli Staphylococcus aureus, Bacillus polymxa, Trychophyton gypseum, Mycobacteria, Erysiphe graminis* and *Plasmopora viticola*. Imines moiety also responsible for several biological mechanisms such as imine linkage Vitamin A and protein opsin in the retina of the eye, this is derived from aldehyde and responsible for chemistry of vision. Similarly imine linkage formed by pyridoxal phosphate, which is active form of Vitamin B_6 and amino acids grouping enzyme, participate in transamination reaction [43]. It is also involved in metabolism and biosynthesis of amino acids. Additionally, quinazolinone and Schiff base derivatives also have a therapeutic advantage as an anti-invasive agent with potential for activity in early and advanced solid tumors, metastatic bone disease and leukemia [44-45]. Based on the importance of quinazolinone as well as Schiff base in medicinal chemistry, our attention was attracted towards synthesis of novel hybrid quinazolinone derivatives in order to find more potent molecules for various types of diseases. If quinazolinone and Schiff base, both moiety are condensed as single molecule and developed new hybrid N-(substituted)-2-[4-Oxo-2-phenylquinazolin-3*(4H)*-yl] acetohydrazide derivatives it would be afford as good bioactive compound. It may enhance the drug activities of compounds to some extent or they might possess some of the above mentioned biological activities.

RESULTS AND DISCUSSION

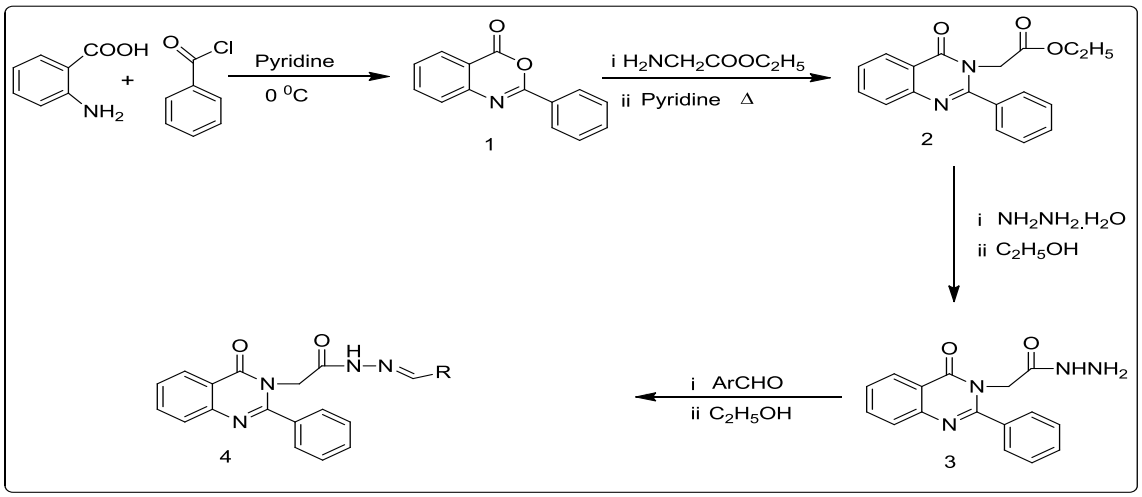
Chemistry:

Here, we have envisioned a short, modular synthetic route for formation of N-(substituted)-2-[4-oxo-2-phenylquinazolin-3*(4H)*-yl] acetohydrazide derivatives, starting from simple, commercially available and relatively cheap starting materials as outlined in **Scheme-1** to synthesize the number of molecules having structural diversity. The reaction of anthranilic acid and benzoyl chloride in pyridine was carried out at refluxing temperature to furnish **1** in quantitative yield (68%). The compound **2** was afford moderate to good yield (62%) by the reaction of compound **1** and glycine ethyl ester hydrochloride in pyridine at refluxing temperature. The compound **3** was furnished by the reaction of compound 2 and hydrazine hydrate in ethanol at reflux temperature in quantitative yield (68%). The reaction of compound 3 and aromatic aldehyde in ethanol was carried out at reflux temperature to produce **4(a-g)** in good quantitative yield. The aromatic aldehydes were selected on the basis of their easy availability, low cost and substituent in various biologically active agents. The substitution patterns of R groups from 4a-g are shown in **scheme 1.** All the

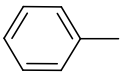
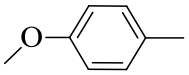
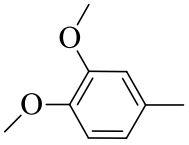
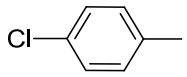
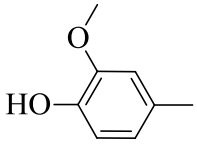
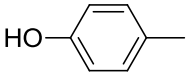
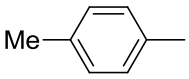
synthesized products were characterised by the IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy and mass spectrometry.

