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STUDIES ON THE DESIGN, SYNTHESIS AND ANTITUBERCULAR ACTIVITY OF SOME NEW QUINAZOLINONE DERIVATIVES

Md Akram*[1], Abdul Sayeed[1], Syed Shah Abdus Salaam[2]

[1]MESCO College of Pharmacy Hyderabad - 500006 (T.S)

[2]NIZAM Institute of Pharmacy, Hyderabad (T.S).

Abstract:

Quinazolinone derivatives are the versatile nitrogen containing heterocyclic compounds displaying a wide variety of biological and pharmacological activities like antibacterial, anthelmintic,neuroleptic,antitubercular,platelet,anti-aggregating,antifungal,anticancer,anti-inflammatory,antiviral,CNSdepressant activity,antiparkinson,bronchodilator etc.

Recently several scientists have elucidated that Quinazolinone system possesses variable sites like position 2 and 3 which can be suitably modified to yield new potent chemotherapeutic and pharmacotherapeutic agents.

Further, Schiff bases are use as substrate in the preparation of number of industrial and biologically Active compound via ring closure, cyclo addition and replacement reactions.Morever,Schiff bases derived from various heterocycles have been reported to posses cytotoxic, anticonvulsant, antiproliferative,antimicrobial, anticancer and antifungal activities.

In view of the above mentioned facts and in continuation of our interest in the synthesis of heterocycles to identify new candidate, that may be value in designing new, potent, selective and less toxic chemotherapeutic agents, the synthesis of some novel structure hybrids incorporating suitably substituted quinazolinone moiety with long aliphatic dicarboxylic acids hydrazides and finally converting them to Schiff bases by reacting with substituted benzaledhydes to yield title compounds.

These are then evaluated for antitubercular activity by Micro plate alamar blue assay method(MABA) and MIC were determined for each drug.During the present investigation 1,3,4-benzoxazinone was prepared from anthranilic acid and acetic anhydride by known method.

Various dihydrazides were prepared from aliphatic α, ω-aliphatic dicarboxylic acids by following literature method. N-3 substituted quinazolinone derivatives were prepared from the equimolar reaction of 1,3,4-benzoxazinone with various dihydrazides to yield the compounds 1AB1 to 1AB5. These are then reacted with substituted benzaledhydes to form Schiff bases 2B1 to 2B5. The homogeneity of all the derivatives was established by TLC technique. The structures of the compounds were successfully established by means of IR, Proton NMR and Mass spectral studies.All the compounds were evaluated for antitubercular activity against Mycobacterium tuberculosis $H_{37}Rv$ by micro plate blue assay method (MABA).One of the compound 2B5 has shown excellent antitubercular property by having lowest MIC of 3.125µg/ml were as the other compounds also exhibited significant growth inhibiting properties against the mycobacterium tested.

Key words: *Quinazolinone, Mycobacterium tuberculosis, antitubercular activity.*

Coressponding authour:

Md akram,

Assistant Professor,

Mesco College of Pharmacy, Hyderabad.

mdakramid43@gmail.com

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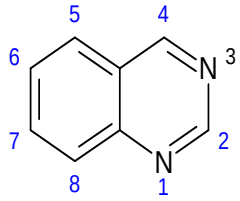
INTRODUCTION:

The quinazolines are a group within the quinoline alkaloids. The scaffold that defines a quinazoline consists of fused benzene and pyrimidine bicyclic structure. These compounds have been described as privileged structures [1,2] and provide various points of attachment for a diverse array of structural elements that can be used to target receptors as agonists or antagonists [3,4].

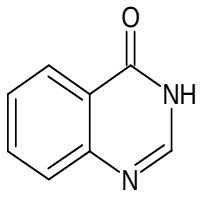
The pharmacological activities that have been discovered amongst the quinazoline include the categories of [5]anticonvulsant,hypnotic, antiparkinsons, sedative, analgesic and muscle relaxant, enzyme inhibiting, antiviral antitumour,anti-inflammatory, cardiovascular, antibacterial, antifungal, antimicrobial, antihelminthics (infestation of parasitic worms such as tapeworm or bookworm), antimalarial, anti mycobacterial, antihistaminic (anti-ulcer) and hypoglycaemic activities.

Quinazolinones (II-IV) are the oxidised form of quinazolines (I) and as also on the nitrogen (NH) and the commonly accepted numbering for part of the quinoline alkaloids. Both naturally occuring and synthetic quinazoline and quinazolinones have attracted widespread attention due to the diverse range or phammacological activities included in the above mentioned treatment categories.

