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SYNTHESIS AND CHARACTERIZATION OF SUBSTITUTED QUINAZOLIN-4-ONES

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ABSTRACT

The present work describes the synthesis and characterization of some substituted furyl-, imidazolyl- and piperazinyl-quinazolin-4-ones. In the synthetic route o-aminobenzoic acid on bromination in presence of glacial acetic acid forms 2-amino- 5-bromo-benzoic acid 1 and 2-amino-3,5-dibromobenzoic acid. Synthesis of the parent quinazolin-4-one ring structure, its molecular modifications by attaching different pharmacophoric groups of existing bioactive agents to the quinazolin-4-one ring system. Piperazinyl-quinazolin-4-ones (16-19) a-f: Compounds 17f, 18a, and 19f demonstrated potent activity among the series compared to standard vincristine. Compounds 16bd, 17b, and 18c had moderate anticancer activity. Hence necessary structural modifications have to be made to improve the potency of these compounds so as to develop them into clinically useful antibacterial and antifungal agents.

Key Words: Quinazolin-4-ones

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INTRODUCTION

Oncology [Greek “oncos” = tumor] is the study of tumors. British oncologist Sir Rupert Willis has defined neoplasm as an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of stimuli (Remers, 1998). All neoplasms are virtually autonomas and purposeless in the growth and depend on the host for their nutrition and vascular Supply, many forms of neoplasia require endocrine support, and ultimately they destroy the host cell (Wall, 2003). Cancer is caused by external factors such as tobacco, chemicals, radiation, and infectious organism’s internal factors such as inherited mutations, hormones, immune conditions, and mutations that occur from metabolism. These casual factors may act together or in sequence to initiate or promote carcinogenesis. Ten or more years often pass between exposure to external factors and detectable cancer. Cancer is treated with surgery, radiation, chemotherapy, hormone therapy, and biological therapy. All cancers involve the malfunction of genes that control cell growth and division. About 5% of all cancers are strongly hereditary, in that an inherited genetic alteration confers a very high risk of developing one or more specific types of cancer

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However, most cancers do not result from inherited genes but from damage (mutation) to genes that occur during one's lifetime. Mutations may result from internal factors such as hormones or the digestion of nutrients within cells, or external factors such as tobacco, chemicals and sunlight. Cancers are classified in two ways: by the type of tissue in which the cancer originates (histological type) and by primary site, or the location in the body where the cancer first developed. From a histological standpoint there are hundreds of different cancers, which are grouped into five major categories: carcinoma, sarcoma, myeloma, leukemia, and lymphoma. In addition, there are also some cancers of mixed types. The first chemicals (Chemotherapy) used to treat cancer were discovered in an indirect manner. Veterans of World War II were experiencing low white blood cell counts. A direct correlation to their being in contact with mustard gas led to the first utilization of anticancer intravenous drugs. Today there are scores of anticancer drugs. They differ in their chemical composition and administration, but their overall goal is to destroy the cancerous cells and prevent their proliferation. Each drug aims a specific stage of the cell cycle in which to kill the cell. Most chemotherapy agents kill cancer cells by affecting DNA synthesis or function, a process that occurs through the cell cycle. Each drug varies in the way this occurs within the cell cycle. The major categories of chemotherapy agents are alkylating agents, antimetabolites, anthracyclines, plant alkaloids, antitumor antibiotics, taxanes, and platinums. The main advantage of chemotherapy treatment is the chance to kill all of the cancerous cells and ultimately cure the patient. This reestablishes a normal life for the individual. On the other hand, there are many disadvantages to using chemotherapeutic drugs. The chemotherapeutic agents are not cancer-specific, so normal, healthy cells are inevitably killed during treatment. Most of these chemotherapeutic agents exhibit severe normal toxicity, resulting in undesirable side effects. Moreover, many of the active molecules sold for the treatment of cancer, are highly expensive, mutagenic, carcinogenic and teratogenic. Hence, there is a need to find alternative drugs, which are highly effective at non-toxic doses, inexpensive and accessible to common man. A need is therefore felt to search newer remedies, which are cheaper economically and do not have severe side effects of the pure compounds. Tuberculosis (TB) is an epidemic disease, which had been controlled to a significant extent during the nineteen sixties and seventies, has re-emerged in recent years as one of the leading causes of death in the world. Nearly 3 million people die every year due to TB. A World Health Organization report of 1997 states that there are, world-wide, 8.8 million new cases every year – meaning about 1,000 new cases every hour (WHO, 1997). Most of these are resistant to the presently available antitubercular drugs. This works out to 52,000 deaths per week, or 7,000 deaths each day and constitutes a grim reminder of the apparent failure of medical science to counter an ancient scourge. Tuberculosis got its present name at the end of the 19th century. Under its previous name of consumption it has been long known as a world-wide phenomenon. It is caused by a bacterium, *Mycobacterium tuberculosis.* A related *organism*, *M. bovis*, causes TB in cattle while *M. leprae* is the causative agent of leprosy in man. The ever growing emergence of strains of *M. tuberculosis* resistant to presently available drugs has made the control of TB, especially in India and other developing countries, a difficult proposition. Drug resistant strains appear initially in patients who are not adequately treated with a combination of three or four drugs simultaneously. Later, because of direct infection via the patient, these strains are also found in persons who have never been treated. The drugs normally used in combination are isoniazid, rifampicin, ethambutol and pyrazinamide. This situation has necessitated the search for newer antitubercular drugs to which the resistant strains are susceptible. One method to accomplish this is to make use of the knowledge about the mechanism of action of presently available drugs and chemically synthesize drugs which inhibit the metabolic activity of the organism.