Synthesis of N-(substituted)-2-[4-oxo-2-phenylquinazolin-3*(4H)*-yl] acetohydrazide derivatives

Scheme-:



Substitution Pattern of R groups in compound 4:

Compound 4	R Groups
4a	
4b	
4c	
4d	
4e	
4f	
4g	

Biological evaluation:

All the synthesized compounds **4**(**a-g**) were screened for their *in vitro* antibacterial and antifungal activities against various microorganisms to determine minimum inhibitory concentrations (MICs) in µg/mL by micro dilution method. Ciprofloxacin and fluconazole were used as standard drugs for parent moieties. The evaluations of bacterial and fungal cultures were maintained on Mueller–

Hinton broth and Sabouraud–dextrose broth at 37^{o}C and 25^{o}C, respectively. DMSO was used as diluents to obtain the desired concentration of compounds and drugs. The bacterial and fungal suspensions were added to MHB and SDB, respectively supplemented with varying concentrations of the test compounds, incubated at 37^{o}C (24 h) and 25^{o}C (48 h), respectively. The growth of test cultures was tested using triphenyltetrazolium chloride (TTC, 0.5 % w/w) aqueous solution. MIC was defined to have lowest concentration of screened compounds that inhibited visible growth (red coloured pellet on the bottom of the wells after the addition of TTC). The observed data based on the *in vitro* antimicrobial evaluations of synthesized compounds **4(a-g)** along with standard drugs are shown as MICs values (lg mL^{-1}) in **Table 1** and **Table 2**.

Antibacterial activity

The *in vitro* antibacterial activities of all the synthesized compounds **4**(**a-g**) were screened against gram-positive bacteria (*Staphylococcus aureus*) and gram-negative bacteria (*Escherichia coli*, *Salmonella typhi*). The preliminary antibacterial evaluations of all synthesized compounds **4**(**a-g**) revealed that all the screened compounds were found to exhibit moderately good antibacterial activity as evidenced from their MIC parameter. Among the tested compounds, (**4d**) has shown equal antimicrobial activities compare to the reference drug ciprofloxacin, while others among the screened compounds found to be less potent to the standard drug. The observed MIC values of all screened compounds with respect to standard drugs were summarized in **Table-1**. The good antibacterial activity of compound **(4d)** was due to chlorine group present at para position. Chlorination increases the lipophilicity due to electron withdrawing capability of chlorine. The compound **4a** do not show activity even at maximum concentration (200 µg/mL). However remaining compounds **4b**, **4c**, **4e**, **4f** and **4g** were found to have low antibacterial activity.

Antifungal activity

In order to extend the antimicrobial evaluation, the antifungal screening was also done, which revealed that the synthesized compounds **4**(**a-g**) are show good inhibition against various tested fungal strains *viz*., *Aspergillus flavus, and Candida albicans.* Here, fluconazole was used as standard drug. The result indicates that among all the screened compounds, compound **4d** exhibited maximum inhibition activity (5.25µg/mL) against *C. albicans.* However other substituted compounds such as **4a**, **4d**, **4g** against *A. flavus*, and **4f** against *Candida* did not show any activity even at maximum concentration (200µg/mL). The introduction of halogen function at *para* position of phenyl groups in compound **4d** shows maximum antifungal potency against *C.*

albicans. Rest of the synthesized compounds presented low antifungal activity with respect to standard drug and observed MIC values are tabulated in **Table 2**.

The antimicrobial screening of all newly synthesized N-(substituted)-2-[4-oxo-2 phenylquinazolin-3(*4H*)-yl] acetohydrazide derivatives have shown good activities with respect to standard drug. The screening results of these compounds are summarized in following tables.

Table-1: In vitro antibacterial activity of N-(substituted)-2-[4-oxo-2-phenylquinazolin-3(*4H*)-yl] acetohydrazide derivatives

Minimum inhibitory concentration (MIC) in µg/mL				
Compounds	**Substituents R**	**Gram Positive bacteria**	**Gram Negative bacteria**	
		S. aureus	***E. coli***	***S. typhi***
4a	R = C_6H_5	>100	100	100
4b	R = 4-$OCH_3C_6H_4$	50	25	50
4c	R = 3-OCH_3 4-OCH_3 C_6H_3	100	50	100
4d	R =4-Cl C_6H4	10.5	100	10.5
4e	R = 3-OCH_3 4-OHC_6H_3	25	12.5	50
4f	R = 4-OHC_6H_5	50	>100	100
4g	R = 4-$CH_3C_6H_5$	100	50	>100
Ciprofloxacin		12.5	12.5	12.5

