**IJPSR (2012), Vol. 3, Issue 11** **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 21 July, 2012; received in revised form 17 October, 2012; accepted 31 October, 2012

# SYNTHESIS AND ANTITUBERCULAR ACTIVITY OF SOME SUBSTITUTED 2, 3-SUBSTITUTED QUINAZOLINONE ANALOGS

S. Rajasekaran*[1], Gopalkrishna Rao [2], H.S. Niranjan [1]

Department of Pharmaceutical Chemistry, Al-Ameen College of Pharmacy [1], Near Lalbagh Main Gate, Hosur Road, Bangalore-560 027, Karnataka, India
Goa College of Pharmacy [2], 18th June Road, Panaji-403 001, Goa, India

**Keywords**:
Quinazolinone,
Thiophene-2-carboxaldehyde,
2-acetyl furan,
Antitubercular activity

**Correspondence to Author:**

**S. Rajasekaran**

Assistant Professor, Department of Pharmaceutical Chemistry, Al-Ameen College of Pharmacy, Near Lalbagh Main Gate, Hosur Road, Bangalore-560 027, Karnataka, India

E-mail: rajasekaranpharm@gmail.com

## ABSTRACT

In recent years, there is a tremendous increase of drug resistant pathogens, leading to the design and development of newer antitubercular agents. A series of 2-(substituted-phenyl)-1,3-benzoxazin-4-ones and 3-amino-2-(substituted-phenyl)quinazolin-4(3*H*)-ones were synthesized by the reaction of substituted benzoyl chloride with anthranilic acid and 2- (substituted phenyl)-1,3-benzoxazin-4-one with hydrazine hydrate in absolute alcohol respectively. The title compounds 2-substituted phenyl-3-(thiophen-2-ylmethyleneamino) quinazolin-4(3*H*)-ones and 2-(substituted phenyl)-3-(1-(furan-2-yl)ethylideneamino) quinazolin-4(3*H*)-ones were obtained by reacting 3-amino-2-(substituted phenyl) quinazolin-4(3*H*)-one with thiophene-2-carboxaldehyde and 2-acetyl furan respectively. The title compounds have been characterized by UV, IR, 1H-NMR and Mass spectra. The synthesized compounds have been evaluated for their antitubercular activity. Few of the compounds exhibited significant antitubercular while other compounds showed moderate activity.

**INTRODUCTION:** Quinazolinones are an interesting class of organic compounds being studied over the years and reported to possess a wide spectrum of biological activities such as antibacterial [1], antifungal [2], Antitubercular [3], anti-inflammatory [4], antioxidant [5] and anticonvulsant [6], antihypertensive [7], bronchodilator [8]. The pharmacodynamic versatility of quinazolin-4-one moiety has been documented not only in many of its synthetic derivatives but also in several naturally occurring alkaloids isolated from animals, families of plant kingdoms and from microorganism [9].

Quinazolinone is a versatile lead molecule for designing potential bioactive agents. Imines (Schiff bases) and their reaction products are an interesting class of organic compounds being studied over the years and reported to possess a wide spectrum of biological activities such as antimicrobial [10, 11] antioxidant [12], cytotoxic [13] and anticonvulsant [14]. They are formed by simple condensation of amine and aldehyde in alcoholic medium to form an azomethine linkage.

Tuberculosis (TB) is one of the oldest and most pervasive diseases in history. According to alarming data from the World Health Organization (WHO), TB has spread to every corner of the globe.

QUICK RESPONSE CODE

**IJPSR:**
ICV (2011)- 5.07

**Website:**
www.ijpsr.com

As much as one-third of the world's population is currently infected and more than 5000 people die from TB every day. It is estimated that between 2002 and 2020, approximately 1000 million people will be newly infected, over 150 million people will develop diseases and 36 million will die of TB if proper control measures are not established. The Directly Observed Treatment, short-course (DOTS) strategy, constitutes the cornerstone of the current protocol for control of TB. However, the three key drugs, isoniazid, pyrazinamide and rifampicin, used in the regimen are potentially hepatotoxic and may lead to drug associated hepatitis.