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The quinazolin-4-one moiety is a building block for approximately 150 naturally occurring alkaloids such as glycosminine, echinozolinone, deoxyvasicinone, rutaecarpine, and drugs like methaqualone (Mhaske and Argade, 2006). The natural quinazolin-4-ones and their synthetic analogues, possess a variety of biological activities (1-7).

MATERIALS AND METHODS

Synthesis and characterization (8-12)

3-amino substituted-quinazolin-4-ones and 2-chloro-*N*-(4-oxo-substituted-quinazolin- 3(4*H*)-yl)-acetamides were synthesized as intermediate compounds. Different furan-2- aldehydes were attached to 3-amino substituted-quinazolin-4-ones and other moieties like imidazoles, and piperazines were attached to 2-chloro-*N*-(4-oxo-substituted- quinazolin-3(4*H*)-yl)-acetamides through appropriate synthetic methodology. The synthesized compounds are characterized through different analytical techniques like Elemental, IR, NMR and Mass Spectral methods.

2, 6, 8-substituted-3-amino-4-oxoquinazolin-3(4*H*)-one **5ac**, and **6bc** (1.8 mmol) was dissolved in 50 mL of dry toluene and cooled to 15 °C. To this chloroacetyl chloride (2 mmol, 2.3 mL) was added drop wise with stirring. The temperature was brought slowly to room temperature and then refluxed for 4 h. Excess toluene was distilled off; precipitate obtained was filtered, washed with dry benzene, dried and recrystallized from aqueous dioxan. The completion of the reaction was monitored on silica gel 60 F_{254} precoated TLC plates by using ethyl acetate, petroleum ether and methanol (1:1:0.3) as the eluent and observed in UV light as a single spot (Table-1).

Table-1 Physical parameters of intermediates

	Compd code	Chemical Name	Mp [° C]	Yield %	Rf
1	3a	2-phenyl-4*H*-3,1-benzoxazin-4-one	109	30	0.92
2	3b	6-bromo-2-phenyl-4*H*-3,1-benzoxazin-4-one	180	30	0.8
3	3c	6,8-dibromo-2-phenyl-4*H*-3,1-benzoxazin-4-one	192	32	0.94
4	4a	6-bromo-2-methyl-4*H*-3,1-benzoxazin-4-one	172	72	0.21
5	4b	6,8-dibromo-2-methyl-4*H*-3,1-benzoxazin-4-one	169	75	0.67
6	4c	6,8-dibromo-2-propyl-4*H*-3,1-benzoxazin-4-one	115	72	0.87
7	5a	3-amino-2-phenylquinazolin-4(3*H*)-one	172	40	0.38
8	5b	3-amino-6-bromo-2-phenylquinazolin-4(3*H*)-one	115	50	0.37
9	5c	mo-2-phenylquinazolin-4(3*H*)- one	235	65	0.63
10	6a	3-amino-6-bromo-2-methylquinazolin-4(3*H*)-one	172	50	0.11
11	6b	mo-2-methylquinazolin-4(3*H*)- one	225	65	0.33
12	6c	mo-2-propylquinazolin-4(3*H*)- one	182	60	0.57
13	7a	oxo-2-phenyl-quinazolin-3(4*H*)-yl)- acetamide	148	55	0.78
14	7b	*N*-(6,8-dibromo-4-oxo-2-phenyl- quinazolin-3(4*H*)-yl)-acetamide	238	58	0.91
15	8a	2-chloro-*N*-(6,8-dibromo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-acetamide	188	60	0.86
16	8b	2-chloro -*N*-(6,8-dibromo-4-oxo-2-propylquinazolin-3(4*H*)-yl)-acetamide	192	75	0.7

Synthesis of 2-(substituted-piperazin-1-yl)-*N*-(2, 6, 8- substituted-4-oxo-quinazolin-3(4H)-yl)-acetamide 17a-f

2-chloro-*N*-(6,8-dibromo-4-oxo-2-phenyl-quinazolin-3(4*H*)-yl)-acetamide **3b**, (0.006 mol) was dissolved in 50 mL of dry dioxan, to this freshly dried anhydrous potassium carbonate (0.9 g, 0.0065 mol) and appropriate substituted-piperazines (0.0067 mol) was added and refluxed for 4 h. Excess dioxan was distilled off; precipitate obtained was washed with hot water, dried and recrystallized from aqueous dioxan. The completion of the reaction was monitored on silica gel 60 F254 precoated TLC plates by using ethyl acetate, petroleum ether and methanol (1:1:0.3) as the eluent and observed in UV light as a single spot. The structural details, physical parameters, and spectral characterization of piperazinyl-quinazolin-4-ones **17a-f** are given in Table 3.2.5.1, Table 3.2.5.2, and Table 3.2.5.3 respectively. The IR and ^{1}H NMR spectra of 2- (1,4-diazepan-1-yl)-*N*-(6,8-dibromo-2-phenyl-4-oxoquinazolin-3(4*H*)-yl)acetamide **17f** are given in Spectrum 3.2.62 and Spectrum 3.2.63 respectively. Elemental analysis and mass spectral data of compounds **17ac** are given in Table-2.