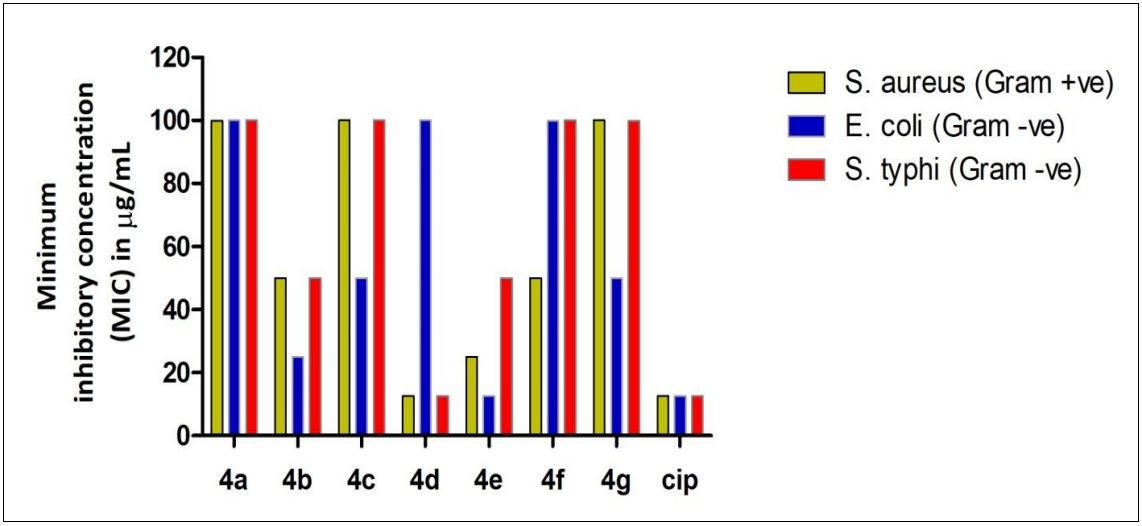


Figure 1 The pictorial representation of antibacterial activity of Quinazolinone and Schiff base based derivatives 4(a-g)

Table-2: In vitro antifungal activity of N-(substituted)-2-[4-oxo-2-phenylquinazolin-3(*4H*)-yl] acetohydrazide derivatives

Compounds	**Substituents R**	***A. flavus***	***C. albicans***
4a	R = C_6H_5	>100	100
4b	R = 4-$OCH_3C_6H_4$	50	25
4c	R = 3-OCH_3 4-OCH_3 C_6H_3	100	50

4d	R =4-Cl C_6H4	>100	5.25
4e	R = 3-OCH_3 4-OHC_6H_3	25	100
4f	R = 4-OHC_6H_5	50	>100
4g	R = 4-$CH_3C_6H_5$	>100	50
Fluconazole		12.5	6.25