Hence, an attempt has been made in the present study to synthesize some novel compounds of quinazolinones containing five membered thiophene or furan substitutions fused through an imine linkage and evaluate the compounds for their antitubercular activity.

**MATERIALS AND METHODS:** Melting points were measured in open capillary tubes and are uncorrected. IR (KBR) spectra were recorded in film or in potassium bromide disks on a Perkin-Elmer 39 spectrophotometer (υ max in cm-1) and 1H NMR spectra on a DPX 300 MHz Bruker FT-NMR spectrophotometer. The chemical shifts were reported as parts per million (δ ppm) tetramethyl silane (TMS) as internal standard.

Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive). Elemental analysis was performed on a Perkin–Elmer 2400 C, H, N analyzer. The progress of the reaction was monitored on a readymade silica gel plates (Merck) using n-hexane: ethyl acetate as a solvent system. Spectral data (IR, $^1$HNMR and Mass spectra) confirmed the structure of the synthesized compounds and the purity of these compounds were ascertained by microanalysis.

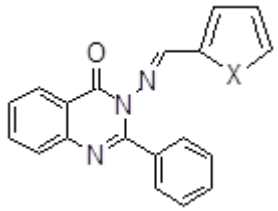
**Procedure:**

**Synthesis of 2-aryl-4*H*-3, 1-benzoxazin-4-one (1) and 3-amino-2-phenyl quinazolin-4(3*H*)-one (2):** These compounds were synthesized by following the reported procedure [15].

**Synthesis of 2-aryl-3-(thiophen-2-ylmethyleneamino) quinazolin-4(3*H*)-one:** 3-Amino-2-substitutedphenyl quinazolin-4(3H)-one (0.008mole) was taken in a round bottomed flask containing absolute alcohol. Thiophene-2-carboxaldehyde (0.008mole) was added and the reaction mixture was refluxed with a catalytic amount of conc. $H_2SO_4$ for 5h. The contents were poured into a beaker containing crushed ice; the solid obtained was filtered, washed with water and recrystallized from ethanol.

All the compounds of the series were synthesized by following the above procedure. The physical and the spectral data of the synthesized compounds are given in **Table 1 and 2** respectively.

**TABLE 1: PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS**




| Comp. Code | R | X | Colour | Mol formula | Mol.wt | m.p °C | % yield | $R_f$* |
|---|---|---|---|---|---|---|---|---|
| SRN 1 | H | S | cream | $C_{19}H_{13}N_3OS$ | 331 | 143-147 | 33.33 | 0.82 |
| SRN 2 | 2-Cl | S | brown | $C_{19}H_{12}ClN_3OS$ | 365 | 100-105 | 15.38 | 0.60 |
| SRN 3 | 4-Cl | S | cream | $C_{19}H_{12}ClN_3OS$ | 365 | 145-148 | 30.00 | 0.70 |
| SRN 4 | 4-$CH_3$ | S | cream | $C_20H_{15}N_3OS$ | 345 | 145-147 | 22.23 | 0.70 |
| SRN 5 | 2-$CH_3$ | S | brown | $C_{20}H_{15}N_3OS$ | 345 | 120-123 | 41.66 | 0.83 |
| SRN 6 | H | O | white | $C_{20}H_{15}N_3O2$ | 329 | 180-185 | 38.50 | 0.41 |
| SRN 7 | 2-Cl | O | brown | $C_{20}H_{14}ClN_3O_2$ | 363 | 195-200 | 18.72 | 0.57 |
| SRN 8 | 4-Cl | O | cream | $C_{20}H_{14}ClN_3O_2$ | 363 | 190-195 | 52.63 | 0.63 |
| SRN 9 | 4-$CH_3$ | O | brown | $C_{21}H_{17}N_3O_2$ | 343 | 155-160 | 30.76 | 0.60 |
| SRN 10 | 2-$CH_3$ | O | brown | $C_{21}H17N_3O_2$ | 343 | 150-153 | 34.24 | 0.60 |