Table-2 Elemental analysis and Mass spectral data of piperazinyl-quinazolin- 4-ones 16f, 17ac, 18cef, and 19a-d

Compd code	Elemental Analysis			Mass *m/z*
	Calculated (Found) in %			
	C	H	N	
16f	66.83 (66.92)	6.14 (6.28)	18.55 (18.69)	377 (M^+)
17a	46.09 (46.35)	3.67 (3.42)	13.44 (13.37)	521 (M^+)
17c	48.11 (48.45)	4.22 (4.35)	12.75 (12.53)	549 (M^+)
18c	41.91 (42.10)	4.34 (4.45)	14.38 (14.42)	487 (M^+)
18e	45.59 (45.97)	3.64 (3.79)	12.66 (12.78)	553 (M^+)
18f	40.61 (40.87)	4.05 (4.21)	14.80 (14.95)	474 (M^+ + H)
19a	41.91 (41.86)	4.34 (4.29)	14.38 (14.45)	487 (M^+)
19b	43.13 (43.48)	4.63 (4.32)	13.97 (13.73)	501 (M^+)
19c	44.29 (44.37)	4.89 (4.56)	13.59 (13.26)	515 (M^+)
19d	47.52 (47.80)	4.16 (4.22)	12.05 (12.35)	581 (M^+)

Invitro cytotoxic activity

The EAC cells were collected, counted and adjusted to 10^6cells/mL in normal saline. The drug dilutions were made with phosphate buffer saline and were further adjusted to concentrations ranging from 125-1000 mg/mL. The drug dilutions were then added to the EAC cells and incubated at 37 °C for 3 h. At the end of 3 h, the cell viability was determined by trypan blue exclusion method. Under identical conditions, standard anticancer agent vincristine was evaluated for its in vitro anticancer activity.

In vitro antimycobacterial activity of furyl-quinazolin-4-ones (9-11)a-f and imidazolyl-quinazolin-4-ones (12-15)a-d

Agar dilution method (National Committee for Clinical Laboratory Standards, 1995) was followed to screen the synthesized quinazolin-4-ones for their antimycobacterial activity against M. tuberculosis H37Rv and M. smegmatis. Briefly, 2-fold serial dilutions of each test compound/drug were incorporated into Middle brook 7H10 agar medium supplemented with Middle brook OADC medium (Hi-Media). Inoculum of M. tuberculosis H37Rv/M.smegmatis was prepared from fresh Lowenstein-Jensen slants adjusted to 1 mg/mL (wet weight) in Tween 80 (0.05%) saline and diluted to 10^{-2} to give a concentration of approximately 10^7 cfu/mL. A 5 mL amount of bacterial suspension was spotted into 7H10 agar tubes containing 2- fold serial dilution of test compounds/drug per mL. The tubes were incubated at 37 °C, and final readings were recorded after 30 days for M. tuberculosis H37Rv and 3 days for M. smegmatis. The MICs were read as the minimum concentration of test compounds and standard drugs like ciprofloxacin, gatifloxacin, isoniazid and rifampicin that completely inhibited the growth of mycobacteria on agar plates, per spot, disregarding a single colony or faint haze caused by the inoculums. A blank was determined under the similar conditions.

RESULTS AND DISCUSSION

The structures of synthesized piperazinyl-quinazolin-4-ones **(16-19)a-f** was substantiated on the basis of IR, ^{1}H NMR, Mass spectral and Elemental Analysis data. The synthesis of piperazinyl-quinazolin-4-ones **(16-19)a-f** is described in Scheme 3.2.5. The ^{1}H NMR spectra of 2-chloro-*N*-(4-oxo-substituted-quinazolin- 3(4*H*)-yl)-acetamides **(7-8)a-b** showed characteristic diastereotopic quartlets at d 4.1- 4.5 due to C=OCH2Cl protons. Presence of ^{1}H NMR signals at d 2.2-2.4 due to piperazine protons established that all the 2-chloro-*N*-(4-oxo-substituted-quinazolin- 3(4*H*)-yl)-acetamides had converted into 2-(1*H*-substituted-piperazin-1-yl)-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides. The compounds **16a-c** and **16f** did not show the presence of chlorine atom, as they gave negative Beilstein test and Lassiaigne's test for halogens. The mass spectrum of compound **18c** (Spectrum 3.2.51), (M^++ H) peak at *m/z* 488 was observed along with the molecular ion peak at *m/z* 487 (Fig-1). (M^++2) peak at *m/z* 489 and (M^++4) peak at 491 was also observed due to the presence of isotopes of bromine atoms in the compound. The molecular ion upon cleavage with the loss of ethyl piperazine ion, produced the peak at *m/z* 374. Resulted ion further lost acetamido ion followed by nitrogen ion to give derivative of indole ion at *m/z* 303, which further lost bromine atom to form ion at *m/z* 143. The peaks at *m/z* 127 and *m/z* 113 was due to fragments of piperazine ions. Base peak was found at *m/z* 487. The mass spectrum of compound **18f** (Spectrum 3.2.54), shows (M^++ H) peak at *m/z* 474. (M^++2) peak at *m/z* 475 and (M^++4) peak at 477 was also observed due to the presence of isotopes of bromine atoms in the compound. The molecular ion upon cleavage with the loss of aceto-diazepan ion, produced the peak at *m/z* 332. Resulted ion further lost NH ion followed by nitrogen ion to give derivative of indole ion at *m/z* 303. The peak at *m/z* 113 was due to fragment ion of piperazine derivative. Base peak was found at *m/z* 474. Fragment ion at *m/z* 332 underwent further fragmentations forming ions at *m/z* 172 and *m/z* 157. The mass spectrum of compound **19a** (Spectrum 3.2.57), showed the molecular ion peak at *m/z* 487 consistent with the molecular formula, $C_{17}H_{21}Br_2N_5O_2$.