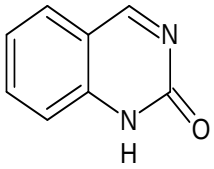
These structures are defined by the location of the oxygen and the hydrogen quinazoline and quinazolinones is described using the quinazoline structure. The major sub classes of qunazolinones fall into the categories of 4(3H)- quinazolinone (3H-1,3-quinazolin-4- one)II, 2(lH)-quinazolinone (1H- 1,3-quinazolin-2-one)III, 2.4(1H,3H)-quinazoline dione (1H,3H-l,.3-quinazoline-2.4-dione)



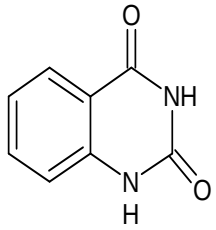
quinazoline



4(3H)-quinazolinone



2(1H)-quinazolinone



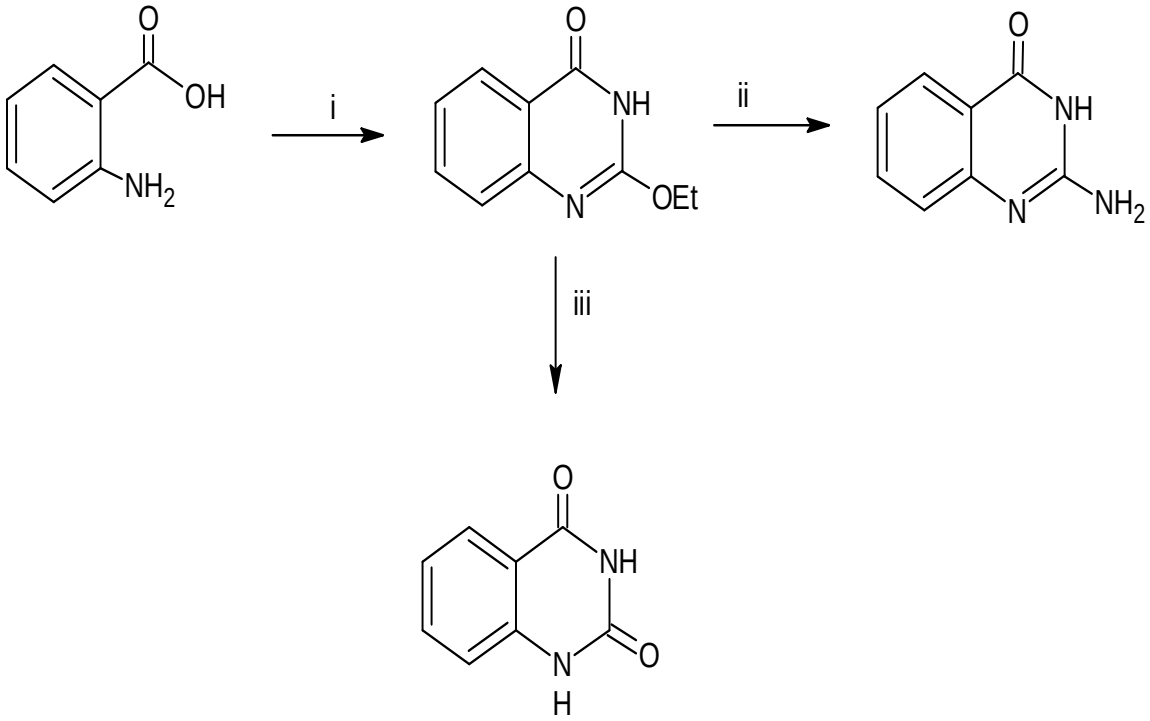
2,4(1H,3H)-quinazolinedione

Of the three quinazolinone structures the 4(3H)-quinazolinones (II) are most prevalent, either as intermediates or as natural products in many proposed biosynthetic pathways [6]**.** This is partly due to the structure being derived from the anthranilates (anthranilic acid or various esters, anthranilamide and anthranilonitrile) while the 2(1H)-quinazolinone is predominantly a product of anthranilonitrile or benzamides with nitriles [7]**.**

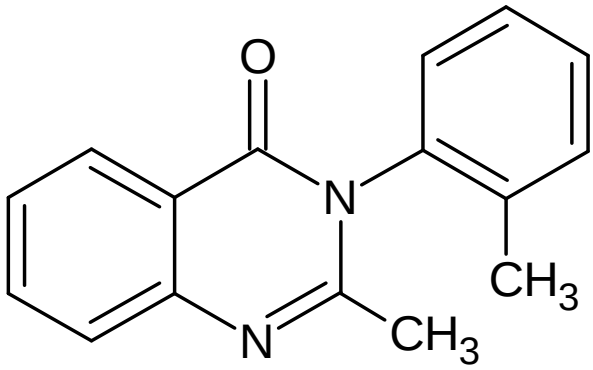
Although quinazolinone chemistry is considered an established area, newer and more complex variants of the quinazolinone structure are still being discovered **[8].**

The first reported synthesis of a quinazolinone occurred in 1869, which was prepared from anthranilic acid and cyanide in ethanol creating 2-ethoxy-4(3H)- quinazolinone [9]**.**These findings were confirmed by the preparation of the derivatives 2-amino-4(3H)-quinazolinone and 2,4(1H.3)-quinazolinedione by reactions with ammonia and water respectively.