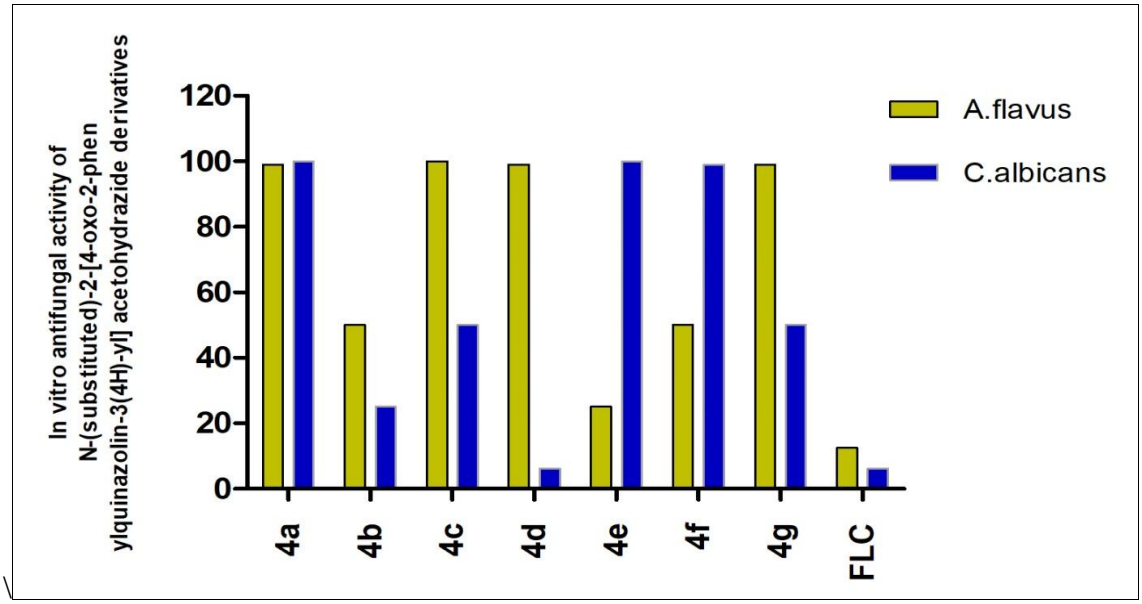


Figure 2 The pictorial representation of antifungal activity of Quinazolinone and schiff base based derivatives 4(a-g)

Among all *in vitro* antimicrobial screened compounds, the compound **(4d)** show excellent antibacterial and antifungal activities because it has chlorine group at para position of phenyl ring. The electron with drawing nature of chlorine group is responsible for increasing lipophilicity of molecule which corresponds to increasing the antibacterial and antifungal activities of newly synthesized compounds. The minimum inhibitory concentration of compound **(4d)** was found to be (12.5 µg/mL) against S. aureus and S. typhi during antibacterial evaluation. However, It has (6.25µg/mL) against *C. albicans* during antifungal screening.

Lipinski Rule:

All the newly synthesized compounds were also checked for compliance to the Lipinski rule of five and the software results of these compounds are depicted in Table-3. According to Dr Christopher A**.** Lipinski rule, synthesized molecules acts as drug molecule evidenced theoretical calculations. According to him, the orally active drug molecule should show no more than one violation of the following four criteria: log P (octane-water partition coefficient) ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10 and number of hydrogen bond donors ≤ 5. Molecular properties of newly synthesized compounds were calculated by

www.molinspiration.com software. The observed result of this software for synthesized molecules were evident that N-(substituted)-2-[4-oxo-2-phenylquinazolin-3(*4H*)-yl] acetohydrazide derivatives have a good potential for development as an oral agent and can be potentially active drug candidate.

Table-3 Molinspiration calculation of molecular properties for the Lipinski Rule

Compound	nViol	MW	miLogP	nON	nOHNH	natoms	nrotb
	≤ 1	≤ 500	≤ 5	≤ 10	≤ 5	–	–
4a	0	382.42	4.24	6	1	29	5
4b	0	412.45	4.30	7	1	31	6
4c	0	442.48	3.89	8	1	33	7
4d	0	416.87	4.92	6	1	30	5
4e	0	428.45	3.58	8	2	32	6
4f	0	398.42	3.10	7	2	30	5
4g	0	396.45	4.69	6	1	30	5

nViol= no. of violations, MW = molecular weight, miLogP = Molinspiration predicted Log P, nON = no. of hydrogen bond acceptors, nOHNH = no. of hydrogen bond donors, natoms = no. of heavy atoms, nrotb = no. of rotatable bond