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The molecular ion underwent fragmentation with the loss of methylene-piperazine ion (*m/z* 99) to give the ion radical at *m/z* 388 that further lost carbonyl ion to give a peak at *m/z* 360. Resulted ion further lost NH ion followed by N ion to form a derivative of indole ion at *m/z* 331.

This ion further lost bromine to form an ion *m/z* 251. The base peak observed at *m/z* 472 could due to loss of methyl ion from parent ion. MS spectrum also shows the (M^{+}+ 2) peak and (M^{+}+ 4) peak at *m/z* 489 and *m/z* 501 respectively (Fig-2).

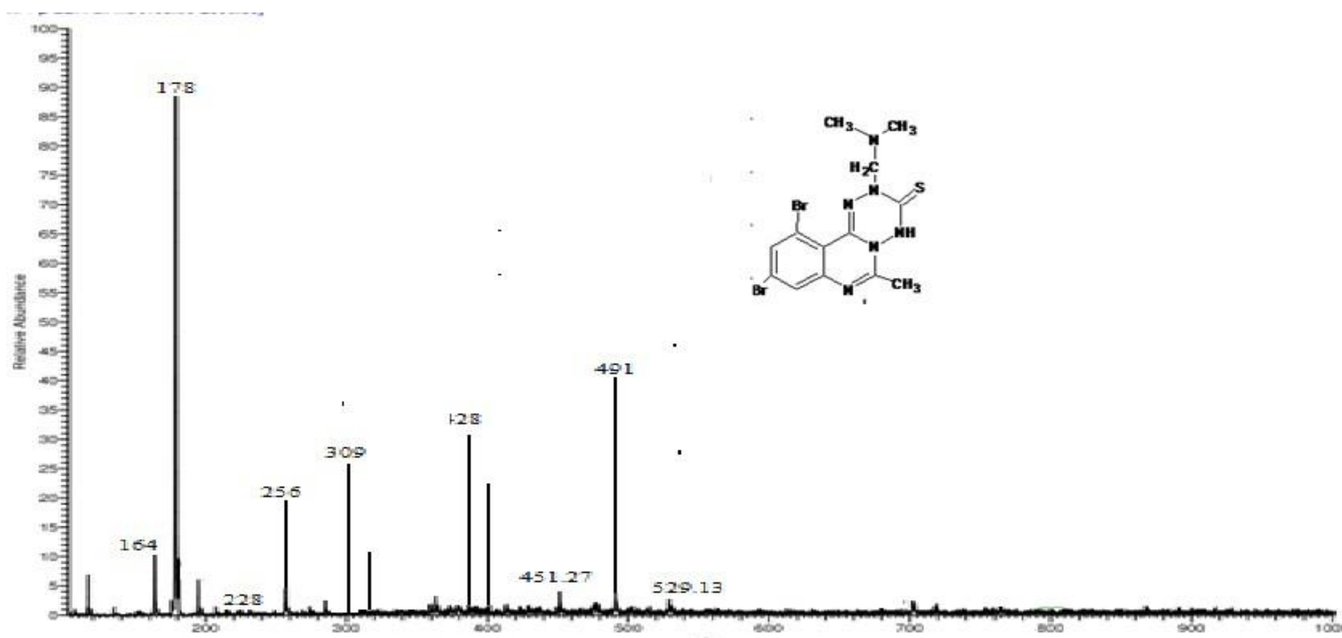

Fig-1 Mass Spectra of derivative

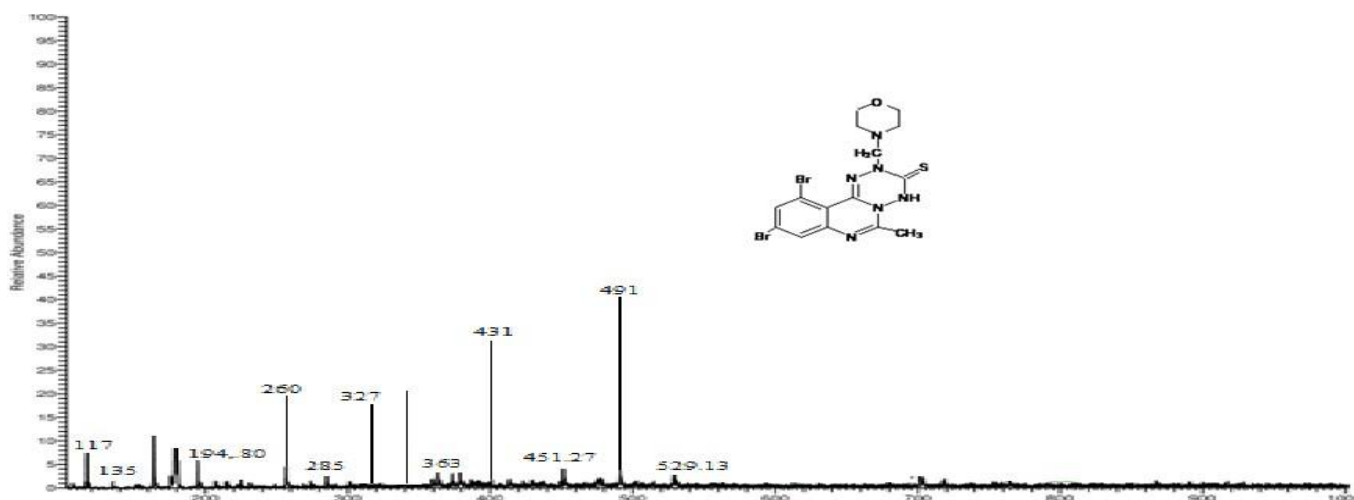

Fig- 2 mass spectrum of compound

In vivo anticancer activity

Furyl-quinazolin-4-ones **9a-c, 10a** and **11(b-d,f)**, imidazolyl-quinazolin-4-ones **12ad, 13ab, 14a**, and **15abd**, and piperazinyl quinazolin-4-ones **16bd**, **17bdf**, **18acf**, and **19bf** with significant *in vitro* anticancer activity were further selected for screening *in vivo* anticancer activity. The animals were divided into various groups and sub groups. Six Swiss albino mice were taken for each group and sub group. Group I served as control and received 0.3% CMC suspension. Group II served as standard and received vincristine. Group III served as test group; test group has several sub groups for furyl quinazolin-4-ones, imidazolyl quinazolin-4-ones and piperazinyl quinazolin-4- ones. The EAC cells containing 10^6 cells/0.1 mL of phosphate buffer saline were injected into the peritoneal cavity of all the animals (six Swiss albino mice in each group). Treatment with test compounds (80 mg/kg body weight) and the standard vincristine (520 mg/kg body weight) was started 24 h after inoculation of cancer cells, once daily as a single dose in 0.3% CMC suspension by