Another quinazolinone compound, methaqualone [10] has been of significance due to its potent sedative and hypnotic effects [11,12] ease of preparation [13,14] and history of abuse “luding out” [15]. The procedure described by Klosa is one of the most efficient preparations of methaqualone. A comprised of a one pot approach using anthranilic acid, acetic acid, ortho toluidine and phosphorus pentachloride, many analogues of methaqualone have been prepared and tested for similar sedative effects [16-18]**.**



Griess' syntheis of 4(3H)-quinazolinones and 2,4(1H,3H)-quinazolinedione from Anthranilic acid. Reagents and conditions : i)HCN, EtOH: ii) NH_4OH. Reflux: iii)H_2O



Structure of the commercial drug methaqualone

Investigations of quinazolinones show there is a strong lactam-lactim tautomeric interaction [19-22] and examples of other tautomeric effects which were observed as a result of the studies undertaken are mentioned at various points in the thesis. The significance of this tautomeric interaction can also be seen when a 4(3H)- quinazolinone containing a methyl in the 3 -position is subjected to chlorination with $POCl_3$. The methyl group is lost and chlorination proceeds [23] and when the methyl group is present in the 2nd position. The tautomeric effect is extended generating an exomelhylene carbon. This compound can be condensed with aldehydes producing 2- styryl-4(3H)-quinazolinones. This particular reaction was performed to create two halogenated 2-styryl-4(3H)-quinazolinones for the demethylation. The significance of these extended tautomeric effects is that they enhance reactivity of the substituted 4(3H)-quinazolinones [24,25].

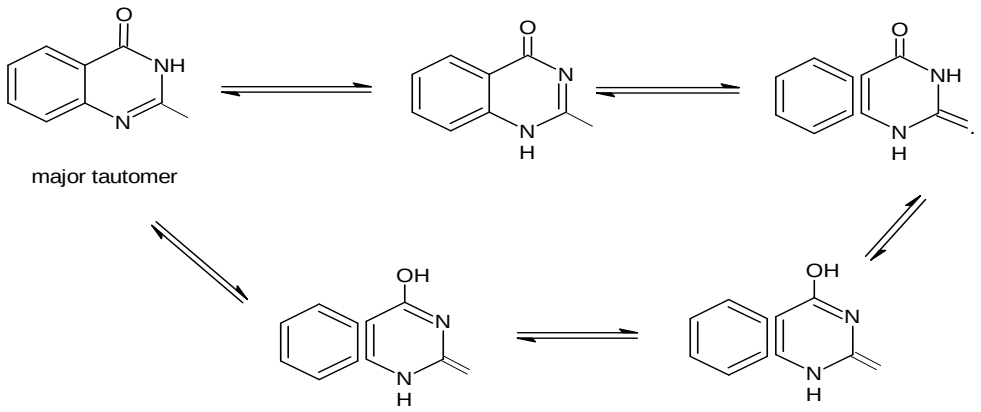


Diagram of the tautomeric states of 2-methy-4(3H)-quinazolinone

Many 4(3H)-quinazolinones possess biological and pharmaceutical activities. For example, some of them exhibited good antiinflammatory and noncompetitive AMPA receptor antagonistical activities, whereas others exhibited good anticancer and antiviral activities. Among them, 2-amino-4(3H)-quinazolinones were found to show significant fungicidal activities or used as potential potassium channel openers.

Recently, combinatorial synthesis of libraries containing small organic molecules has become a rapid evolving area of research. It includes solid-phase and solution-phase synthetic techniques. Although a solid phase synthetic method for 4(3H)-quinazolinones has been reported, there is no solution phase synthetic route to 2-amino-4(3H)-quinazolinones.

OBJECTIVES:

Tuberculosis is currently the leading killer of the youth, women and AIDS patients throughout the world. Although many active antitubercular agents have since been developed, a disturbing co-occurrence with the use of present drugs as single agent has developed drug resistance.The development of this resistance can be forestalled through the use of combination regimens ,it is clear that drug resistance will continue to be a problem. Therefore, there is a clear need for the discovery of new derivatives with antituberculor activity for the management of tuberculosis [1].

Pharmacologically Quinazolinones are among the most important classes of heterocyclic compounds displaying a wide variety of biological and pharmacological activities like antibacterial, anthelmintic, neuroleptic, antitubercular, platelet anti- aggregating, antifungal, anticancer, anti-inflammatory, antiviral, CNS depressant activity, antiparkinson, bronchodilator etc.

Recently several scientists have elucidated that Quinazolinone system possesses the variable sites like position 2 and 3 which can be suitably modified to yield potent chemotherapeutic and pharmacotherapeutic agents.

Further, Schiff bases are use as substrate in the preparation of number of industrial and biologically active compound via ring closure, cyclo addition and replacement reactions. Morever,Schiff bases derived from various heterocycles have been reported to Posses cytotoxic, anticonvulsant, antiproliferative, antimicrobial, anticancer and antifungal activities.