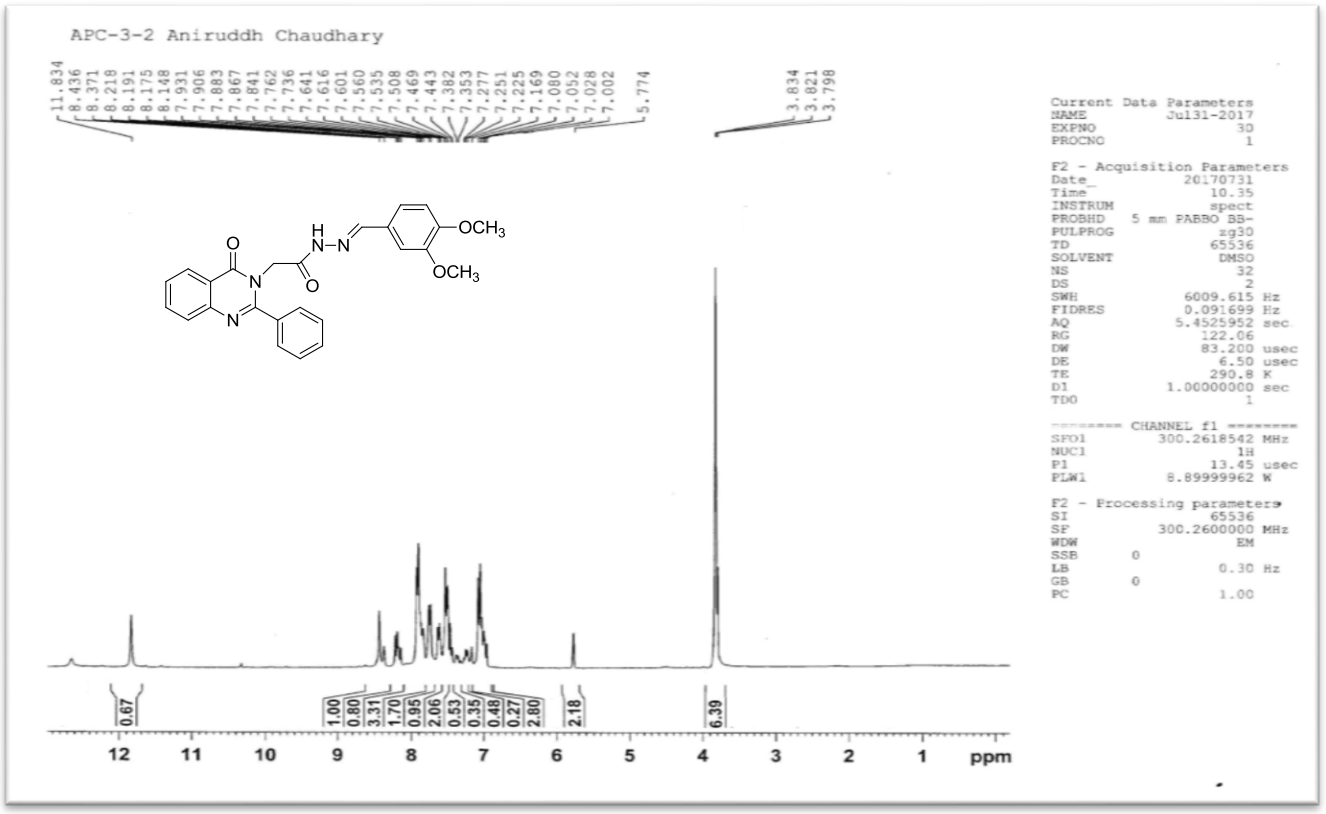


Figure 1 Experimental ^{1}H NMR spectrum of in DMSO-d6 solvent.