***** TLC Solvent - *n* Hexane: Ethyl acetate = 1:1

**TABLE 2: SPECTRAL DATA OF THE SYNTHESIZED COMPOUNDS**

| Comp Code | Compound | UV ($\lambda_{max}$) | IR (KBr)$cm^{-1}$/$^1$H NMR ($CDCl_3$, δ) |
|---|---|---|---|
| SRN 1 | 2-Phenyl-3-(thiophen-2-ylmethyleneamino)quinazolin-4(3*H*)-one | 298 | 3103 Ar CH str, 1679 CO str/ 9.25 s,1H, N=CH, 7.43-8.38 m,9H, ArH, 7.26-7.43 m,3H, ArH of thiophene |
| SRN 2 | 2-(2-Chlorophenyl)-3-(thiophen-2-ylmethyleneamino)quinazolin-4(3*H*)-one | 330 | 3115 Ar CH str, 1654 CO str, Ar C=C str 1570 |
| SRN 3 | 2-(4-Chlorophenyl)-3-(thiophen-2-ylmethyleneamino)quinazolin-4(3*H*)-one | 237 | 3054 Ar CH str, 1673 CO str, 1590 Ar C=C str |
| SRN 4 | 3-(Thiophen-2-ylmethyleneamino)-2-4 -tolylquinazolin-4(3*H*)-one | 303 | 3220 Ar CH str, 1684 CO str, 1591 Ar C=C str |
| SRN 5 | 3-(Thiophen-2-ylmethyleneamino)-2-2-tolylquinazolin-4(3*H*)-one | 331 | 3024 Ar CH str, 1672 CO str, 1596 Ar C=C str |
| SRN 6 | 3-(1-(Furan-2-yl)ethylideneamino)-2-phenylquinazolin-4(3*H*)-one | 282 | 3214 Ar CH str, 1661 CO str/ 7.52-8.34 m,9H,ArH, 7.26-7.50 m,3H, ArH of furan, 1.63 s,3H,$CH_3$ |
| SRN 7 | 2-(2-Chlorophenyl)-3-(1-(furan-2-yl)ethylideneamino)quinazolin-4(3*H*)-one | 284 | 3140 Ar CH str, 1678 CO str, |
| SRN 8 | 2-(4-Chlorophenyl)-3-(1-(furan-2-yl)ethylidene amino)quinazolin-4(3*H*)-one | 232 | 3214 Ar CH str, 1654 CO str, |
| SRN 9 | 3-(1-(Furan-2-yl)ethylideneamino)-2-4-tolylquinazolin-4(3*H*)-one | 271 | 3115 Ar CH str, 1682 CO str, |
| SRN 10 | 3-(1-(Furan-2-yl)ethylideneamino)-2-2-tolylquinazolin-4(3*H*)-one | 284 | 3273 Ar CH str, 1659 CO str, |