intraperitoneal route for 10 days (The LD50 value of compounds **10a**, **15d**, and **19f** were found to be 800 mg/kg body weight (Licthfield and Wilcoxon, 1949); The LD50 of vincristine is 5200 mg/kg body weight; Hence $1/10^{th}$ of this dose was used for *in vivo* anticancer study). *In vivo* anticancer activity was screened by determining different parameters like body weight analysis, mean survival time (MST) and percentage increase in life span (%ILS) (Table-3 and 4).

Table-3 *In vitro* and *in vivo* anticancer activity of furyl-quinazolin-4-ones (9- 11)a-f

Compd code	*In vitro* anticancer activity				*In vivo* anticancer activity			
	Percentage cytotoxicity of drug at various concentrations on EAC cells [mg/mL]				Gain in body weight	%Decrease in body weight	MST ± SE	% ILS
	1000	500	250	125				
Control	-	-	-	-	5.46 ± 0.19	-	14.6 ± 0.21	-
9a	46.8	39.6	33.4	16.7	1.24 ± 0.087	77.28	25.0 ± 0.44	71.23***
9b	66.7	32.7	30.0	16.7	3.78 ± 0.398	30.76	18.6 ± 1.33	27.39*
9c	80.6	47.6	41.6	30.0	0.84 ± 0.0244	84.61	33.5 ± 0.76	129.45***
9d	25.4	24.5	24.5	18.0	ND	ND	ND	ND
9e	20.2	20.2	18.2	18.2	ND	ND	ND	ND
9f	18.5	18.5	17.5	18.5	ND	ND	ND	ND
10a	81.9	38	28.5	13.4	0.74 ± 0.06	86.44	36.6 ± 1.2	150.68***
10b	20.0	18.6	13.4	13.4	ND	ND	ND	ND
10c	30.9	25.0	20.0	8.3	ND	ND	ND	ND
10d	20.5	18.2	15.0	15.4	ND	ND	ND	ND
10e	19.5	18.5	18.5	10.0	ND	ND	ND	ND
10f	17.0	15.4	15.4	15.4	ND	ND	ND	ND
11a	33.3	26.2	16.3	16.3	ND	ND	ND	ND
11b	41.0	34.4	25.0	15.0	0.84 ± 0.024	84.61	24.1 ± 0.30	65.06***
11c	75.0	50.8	36.6	16.7	1.62 ± 0.1463	70.32	21.0 ± 0.36	43.83***
11d	50.0	38.4	25.0	13.4	0.92 ± 0.037	83.15	26.0 ± 0.57	78.08***
11e	13.7	13.4	13.4	13.4	ND	ND	ND	ND
11f	43.8	42.3	16.7	13.4	4.02 ± 0.037	26.37	16.0 ± 0.36	9.58*
Vincristine	86.7	69.0	46.0	43.0	0.9 ± 0.1183	83.51	32.0 ± 0.68	119.17***

MST = Mean survival time; SE =Standard error; ND = Not determined; * P <0.05; *** P <0.0001.