In view of the above mentioned facts and in continuation of our interest in the synthesis of heterocycles to identify new candidate, that may be value in designing potent, selective and less toxic chemotherapeutic agents. We propose herein, for the synthesis of some novel structure hybrids incorporating suitably substituted Quinazolinone moiety with long aliphatic chains of varied lengths.

This combination suggested is an attempt to investigate the influence of such hybridization and structure variation on the anticipated biological activities hoping the possibility that the target derivatives might be more efficacious as antimicrobial and antitubercular agents.

Substituted 1,3,4 benzoxazinones will be prepared following literature method and further followed by condensing with active hydrogen atoms of amino group of hydrazides prepared from various alkyl dicarboxylic acid by conventional synthetic methods. And are then used to prepare Schiff bases by known methods.

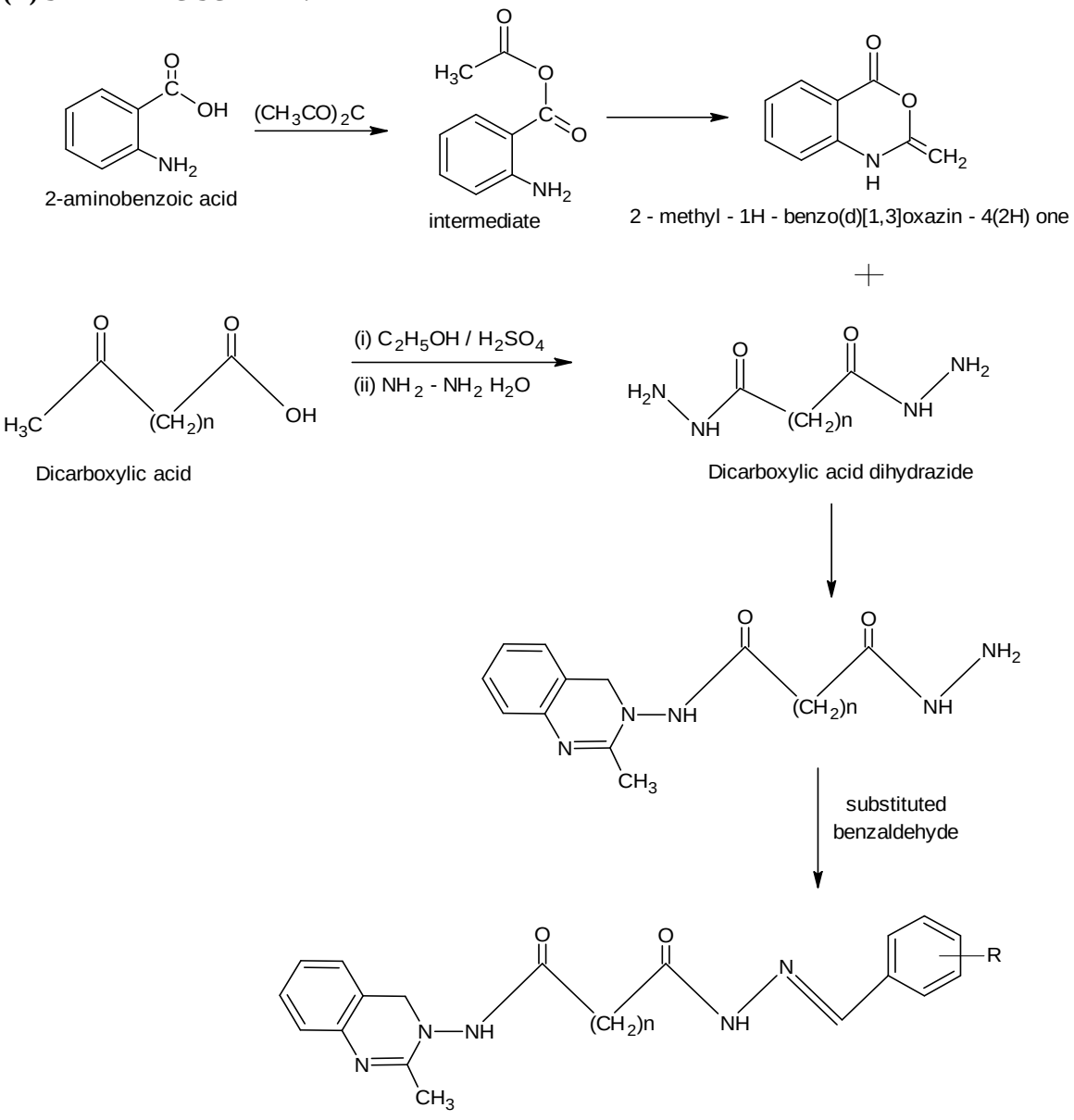
All the reactions are monitored by TLC technique and chemical tests as applicable.
The structures of these compounds will be established by means of IR, Proton NMR and Elemental analysis.
The title compounds will be evaluated for antifungal activity. Few of the compounds will also be evaluated for their antitubercular activity profile.

MATERIAL AND METHODS:

The entire chemicals used were procured from Qualingens, Himedia and Loba- chemicals. Purity of starting materials used for reaction was confirmed by checking their melting point or boiling point and by thin layer chromatography.