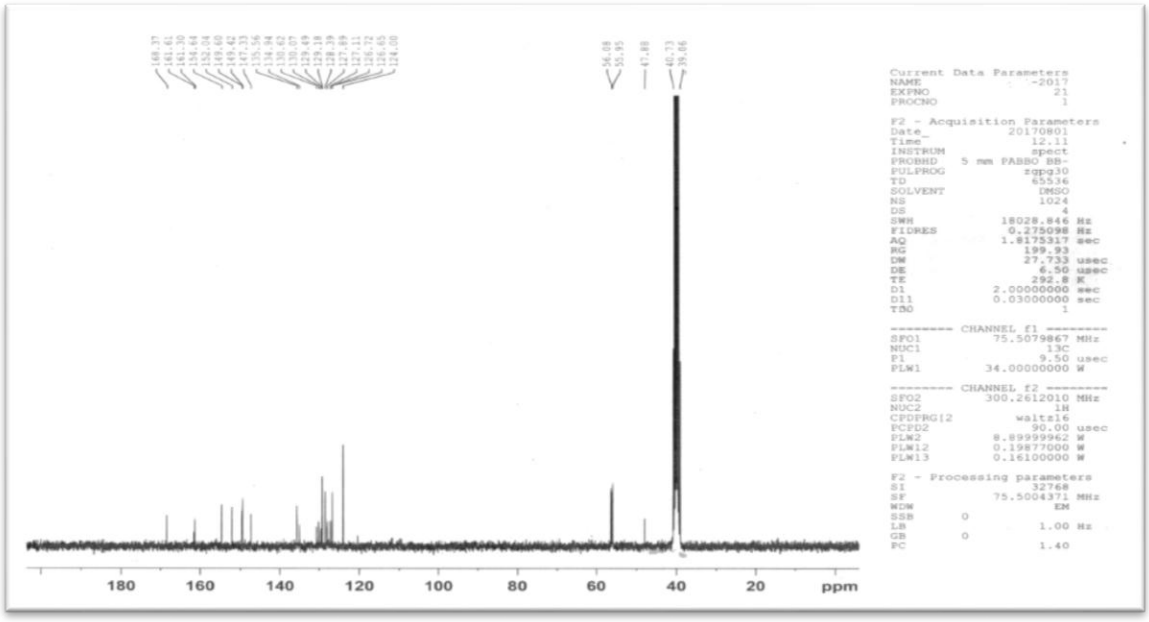


Figure 2 Experimental ^{13}C NMR spectrum of in DMSO-d6 solvent

CONCLUSION

Using a facile, efficient and convenient multi-step synthetic approach, a series of newly designed structurally diverse and hybrid heterocycles **4(a-g)** were developed which have been assembled using quinazolinone and Schiff base moieties to a single molecular framework, in high yield. Further, the results of *in vitro* antimicrobial evaluations of all newly synthesized compounds revealed that compounds **4(a-g)** found to possess varied degree of antibacterial and antifungal activities Therefore, it can be inferred that presence of Schiff base nucleus in newly synthesized compounds can act as better system for antimicrobial activity. The significance of such work lies in the possibility that the new compounds might become more valuable drug against bacteria and fungi for which a thorough investigation regarding the structure activity relationship, toxicity and its biological effects is essential. This investigation can provide insight for the rational designing of the more potent antimicrobial agents for therapeutic use.

Experimental Protocol:

Commercially available reagent grade chemicals were used as received. All reactions were followed by TLC on E. Merck Kieselgel 60 F_{254}, with detection by UV light. Column chromatography was performed on silica gel (100-200 mesh E. Merck). IR spectra were recorded as thin films or in KBr solution with a Perkin Elmer Spectrum RX-1 (4000-450 cm^{-1}) spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker DRX-200 in $CDCl_3$ and DMSO-d_6.Chemical shift values are reported in ppm relative to TMS (tetramethylsilane) as

internal reference, unless otherwise stated, s (singlet), d (doublet), m (multiplet), *J* in hertz. ESI mass spectra were performed using Quattro II (Micromass).

General Procedure:

Synthesis of ethyl 2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetate (2)

2-phenyl 1,3,4- benzaoxinone (0.1 mol) and glycine ethyl ester hydrochloride (0.1 mol) are taken in round bottom flask then pyridine (dried) is added slowly while shaking. The mixture is heated under reflux condition for 8 hrs. Excess of pyridine was distilled off under reduced pressure and then the solution is poured into a beaker, concentrated with crushed ice to get the product. It was filtered under suction pump, washed with portions of ice cold water and dried at 100^{o}C. The product is purifies by recrystallization with EtOH to get a colourless crystalline solid.

Synthesis of 2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) acetohydrazide (3)

A mixture of compound **2** (0.1 mole) and hydrazine hydrate (0.1mole) in absolute ethanol, (25ml) was heated under reflux for 6-8 hrs. After completion of reaction (Monitored by TLC), the reaction mixture was cooled at room temperature, precipitated solid was recrystallized in absolute ethanol. The crystalline compound 2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) acetohydrazide **(3)** was obtained in good yield (62%)

N-benzylidene-2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) acetohydrazide (4a)

A mixture of compound **(3)** (0.1M) and benzaldehyde (0.1M) in absolute alcohol (50 ml) containing a few drops of concentrated hydrochloric acid, was refluxed for 4 hours on a steam bath. The reaction mixture was cooled to room temperature. The Schiff bases **(4a)** separated was filtered, washed, dried and recrystallised from alcohol.

Molecular Formula $C_{23}H_{18}N_4O_2$ IR (KBr Solid), 3370, 3060, 1699, 1635, 1575, 1340, 1036; ^{1}H NMR (300MHz, DMSO-d_6): δ 4.78 (2H, s), 9.93 (1H, s, NH) 8.04 (1H, d, *J* = 8.0 Hz), 7.93-7.84 (6H,m, 5xAr-H+1H Schiff base), 7.48-7.59 (3H, m), 7.51-7.40 (2H, m), 7.38 (1H, d, *J* = 7.2 Hz) 7.10-7.02 (2H, t, *J* = 7.2 Hz) ^{13}C-NMR (75MHz, DMSO-d6) δ-(ppm) 46.83, 113.17, 117.54, 120.65, 121.42, 121.51, 123.89, 123.39, 124.14, 124.41, 125.26, 126.06, 126.06, 127.62, 127.94, 128.56, 128.33, 130.42, 142.34, 143.04, 156.64, 159.31, 165.27: MP 108-110 ^{o}C: ESMS: m/z 383.41 $[M + 1]^+$ Calculated m/z 382.

N-(4-methoxybenxylidene)-2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) acetohydrazide (4b)

A mixture of compound **(3)** (0.1M) and substituted 4-methoxybenzaldehyde (0.1M) in absolute alcohol (50 ml) containing a few drops of concentrated hydrochloric acid, was refluxed for 4 hours

on a steam bath. The reaction mixture was cooled to room temperature. The Schiff bases **(4b)** separated was filtered, washed, dried and recrystallised from alcohol.