Table-4 *In vitro* and *in vivo* anticancer activity of imidazolyl-quinazolin-4-ones (12-15)a-d

Compd code	*In vitro* anticancer activity				*In vivo* anticancer activity			
	Percentage cytotoxicity of drug at various concentrations on EAC cells [mg/mL]				Gain in body weight	Percentage Decrease in body weight	MST ± SE	% ILS
	1000	500	250	125				
Control	-	-	-	-	5.46 ± 0.19	-	14.6 ± 0.21	-
12a	36.0	32.0	25.0	20.0	3.78 ± 0.398	30.76	15.0 ± 0.25	2.73
12b	70.0	50.0	41.6	33.4	0.74 ± 0.06	86.44	25.0 ± 1.12	71.23***
12c	55.1	24.2	23.3	16.7	1.6 ± 0.2449	70.69	26.6 ± 1.89	82.19**
12d	45.7	13.7	13.3	13.3	3.28 ± 0.08	39.92	19.6 ± 1.25	34.24*
13a	50.8	36.6	33.3	31.7	1.96 ± 0.2874	64.1	28.5 ± 1.08	95.2***
13b	36.6	26.2	24.5	21.6	3.84 ± 0.1208	29.67	16.1 ± 0.60	10.27
13c	19.3	18.3	16.9	16.9	ND	ND	ND	ND
13d	13.3	11.6	10.1	3.4	ND	ND	ND	ND
14a	86.6	79.0	70.0	55.6	0.68 ± 0.02	87.54	21.8 ± 0.87	49.31***
14b	23.7	23.7	16.9	16.9	ND	ND	ND	ND
14c	26.6	13.2	13.5	13.7	ND	ND	ND	ND
14d	24.1	13.5	13.3	13.5	ND	ND	ND	ND
15a	46.7	32.7	32.2	16.1	2.54 ± 0.1691	53.47	28.0 ± 1.88	91.78***
15b	90.0	66.7	57.3	40.9	0.48 ± 0.073	91.2	33.6 ± 1.28	126.71***
15c	19.3	14.7	13.4	13.4	ND	ND	ND	ND
15d	85.7	81.8	66.7	50.0	0.6 ± 0.07071	89.01	42.3 ± 0.33	189.72***
Vincristine	86.7	69.0	46.0	43.0	0.9 ± 0.1183	83.51	32.0 ± 0.68	119.17***

MST = Mean survival time; SE = Standard error; ND = Not determined; * P <0.05; ** P <0.001; *** P <0.0001.

In vitro and *in vivo* anticancer activity studies prompted compounds **17f**, **18a**, and **19f** as most potent compounds among the series as their activities are comparable to standard vincristine. Compounds **16b, 17b** and **18c** had moderate anticancer activity. Compounds **17d**, **18f,** and **19b** showed less activity among the series. Structure activity relationship studies of piperazinyl-quinazolin-4-ones showed important structural features which influence the biological activity.

Presence of diazepan (homopiperazine) moiety at the 3rd position of quinazolin-4-one ring through acetamido side chain proves highly beneficial for anticancer activity than piperazine moiety as compounds 19f (%ILS, 112.32) and 17f (%ILS, 106.16) are more active than 19a (%ILS, 27.39) and 17a (%ILS was not determined as its in vitro activity was negligible) respectively. Piperazines with electron donating group (compounds 17b (%ILS, 69.86) and 16b (%ILS, 71.91)) are more active than unsubstituted piperazines (17a and 16a; %ILS was not determined as their in vitro activity was negligible). Presence of bromine at position 6 and 8 of quinazolin-4-one ring decreases activity as compound 17b (%ILS, 69.86) is less active than unsubstituted compound 16b (%ILS, 71.91). Presence of fluorine in phenyl piperazines does not increase the anticancer activity as compounds 16e, 17de, 18de, and 19de are not having significant activity except compound 16d (%ILS, 61.46) which is moderately active. Presence of methyl group at position 2 of quinazolin-4-one (compound 18a (%ILS, 91.78)) favors anticancer activity than phenyl group (compound 17a (%ILS was not determined as its in vitro activity was negligible) (Fig-3).