EXPERIMENTAL:

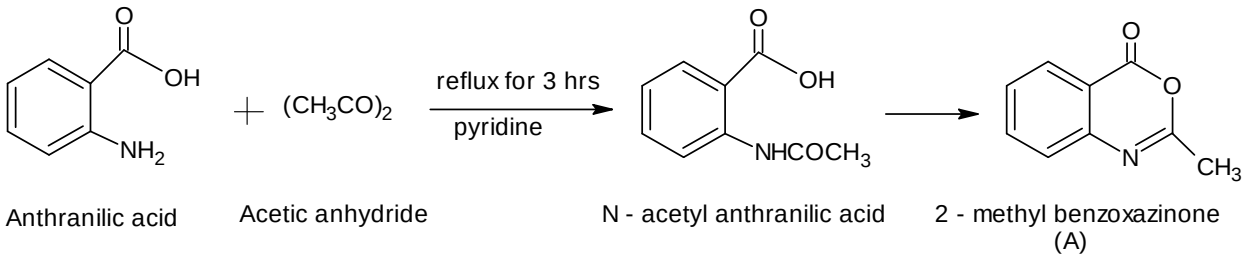
(A) SYNTHETIC SCHEME:



(E) 3 - (2 -substituted benzylidenhydrazinyl) -N - (2 -methyl - 4 - oxquinazolin - 3(4H) - 3 -oxoalknamide)

(B) SYNTHETIC STUDIES:

STEP 1: Preparation Of 2-Methyl 1,3,4-Benzoxazinone(A) :-



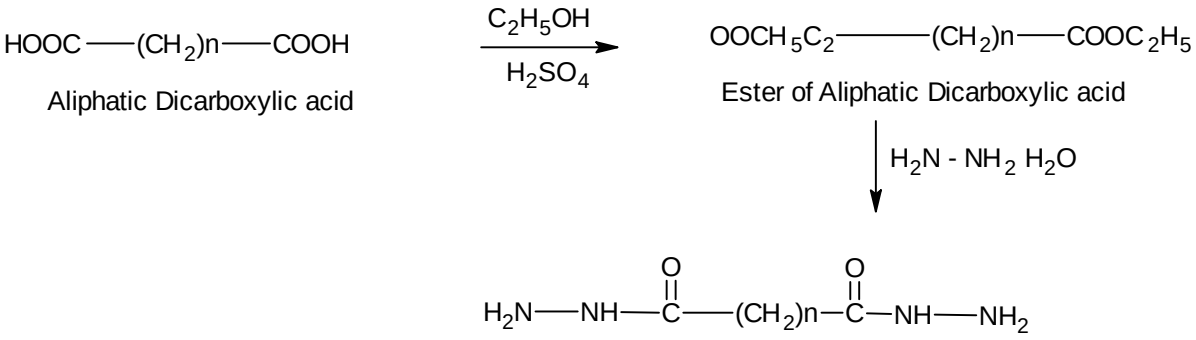
Anthranilic acid — Acetic anhydride — N - acetyl anthranilic acid — 2 - methyl benzoxazinone (A)

A Mixture of anthranilic acid (0.12 mol) in acetic anhydride (0.2 mol) with few drops of pyridine was refluxed for 3hr. The reaction mixture was filtered, washed and recrystallised from absolute ethanol, to get the crystals of 2-methyl 1,3,4- benzoxazinone**(A).** The physical data of compound **(A)** are summarized in **Table-1.**

Table-1: Physical data of 2-methyl 1,3,4- benzoxazinone (A)

Molecular formula	$C_9H_7O_2N$
Molecular weight	161.18
Physical state	Solid crystals
Melting point	146^0C
R_f Value	0.59
% yield	78.43 %

STEP 2: Preparation of Acid Hydrazide



Aliphatic Dicarboxylic acid — Ester of Aliphatic Dicarboxylic acid — Acid hydrazide (B)