Molecular Formula $C_{24}H_{20}N_4O_3$ IR (KBr Solid), 3389, 3011, 1759, 1610, 1400, 1314, 1029; ^{1}H NMR (300MHz, DMSO-d_6): δ 3.79 (3H, s), 5.24 (2H, s), 10.83 (1H, s) 8.67 (1H, s Schiff base H), 8.03-7.97 (1H, m), 7.89-7.83 (3H,m), 7.59-7.67 (2H, m), 7.51-7.39 (2H, m), 7.43-7.40 (2H, m), 7.29 (1H, m) 7.10-6.95 (2H, m) ^{13}C-NMR (75MHz, DMSO-d6) δ-(ppm) 45.28, 55.18, 123.13, 125.63, 125.63, 126.79, 127.14, 127.49, 128.19, 129.12, 129.39, 130.37, 130.37, 131.42, 133.93, 135.56, 136.33, 136.42, 136.60, 149.04, 152.64, 154.30, 159.61, 164.27 MP 115-120^{o}C ESMS: m/z 413.4 $[M + 1]^+$ Calculated m/z 412.

N-(3,4-dimethoxybenxylidene)-2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) acetohydrazide (4c)

A mixture of compound **(3)** (0.1M) and substituted 3,4-dimethoxybenzaldehyde (0.1M) in absolute alcohol (50 ml) containing a few drops of concentrated hydrochloric acid, was refluxed for 4 hours on a steam bath. The reaction mixture was cooled to room temperature. The Schiff bases **(4c)** separated was filtered, washed, dried and recrystallised from alcohol.

Molecular Formula $C_{25}H_{22}N_4O_4$ IR (KBr Solid), 3268, 3010, 1859, 1417, 1400, 1226, 1014; ^{1}H NMR (300MHz, DMSO-d_6): δ 3.83 (6H, s), 5.77 (2H, s), 11.83 (1H, s) 8.43 (1H, s Schiff base H), 8021-8.14 (1H, m), 7.93-7.84 (3H,m), 7.56-7.64 (2H, m), 7.53-7.44 (2H, m), 7.46-7.44(1H, m), 7.38 (1H, m) 7.08-7.00 (2H, m) ^{13}C-NMR (75MHz, DMSO-d6) δ-(ppm) 47.88, 56.08, 55.95, 124.00, 124.00, 126.65, 126.72, 127.11, 127.89, 128.39, 129.18, 129.49, 129.49, 130.07, 130.62, 134.94, 135.56, 147.33, 149.42, 149.60, 152.04, 154.64, 161.30, 161.61, 168.37: MP 110-113^{o}C: ESMS: m/z 443.47 $[M + 1]^+$ 442

N-(4-chlorobenxylidene)-2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) acetohydrazide (4d)

A mixture of compound **(3)** (0.1M) and 4-chlorobenzaldehyde (0.1M) in absolute alcohol (50 ml) containing a few drops of concentrated hydrochloric acid, was refluxed for 4 hours on a steam bath. The reaction mixture was cooled to room temperature. The Schiff bases **(4d)** separated was filtered, washed, dried and recrystallised from alcohol.

Molecular Formula $C_{23}H_{17}N_4O_2Cl$ IR (KBr Solid), 3208, 3132, 1692, 1532, 1442, 1248, 1035; ^{1}H NMR (300MHz, DMSO-d_6): δ 3.83 (6H, s), 5.77 (2H, s), 11.83 (1H, s) 8.43 (1H, s Schiff base H), 8.21-8.14 (1H, m), 7.93-7.84 (3H,m), 7.56-7.64 (2H, m), 7.53-7.44 (2H, m), 7.46-7.44(1H, m), 7.38 (1H, m) 7.08-7.00 (2H, m) ^{13}C-NMR (75MHz, DMSO-d6) δ-(ppm) 47.88, 56.08, 55.95, 124.00, 124.00, 126.65, 126.72, 127.11, 127.89, 128.39, 129.18, 129.49, 129.49, 130.07, 130.62,

134.94, 135.56, 147.33, 149.42, 149.60, 152.04, 154.64, 161.30, 161.61, 168.37: MP 110-113^{o}C: ESMS: m/z 417.86

$[M + 1]^{+}$ 416.

N-(4-hydroxy-3-methoxybenzylidene)-2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) Acetohydrazide (4e)

Taken equimolar ratio of compound **(3)** (0.5M) and 4-hdroxy 3-methoxy benzaldehyde (0.5M) in round bottom flask while some amount of dry methanol was added as a solvent. Refluxed the above solution was for about 2 hours. Upon cooling precipitate of Schiff a base (4e) was appeared. Recrystallize the product to obtained good quality product.