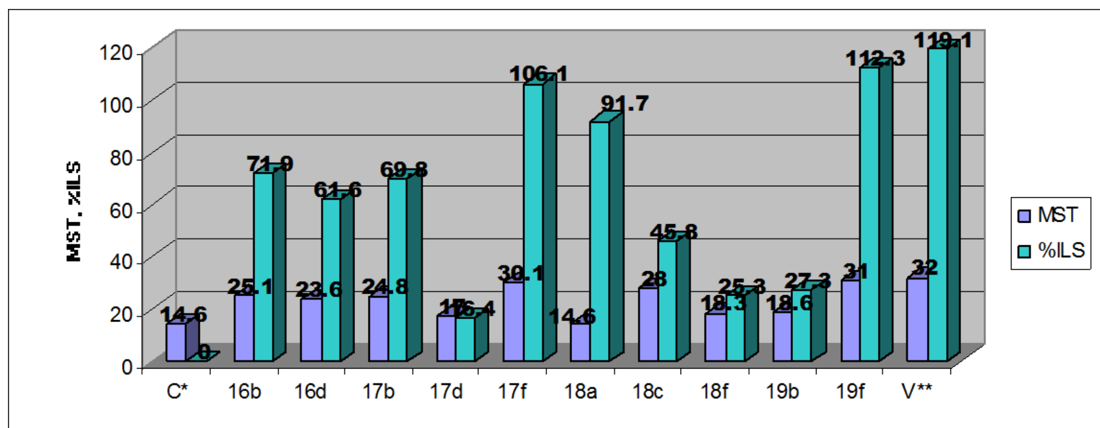

Fig-3 Anticancer activity of piperazinyl-quinazolin-4-ones

The *in vitro* antimycobacterial activity of furyl-quinazolin-4-ones **(9-11)a-f** and imidazolyl-quinazolin-4-ones **(12-15)a-d** are given in Table-5 and Table-6 respectively.

Table-5 *In vitro* antimycobacterial activity of furyl quinazolin-4-ones (9-11)a-f

Compd code	MIC in [μg/mL] *M. tuberculosis*	MIC in [μg/mL] *M. smegmatis*
9a	>12.5	50
9b	12.5	50
9c	>12.5	100
9d	>12.5	50
9e	>12.5	50
9f	>12.5	50
10a	1.56	12.5
10b	3.13	12.5
10c	0.2	0.78
10d	>12.5	50
10e	>12.5	50
10f	>12.5	50
11a	6.25	25
11b	6.25	25
11c	0.78	6.25
11d	0.78	3.13
11e	3.13	12.5
11f	0.78	3.13
Ciprofloxacin	1.56	<0.78
Gatifloxacin	0.39	0.78
Isoniazid	0.05	6.25
Rifampicin	0.2	1.56

Table-6 ***In vitro*** **antimycobacterial activity of imidazolyl-quinazolin-4-ones (12-15)a-d**

Compd code	MIC in (µg/ml) *M. tuberculosis*	MIC in (µg/ml) *M. smegmatis*
12a	>12.5	50
12b	1.56	6.25
12c	6.25	25
12d	12.5	25
13a	>12.5	25
13b	0.4	0.78
13c	>12.5	50
13d	12.5	25
14a	12.5	50
14b	6.25	50
14c	6.25	25
14d	12.5	50
15a	>12.5	50
15b	6.25	50
15c	1.56	25
15d	6.25	25
Ciprofloxacin	1.56	<0.78
Gatifloxacin	0.39	0.78
Isoniazid	0.05	6.25
Rifampicin	0.2	1.56

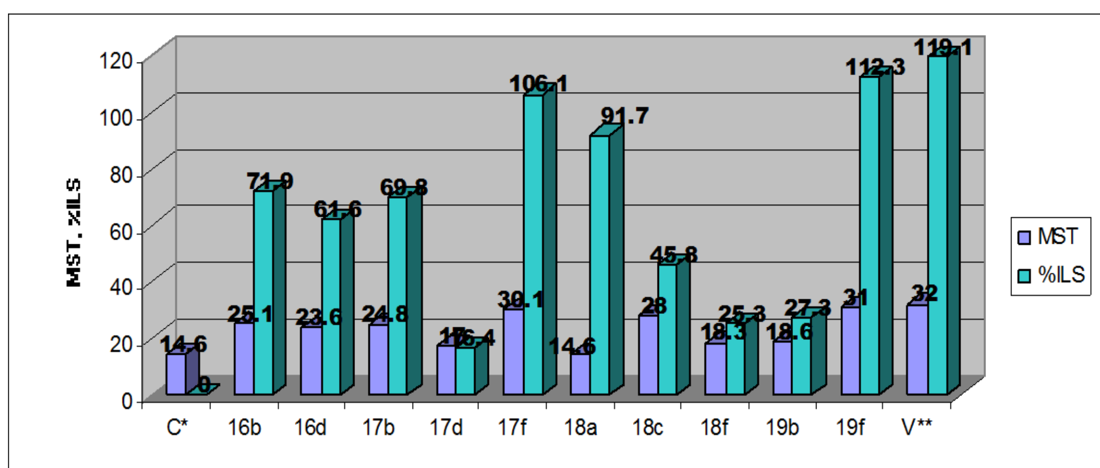

Fig-3 Anticancer activity of piperazinyl-quinazolin-4-ones

The *in vitro* antimycobacterial activity of furyl-quinazolin-4-ones **(9-11)a-f** and imidazolyl-quinazolin-4-ones **(12-15)a-d** are given in Table-5 and Table-6 respectively

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Table-5 *In vitro* antimycobacterial activity of furyl quinazolin-4-ones (9-11)a-f