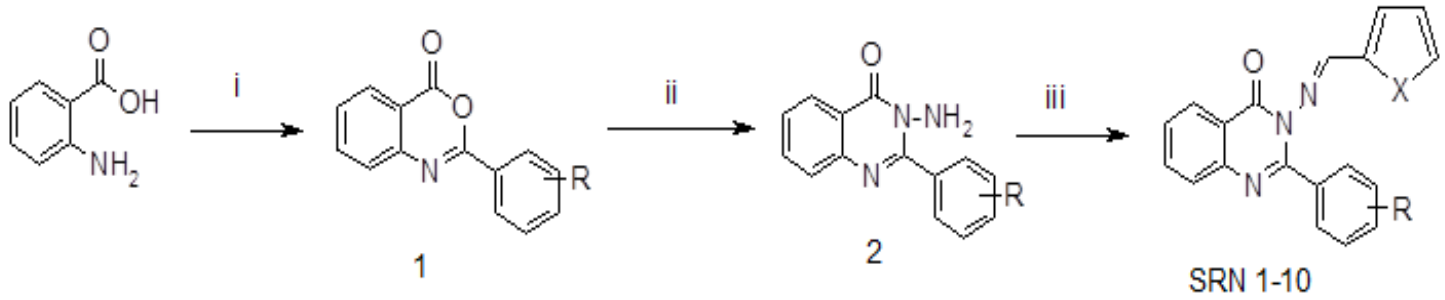



**FIGURE 1: SCHEME OF SYNTHESIS, (I) VARIOUS SUBSTITUTED ARYL ACID CHLORIDES, (II) HYDRAZINE HYDRATE, (III) THIOPHENE 2-CARBOXALDEHYDE/FURAN 2- CARBOXALDEHYDE**

**Antitubercular Activity:** The antitubercular activity [16] of compounds evaluated against *M. tuberculosis* 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 minimize 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 37°C for five days. After the specified period, 25µl of freshly prepared 1:1 mixture of Almar 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 was defined as lowest drug concentration which prevented the color change from blue to pink.

**TABLE 3: ANTITUBERCULAR ACTIVITY OF SYNTHESIZED COMPOUNDS**

| Comp. Code | Concentration in µg/ml | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 100 | 50 | 25 | 12.5 | 6.25 | 3.125 | 1.6 | 0.8 | 0.4 | 0.2 |
| SRN 1 | S | S | R | R | R | R | R | R | R | R |
| SRN 2 | S | S | S | S | S | S | R | R | R | R |
| SRN 3 | S | S | S | S | R | R | R | R | R | R |
| SRN 4 | S | S | S | S | R | R | R | R | R | R |
| SRN 5 | S | S | S | R | R | R | R | R | R | R |
| SRN 6 | S | S | R | R | R | R | R | R | R | R |
| SRN 7 | S | R | R | R | R | R | R | R | R | R |
| SRN 8 | S | S | S | R | R | R | R | R | R | R |
| SRN 9 | S | S | S | S | R | R | R | R | R | R |
| SRN 10 | S | S | R | R | R | R | R | R | R | R |

*S=Sensitive, R=Resistant

**RESULTS & DISCUSSION:** The compounds SRN 3, 4 and 9 possessing 4-chloro, 4-methyl substitution and thiophene side chain linked to quinazolinone moiety through imine group have shown activity at a concentration of 12.5 µg/ml, while other derivatives have shown activity above 50 µg/ml. the compound SRN2 which possess 2-chlorophenyl substitution at 2$^{nd}$ position of quinazolinne moiety and has thiophene ring system in the side chain has shown significant activity (3.125 µg/ml), highlighting the effect of substitutions on the quinazolinone moiety for their biological property. Hence these compounds shall be exploited further for their antitubercular activity to attain a potential pharmacophore.

**ACKNOWLEDGEMENT:** The authors wish to thank Prof. B.G. Shivananda, Principal, Al-Ameen College of Pharmacy, Bangalore, for encouraging and providing facility to carry out the research work and Dr.Venugopal, Astra Zeneca, Bangalore for providing the spectral data. Dr Kishore G Bhat, Professor Department of Biotechnology, MM'S Halgekar Institute of Dental Sciences and Research Centre, Belgaum for screening the synthesized compounds for antitubercular activity.