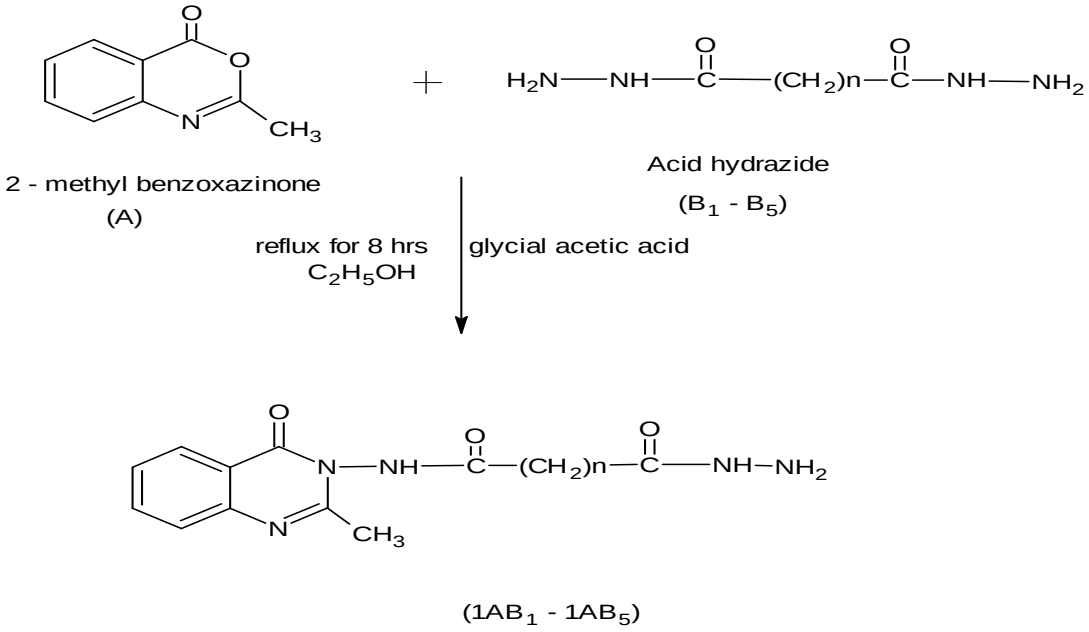
The acid (0.1 mole) and absolute ethanol (50 ml) were taken with a few drops conc. H_2SO_4 and was refluxed for 6 hours. The reaction mixture was concentrated by distilling off the excess of ethanol under reduced pressure. The ester obtained was used for the preparation of hydrazide directly.

The ester (0.1 mole) was dissolved in appropriate quantity of ethanol and to this hydrazine hydrate (0.2 mole) was added. The reaction mixture was refluxed for a period of 12-18 hours. Excess of ethanol was distilled off under reduced pressure. It was then poured into ice cold water and the solid obtained was filtered and dried. It was recrystallized from aqueous ethanol. The physical data of compounds aliphatic dicarboxylic acid hydrazides **(B1-B5)** are summarized in **Table-2.**

Table-2: Physical data of aliphatic dicarboxylic acid hydrazides (B1-B5)

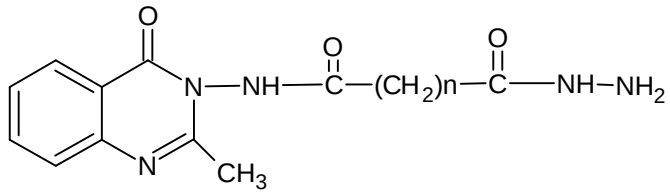
COMPOUND	n	MOLECULAR FORMULA	MOLECULAR WEIGHT	MELTING POINT	R_f VALUE	% YIELD
B1	0	$C_2H_6N_4O_2$	90.43	154^0C	0.60	62.09%
B2	1	$C_3H_8N_4O_2$	104.43	0 156 C	0.72	62.80%
B3	2	$C_4H_{10}N_4O_2$	118.43	0 168 C	0.67	66.75%
B4	3	$C_5H_{12}N_4O_2$	132.43	0 143 C	0.59	60.00%
B5	4	$C_6H_{14}N_4O_2$	146.43	0 161 C	0.76	64.59%

Step 3: Preparation of the 3-hydrazinyl-*n*-(2-methyl-4-oxoquinazolin-3(4*h*)-yl)-3-oxo substituted amide (1ab1-1ab5) :



0.1 mol of 2-methyl benzoxazinone**(A)** and 0.1 mol of acid hydrazide **(B_1-B_5)** in the presence of glacial acetic acid taken in 50 ml of ethyl alcohol and refluxed in an anhydrous condition for 8hr. The reaction mixture was cooled to room temperature and filtered the product and separated. It was dried and recrystallised from absolute ethanol. The physical data of compounds 3-hydrazinyl-*N*-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxo substituted amide **($1AB_1$-$1AB_5$)** are summarized in **Table-3.**

Table-3: Physical data of the compounds 3-hydrazinyl-*N*-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-3-oxo substituted amides [1AB1-1AB5]



COMPOUND	n	MOLECULAR FORMULA	MOLECULAR WEIGHT	MELTING POINT	Rf VALUE	% YIELD
1AB1	0	$C_{11}H_{11}N_5O_3$	261.26	121^0C	0.75	60.23%
1AB2	1	$C_{12}H_{13}N_5O_3$	275.26	106^0C	0.62	59.75%
1AB3	2	$C_{13}H_{15}N_5O_3$	289.26	117^0C	0.79	70.64%
1AB4	3	$C_{14}H_{17}N_5O_3$	303.26	111^0C	0.67	61.89%
1AB5	4	$C_{15}H_{19}N_5O_3$	317.26	162^0C	0.59	63.71%

STEP 4: Preparation of (e)-3-(2-substituted benzylidenehydrazinyl)-n-(2-methyl-4- oxoquinazolin-3(4h)-yl-3-oxoalkanamides (2b1-2b5) :

The corresponding aldehyde (0.005 mole) was added to a solution of compound **(1AB1-1AB5)** (0.005 mole) in glacial acetic acid (20 ml) and the mixture was refluxed for 5 hours. After cooling, the mixture was poured into a beaker containing 100 ml of ice-cold water.