Molecular Formula $C_{24}H_{20}N_4O_4$ IR (KBr Solid), 3510, 3036, 1712, 1522, 1401, 1225, 1010; ^{1}H NMR (300MHz, DMSO-d_6): δ 3.91 (3H, s), 5.77 (2H, s), 12.83 (1H, s) 4.47 (1H, s, OH), 8.13 (1H, s Schiff base H), 8.09-8.01 (1H, m), 7.83-7.74 (1H,m), 7.53-7.44 (2H, m), 7.43(5H, m), 7.39 (1H, m) 6.95 (1H, d, *J* = 7.5 Hz) 7.00 (1H, d, *J* = 7.5 Hz) ^{13}C-NMR (75MHz, DMSO-d6) *δ*-(ppm) 43.78, 54.65, 123.01, 125.35, 126.52, 127.31, 127.69, 128.14, 128.23, 129.33, 129.51, 130.17, 131.62, 131.62, 134.94, 135.56, 147.33, 149.42, 149.30, 151.03, 154.54, 157.36, 158.31, 162.47: MP 130-135^{o}C: ESMS: m/z 429.44 $[M + 1]^{+}$ 428.

N-(4-hydroxybenzylidene)-2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) Acetohydrazide (4f)

Taken equimolar ratio of compound **(3)** (0.5M) and 4-hdroxy benzaldehyde (0.5M) in round bottom flask while some amount of dry methanol was added as a solvent. Refluxed the above solution was for about 2 hours. Upon cooling precipitate of Schiff bases **(4f)** were appeared. Recrystallize the product to obtained good quality product.

Molecular Formula $C_{23}H_{18}N_4O_3$ IR (KBr Solid), 3440, 3020, 1705, 1460, 1416, 1240, 1080; ^{1}H NMR (300MHz, DMSO-d_6): δ 5.03 (2H, s), 5.19 (1H, s OH), 7.17 (2H, d, *J* = 8.3 Hz), 7.31 (2H, d, *J* = 8.3 Hz), 7.44-7.50 (5H, m), 7.56 (1H, d, *J* = 8.0 Hz), 7.66 (1H, t *J* = 7.4 Hz)), 8.12 (1H, d, *J* = 7.9 Hz), 8.30 (1H, t, *J* = 7.4 Hz), 8.07(1H, m, Schiff base H) 10.46 (1H, s, NH). ^{13}C-NMR (75MHz, DMSO-d6) *δ* 52.81, 115.61, 122.18, 123.60, 124.37, 126.43, 127.21, 127.76, 127.83, 128.34, 128.56, 128.64, 128.94, 129.36, 129.60, 129.80, 130.01, 131.63, 135.57, 135.85, 146.29, 157.01, 161.83: MP 128-132^{o}C: ESMS: m/z 399.41 $[M + 1]^{+}$ 398.

N-(4-methylbenzylidene)-2-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) Acetohydrazide (4g)

Taken equimolar ratio of compound **(3)** (0.5M) and 4-methyl benzaldehyde (0.5M) in round bottom flask while some amount of dry methanol was added as a solvent. Refluxed the above

solution was for about 2 hours. Upon cooling precipitate of Schiff bases **(4g)** were appeared. Recrystallize the product to obtained good quality product.

Molecular Formula $C_{24}H_{20}N_4O_4$ IR (KBr Solid), 3240, 3120, 1710, 1560, 1450, 1205, 1045; ^{1}H NMR (300MHz, DMSO-d_6): δ 2.21 (3H, s), 4.19 (2H, CH_2), 7.06 (2H, d, *J* = 8.3 Hz), 7.21 (2H, d, *J* = 8.3 Hz), 7.41-7.48 (6H, m, 5x Ar-H+ 1H Schiff base), 7.61 (1H, d, *J* = 8.0 Hz), 7.51 (1H, t *J* = 7.4 Hz)), 8.13 (1H, d, *J* = 7.9 Hz), 7.78 (1H, t, *J* = 7.4 Hz), 12.23 (1H, s, NH). ^{13}C-NMR (75MHz, DMSO-d6) *δ* 26.97, 49.21, 118.21, 119.13, 123.66, 124.35, 126.48, 127.01, 127.16, 127.43, 128.54, 128.73, 128.89, 128.97, 129.56, 129.68, 129.84, 130.11, 131.83, 135.17, 143.35, 144.29, 153.14, 159.03: MP 120-125^{o}C: ESMS: m/z 397.44 $[M + 1]^+$ 397.

ACKNOWLEDGEMENT

The authors are thankful to the Head, Department of Chemistry, University of Lucknow, Lucknow, for providing necessary Laboratory facilities, spectral analysis and to the Director, National botanical research institute (NBRI), Lucknow, India for providing biological activity data. Authors are also thankful to UGC JRF for providing financial support.

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