**REFERENCES**:

1. Vashi RT, Shelat CD, Patel H.Synthesis and antifungal activity of 6-bromo-2[(4-(2, 3- dichlorophenyl)) piperazine-1-yl)methyl]-3-[8-hydroxy quinoline -5-yl]-3-quinazolin-4-one ligand and its transition metal chelates . IJABPT 2010; 1:883.
2. Rajput CS, Kumar S, Kumar A. Synthesis and antifungal activity of substituted quinazolinones. Int J Chem Tech Res 2010; 2(3):1653.
3. Mosaad SM, Mohammed KI, Ahmed MA, Hamide SGA. Synthesis of certain new iodoquinazolines as poiential antitubercular agents. J App Sci 2004;4(2):302.
4. Kiruthiga B, Ilango K, Valentina P, Umarani N, Patel R. Synthesis of some new 2-substituted quinazolin-4-one derivatives and their biological activties. Int J Pharm Tech Res. 2009; 1(4):1503
5. Rajasekaran S, Rao GK, Pai S, Virya GK, Sodhi GS. Synthesis and *in vitro* study of biological activity of 2,3-substituted quinazolin-4(3*H*)-ones. J Chem Pharm Res. 2010; 2(2):462.
6. Laddha SS, Bhatnagar SP. Novel Fused quinazolinones: Further studies on the anticonvulsant activity of 1, 2, 9, 11 tetra substituted-7*H*-thieno[2', 3': 4, 5]pyrimido[6, 1-b]- quinazolin-7-one and 1, 3, 10, 12-tetrasubstituted-8*H*-pyrido[2', 3': 4, 5]pyrimido[6,1-b]quinazolin-8-one. ECSOC-13 2009.
7. Levin JI, Venkatesan AM, Bailey TK, Vice G and Coupet J. 6-Substituted Quinazolinone Anglotensin II Receptor Antagonists. Bioorg Med Chem. 1994; 4(15): 1819-24.
8. Ahmed K, Ramana KV, Ankati HB and Ramana AV. Mild and efficient reduction of azides to amines: synthesis of fused [2,1-*b*]quinazolinones. Tetrahedron Lett.2002; 43: 6863.
9. Pandey SK, Singh A, Nizamuddin. Antimicrobial studies of some novel quinazolinones fused with [1,2,4]-triazole, [1,2,4]-triazine and [1,2,4,5]-tetrazine rings. Eur J Med Chem. 2008; xx: 1-10.
10. Sridhar SK, Sarvanan M, Ramesh A. Synthesis and antibacterial screening of hydrazones, Schiff and Mannich bases of isatin derivatives. Eur J Med Chem.2001; 36(7): 615-25.
11. Panneerselvam P, Nair RR, Vijayalakshmi, Subramanian E.H, Sridhar S.K. Synthesis of Schiff bases of 4-(4-aminophenyl)-morpholine as potential antimicrobial agents. Eur J Med Chem. 2005; 40(2):225-9.
12. Gacche RN, Gond DS, Dhole NA. Coumarin Schiff-bases: as antioxidant and possibly anti-inflammatory agents. J Enzyme Inhib Med Chem. 2006; 21(2):157-61.
13. Dao VT, Dowd MK, Martin MT, Mayer M. Cytotoxicity of enantiomers of gossypol Schiff's bases and optical stability of gossypolone. Eur J Med Chem. 2004; 39(7):619-24.
14. Sridhar SK, Pandeya SN, Stables JP, Ramesh A. Anticonvulsant activity of hydrazones, Schiff and Mannich bases of isatin derivatives. Eur J Pharm Sci. 2002; 16(3):129-32.
15. N R Manjunatha; P Thampi; P M Gurubasavarajaswamy; D Sriram D. *Chem.Pharm.Bull*, **2007**, 55 (11), 1615.
16. Lourenco MCS, DeSouza MVN, Pinheiro AC, Ferreira ML, Rasnisb B, Goncalves, et al., Evaluation of anti-tubercular activity of nicotinic and isoniazid analogues. ARKIVOC2007; (xv):181.

**How to cite this article**:
Rajasekaran S, Rao G and Niranjan HS: Synthesis and Antitubercular Activity of Some Substituted 2, 3-Substituted Quinazolinone Analogs. *Int J Pharm Sci Res*. 3(11); 4394-4397.