The precipitate formed was filtered. After drying in vacuum, the product was recrystallized from aqueous ethanol to give the desired compounds (**2B1-2B5)**. The physical data of compounds **(2B1-2B5)** are summarized in **Table-4.**

Table-4: Physical data of the compounds (E)-3-(2-substituted benzylidenehydrazinyl)-N-(2-methyl-4-oxoquinazolin-3(4H)-yl-3-oxoalkanamides (2B1-2B5)

COMPOUND	n	MOLECULAR FORMULA	MOLECULAR WEIGHT	MELTING POINT	Rf VALUE	% YIELD
2B1	0	$C_{18}H_{14}N_5O_3Cl$	384	181^0C	0.72	62.23%
2B2	1	$C_{19}H_{16}N_6O_5$	408	208^0C	0.62	62.75%
2B3	2	$C_{20}H_{18}N_5O_3Cl$	412	223^0C	0.75	64.64%
2B4	3	$C_{21}H_{20}N_6O_5$	436	226^0C	0.67	62.89%
2B5	4	$C_{22}H_{22}N_5O_3Cl$	440	228^0C	0.59	59.71%

Anti-Tubercular Activity:

All the synthesised 1,2,4- triazole derivatives have been evaluated for Anti- tubercular activity against ***Mycobacterium tuberculosis* H37Rv** using Microplate alamar blue dye assay(MABA).The minimum inhibitory concentration(MIC) was determined for each of the sample. The first line antitubercular drug INH was used as a refrence standard. The results are tabulated in table no-5 and graphically depicted in **figure no-1**.

Anti tubercular activity using Alamar Blue Dye Method [26]

The anti-mycobacterial activity of the title compounds were assessed against ***Mycobacterium tuberculosis* H37Rv** using Microplate Alamar Blue Assay (MABA) method. This method is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. Briefly, 200µl of sterile deionzed water

was added to all outer perimeter wells of sterile 96 wells plate to minimized evaporation of medium in the test wells during incubation. The 96 wells plate received 100 µl of the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate. The final drug concentrations tested were 100 to 0.2 µg/ml. Plates were covered and sealed with parafilm and incubated at 37ºC for seven days. After this time, 25µl of freshly prepared 1:1 mixture of Alamar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs. A blue color in the well was interpreted as no bacterial growth and pink color was scored as growth. The MIC is defined as lowest drug concentration which prevented the color change from blue to pink.

RESULTS:

The literature survey has revealed that, the moieties containing quinazolinone nucleus have shown to posses antitubercular activity. Hence, in the present investigation all the synthesised quinazolinone derivatives (**2AB1-2AB5)**.

Have been evaluated for antitubercular activity against ***mycobacerium tuberculosis H37Rv following* microplate alamar** blue assay method. MICwas determined for each of the compound and first line antitubercular drug INH was used as the refrence standard. The results of the study are tabulated in Table no-5 and graphically depicted in **Figure no-1.**

Table-5: Antitubercular activity of (E)-3-(2-substituted benzylidene hydrazinyl)-N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3-oxoalkanamides (2B1-2B5) against mycobacterium tuberculosis H37Rv

Sl.No.	Samples	100	50	25	12.5	6.25	3.125	1.6	0.8	0.4	0.2
1.	2AB1	S	S	R	R	R	R	R	R	R	R
2.	2AB2	S	S	S	R	R	R	R	R	R	R
3.	2AB3	S	S	S	R	R	R	R	R	R	R
4.	2AB4	S	S	R	R	R	R	R	R	R	R
5.	2AB5	S	S	S	S	S	S	R	R	R	R
6.	INH	S	S	S	S	S	S	S	S	S	S