Compd code	MIC in [µg/mL] *M. tuberculosis*	MIC in [µg/mL] *M. smegmatis*
9a	>12.5	50
9b	12.5	50
9c	>12.5	100
9d	>12.5	50
9e	>12.5	50
9f	>12.5	50
10a	1.56	12.5
10b	3.13	12.5
10c	0.2	0.78
10d	>12.5	50
10e	>12.5	50
10f	>12.5	50
11a	6.25	25
11b	6.25	25
11c	0.78	6.25
11d	0.78	3.13
11e	3.13	12.5
11f	0.78	3.13
Ciprofloxacin	1.56	<0.78
Gatifloxacin	0.39	0.78
Isoniazid	0.05	6.25
Rifampicin	0.2	1.56

Table-6 *In vitro* antimycobacterial activity of imidazolyl-quinazolin-4-ones (12-15)a-d

Compd code	MIC in (µg/ml) *M. tuberculosis*	MIC in (µg/ml) *M. smegmatis*
12a	>12.5	50
12b	1.56	6.25
12c	6.25	25
12d	12.5	25
13a	>12.5	25
13b	0.4	0.78
13c	>12.5	50
13d	12.5	25
14a	12.5	50
14b	6.25	50
14c	6.25	25
14d	12.5	50
15a	>12.5	50
15b	6.25	50
15c	1.56	25
15d	6.25	25

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Ciprofloxacin	1.56	<0.78
Gatifloxacin	0.39	0.78
Isoniazid	0.05	6.25
Rifampicin	0.2	1.56

In vitro antimycobacterial activity indicates that some of the furyl-quinazolin-4- ones compounds are promising candidates having good activity against *M. tuberculosis* H37Rv and *M. smegmatis*. Compounds 10c and 11cdf showed more activity than standard ciprofloxacin against *M. tuberculosis* H37Rv. The compound 10c is equipotent as rifampicin. Compound 10a is found be equipotent as ciprofloxacin against *M. tuberculosis*. Compounds 10b and 11abe were moderately active (Table-5). Structure activity relationship studies of the test compounds for antimycobacterial activity against *M. tuberculosis* H37Rv indicates unsubstituted furan or nitrofuran as in compounds 10c (MIC, 0.2 mg/mL) and 11f (MIC, 0.78 mg/mL) seems to be more effective than methylfuran at position 3 of the quinazolin-4-one ring as in compound 10f (MIC, >12.5 mg/mL). Electron withdrawing group on the aromatic portion of quinazolin-4-one as in compound 11c (MIC, 0.78 mg/mL) favors antimycobacterial activity against *M. tuberculosis* than non halogen derivatives as in compound 11a (MIC, 6.25 mg/mL). Alkyl substitutions are more effective than aryl substitution at position 2 of quinazolin-4-one, as compound 10a (MIC, 1.56 mg/mL) is more potent than compound 9b (MIC, 12.5 mg/mL).

Antimycobacterial activity of the imidazolyl-quinazolin-4-ones proves that some of the tested compounds are promising candidates having good activity against *M. tuberculosis* H37Rv and *M. smegmatis*. Compound 13b exhibited the highest degree of antimycobacterial activity than ciprofloxacin against *M. tuberculosis* H37Rv. Compounds 12b and 15c showed good antimycobacterial activities comparable to standard antimycobacterial agents. Rest of the compounds does not show any significant antimycobacterial activity as compared with standard agents (Table-6). Structure activity relationship studies of the test compounds for antimycobacterial activity against *M. tuberculosis* indicates compound 13b (MIC, 0.4 mg/mL) having phenyl group at position 2 of the quinazolin-4-one ring is more active than propyl derivative compound 15b (MIC, 6.25 mg/mL) and methyl derivative compound 14b (MIC, 6.25 mg/mL). Methyl substituted azoles attached to acetamido side chain at position 3 of quinazolin-4-one proves more beneficial than unsubstituted azoles as compound 12b (MIC, 1.56 mg/mL), 15c (MIC, 1.56 mg/mL) are more active than compound 12a (MIC, >12.5 mg/mL) and 15a (MIC, >12.5 mg/mL) respectively. Replacement of hydrogen by bromine at position 6 and 8 of the quinazolin-4-one ring as in compound 13b (MIC, 0.4 mg/mL) favors antimycobacterial activity than non-halogen derivative compound 12b (MIC, 1.56 mg/mL).

CONCLUSION

A new approach for developing substituted quinazolin-4-ones as chemotherapeutic agent has been adopted. Synthesis of the parent quinazolin-4-one ring structure, its molecular modifications by attaching different pharmacophoric groups of existing bioactive agents such as furans, imidazoles and piperazines to the quinazolin-4-one ring system has been done. Synthesized compounds were characterized, screened for their anticancer, antimycobacterial, antibacterial and antifungal activities. It was found that furyl-quinazolin-4-ones 9c and 10a, imidazolyl- quinazolin-4-ones 13a and 15abd, and piperazinyl-quinazolin-4-ones 17f, 18a and 19f exhibited excellent anticancer activity against Ehrlich ascites carcinoma. In case of antimycobacterial activity furyl quinazolin-4-ones 10ac and 11cdf and imidazolyl- quinazolin-4-ones 12b, 13b and 15c exhibited potent antimycobacterial activity. Hence it is concluded that these drugs can be developed into clinically useful agents for their anticancer and antimycobacterial activity.

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