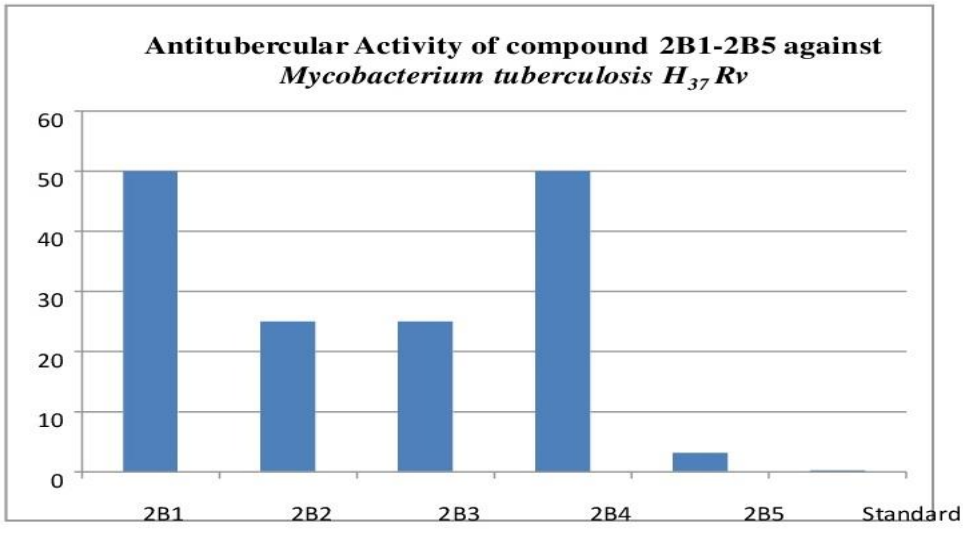


Figure-1: Antitubercular activity of *(E)-3-(2-substituted benzylidene hydrazinyl)-N-(2-methyl-4 oxoquinazolin-3(4H)-yl)-3-oxoalkanamides(2B1- 2B5)* against *Mycobacterium tuberculosis H37Rv*

DISCUSSION:

All the compounds synthesized were evaluated for antitubercular activity by micro plate alamar blue assay (MABA) method. The compounds evaluated have shown to possess significant antitubercular potency. Particularly the compound 2B5 obtained as a adipic acid derivative (n=4) is emerged as most potent antitubercular agent by possing the least MIC of 3.125µg/ml.The compounds 2B2 and 2B3 have shown to posses MIC of 25µg/ml.The other compounds 2B1 and 2B4 have shown to posses antitubercular activity by having MIC of 50 µg/ml.

Thus, the title derivatives synthesized have shown to Posses Significant Antitubercular property.

SUMMARY AND CONCLUSION:

The synthesis of new heterocyclic compounds has always drawn the attention of medicinal chemist over the years mainly because they posses diverse biological properties. The general strategy to synthesize new effective drugs is to explore the lead compound.The molecular manipulation of a promising lead compound is still a major line of approach for the discovery of new candidates as more effective drugs. Combination of the two or more active moieties into one is a common procedure of manipulation and this can possibly result in augmenting the biological activity of the newly synthesized derivatives.

Quinazolinone derivatives are the versatile nitrogen containing heterocyclic compounds displaying A Wide Variety Of Biological And Pharmacological Activities Likeantibacterial, anthelmintic, neuroleptic, antitubercular,platelet,antiaggregating,antifungal,anticancer, anti-inflammatory, antiviral, CNS depressant activity, antiparkinson, bronchodilator etc.Recently several scientists have elucidated that Quinazolinone system possesses variable sites like position 2 and 3 which can be suitably modified to yield new potent chemotherapeutic and pharmacotherapeutic agents.

Further, Schiff bases are use as substrate in the preparation of number of industrial and biologically active compound via ring closure, cyclo addition and replacement reactions. Morever, Schiff bases derived from various heterocycles have been reported to Posses cytotoxic,anticonvulsant,antiproliferative,antimicrobial,anticancer and antifungal activities.

In view of the above mentioned facts and in continuation of our interest in the synthesis of heterocycles to identify new candidate, that may be value in designing new, potent, selective and less toxic chemotherapeutic agents, in the present study we have synthesized some novel structure hybrids incorporating suitably substituted quinazolinone moiety with aliphatic amide chains differing in their number of carbon atom content. Various aliphatic dicarboxylic acids like oxalic acid, malonic acid, succinic acid, glutaric acid and adipic acid were converted into their corresponding dihydrazides and were utilized for the synthesize of N-3 substituted 2-methyl quinazolinones derivatives. Finally, these compounds were reacted with aryl aldehydes to arrive at title derivatives.

This combination suggested is an attempt to investigate the influence of such hybridization and structure variation on the anticipated biological activities hoping the possibility that the target derivatives might be more efficacious as antimicrobial and anticancer agents.

During the present investigation 1, 3,4-benzoxazinone was prepared from anthrnilic acid and acetic anhydride by known method. Various dihydrazides were prepared from α, ω- aliphatic dicarboxylic acids by following literature method.N-3 substituted quinazolinone derivatives were prepared from the equimolar reaction of 1,3,4-benzoxazinone with various dihydrazides to yield the compounds 1AB1-1AB5,which are then converted into Schiff bases by reacting with substituted benzaldehydes to form the compounds 2B1-2B5.

The homogeneity of all the derivatives was established by TLC technique. The structures of the compounds were successfully established by means of IR, Proton NMR and Mass spectral studies.

All the compounds were evaluated for antitubercular activity against ***Mycobacterium tuberculosis*** H37RV by MABA assay method and MIC for each drug were determined.INH; a first line drug used in tuberculosis therapy was used as a reference standard in the present investigation.

The result of the antitubercular activity were interesting and encouraging because, the compound **2B5** has shown excellent growth inhibiting property against the mycobacterium tested. The other compounds evaluated for antitubercular activity have shown to posses' significant antitubercular potency.
All these results of antitubercular activity revealed that the compounds of the above type have shown to posses significant properties as antitubercular. It only indicates that the quinazolinone moiety needs more attention and if this moiety is suitably exploited can still give better lead compounds.

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