



Synthesis of novel 4-oxo-N-(4-oxo-3-substituted-3,4-dihydroquinazolin-2-yl amino)-2-phenylquinazoline-3(4H)-carboxamidines as AntiHIV, antitubercular and antibacterial agents

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ABSTRACT

A series of novel 4-oxo-N-(4-oxo-3-substituted-3,4-dihydroquinazolin-2-yl amino)-2-phenylquinazoline-3(4H)-carboxamidines are prepared from methyl 4-oxo-2-phenylquinazoline-3(4H)-carbthioimidate & 3-(substituted)-2-hydrazino-quinazoline-4(3H)-ones. The starting material 4-oxo-2-phenylquinazoline-3(4H)-carbthioimidates were prepared from anthranilic acid while the 3-(substituted)-2-hydrazino-quinazolin-4(3H)-one was prepared from a range of 1° amines using multistep preparation. Entire synthesized analogues were screened for their antitubercular, anti-HIV and antibacterial activity. Among the series, N-(3-(4-nitrophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl amino)-4-oxo-2-phenylquinazoline-3(4H)-carboxamidine (BQC7) and N-(3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl amino)-4-oxo-2-phenylquinazoline-3(4H)-carboxamidine (BQC9) showed most potent activity against *S. epidermidis*, *S. aureus* & *B. subtilis* with the MIC of 3 µg/mL. The compound BQC7 displayed the antitubercular potency at 12.5 µg/mL and anti-HIV activity at 8.53 µg/mL against HIV1 and HIV2. Thus, these derivatives are useful in the development of novel antitubercular & antiHIV agents. The results obtained from this study confirm that the synthesized and biologically evaluated quinazolines showed promising antimicrobial, antitubercular and anti-HIV activities and are new scaffolds for antimicrobial activity.



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INTRODUCTION

Tuberculosis (TB) is an opportunistic infection that occurs more frequent/stern in weakened immune system peoples compared to healthy immune system peoples. The immune system is weakened & risk of TB is increased by human immunodeficiency virus (HIV). For control of TB, co-infection of TB along with HIV creates a terrific defy, mainly in resource-limited treatment option. In 2015, it was estimated 1,04,00,000 TB cases, among that 11 % (12,00,000) people living with HIV & from HIV-associated TB 4,56,000 death was predicted (WHO, 2018; Reid and Shah, 2009; WHO, 2019). Although exhaustive efforts to prevent

and treat TB is taken, the problem still continues due to multi-drug-resistant (MDR-TB) to isoniazid, rifampicin, quinolones and aminoglycosides. Recently TB threat has an additional challenge with the appearance of MDR-TB & extensively drug resistant TB (XDR-TB) strains. It obviously highlights the vital need to develop new "druggable" molecules for the co-infection treatment and strains of MDR-TB and XDR-TB. Recent year's quinazoline derivatives & its condensed analogs gained much interest to medicinal chemists and pharmacologist because of its potential druggable behavior (Alagarsamy *et al.*, 2018). Amongst that antimicrobial activity of 2,3-disubstituted quinazolines are encouraging for further development. Recent literature is evident that the 2,3-disubstituted quinazolines nucleus displayed significant antitubercular potency (Alagarsamy *et al.*, 2018; Hameed *et al.*, 2018). Quinazolines and bisquinazolines have been explored for various medicinal chemistry properties due to their widespread pharmacological activities including antineoplastic, antimycobacterial, antibacterial, antifungal, antiviral, and antimalarial. In recent literature, many quinazoline derived compounds were prepared and screened for its antimicrobial activity. The current uses of these agents in bacterial and viral infections have led to the development of novel antiHIV, antibacterial and antitubercular agents (Saripinar *et al.*, 1996; Pandeya *et al.*, 2005; Karali *et al.*, 2007; Turan-Zitouni *et al.*, 2008; Srimam *et al.*, 2006, 2009). In this study, using the quinazoline scaffold we developed 4-oxo-N-(4-oxo-3-substituted-3,4-dihydroquinazolin-2-ylamino)-2-phenylquinazoline-3(4H)-carboxamidines from 3-(substituted)-2-hydrazino-quinazoline-4(3H)-ones & methyl 4-oxo-2-phenylquinazoline-3(4H)-carbthioimide as potent antiHIV, antitubercular & antibacterial agents based on pharmacophore approach. In this approach, a molecule was created by merging two quinazolines called as bisquinazolines. The active site of targets may be addressed by this pharmacophore, which increased the opportunity for selectivity. In addition, it also expected to reduce the undesirable side effects.

MATERIALS AND METHODS

Melting points (mp) were measured in open capillaries using Thomas Hoover melting point apparatus (Thomas Hoover, USA) & are uncorrected. Using KBr disks on Bruker FT-IR spectrometer (Bruker, USA) the IR spectrum (ν , cm^{-1}) was documented. At 300 MHz in CDCl_3 , the ^1H -NMR spectra were recorded using Bruker FT-NMR spectrometer (Bruker, USA) using tetramethylsilane (TMS) as an internal standard as parts per million (δ , ppm)

the chemical shifts are reported. Using FAB (fast atom bombardment), positive mass spectra were obtained on a JEOL SX 102 instrument (JEOL, Japan). Perkin Elmer's (USA) 2400 CHN analyzer was used to perform elemental analysis estimation. Using Merck, Norway, readymade silica gel plates, the progress of the product formation were observed. The entire reagents & chemicals employed in this work were used without further purification & were obtained from Merck, Spectrochem (India) or Lancaster (USA), or SD fine chemicals, & Aldrich (USA).

Procedure for the synthesis of compounds

Preparation of 2-phenyl-3,1-benzoxazin-4-one (1)

14.05 g (0.2 mol) of benzoyl chloride were mixed to a mixture of 13.7 g of anthranilic acid (0.1 mol) dissolved in pyridine (60 ml). The obtained solutions were stirred for a 30 min period & added 15 ml of 5 % NaHCO_3 . The products separated were crystallized from alcohol. Yield: 81%; mp: 120-121 °C. Reported 120 °C (Hogale and Deshmukh, 1995).

4-Oxo-2-phenylquinazoline-3(4H)-carbthioamide (2)

A solution of 0.01 mole 2-phenyl-3,1-benzoxazine-4-one (1) and 0.10 mole thiourea in dry pyridine was refluxed for ten h. Then the mixtures were kept at room temperature to cool & transferred in to ice (crushed) containing dilute HCl. The product formed was filtered, washed with water, dried and recrystallised using acetic acid. Yield: 81%; mp: 190-191 oC; IR (KBr) cm^{-1} : 3342 & 3276 (NH), 3089 (Ar-CH), 1721 (C=O), 1640 (C=N), 1617 (C=C), 1254 (C=S); ^1H NMR (CDCl_3) d: 7.15-8.29 (m, 9H, Ar-H), 9.02 (s, 2H, CSNH₂); MS (m/z): 281 [M⁺]; Anal. Calcd. for $\text{C}_{15}\text{H}_{11}\text{N}_3\text{OS}$: C, 64.04; H, 3.94; N, 14.94. Found: C, 64.26; H, 3.93; N, 14.89.

Preparation of methyl 4-oxo-2-phenylquinazoline-3(4H)-carbthioimide (3)

The compound 2 (mole) was dissolved in 0.01 mole alcoholic NaOH. To the above solution with stirring drop wise dimethyl sulphate was added. Continuously stirred for 3 h & added in to water (ice cold). The solid separated were filtered, dried and recrystallised using alcohol. Yield: 83%; mp: 178-180 oC; IR (KBr) cm^{-1} : 3308 (NH), 3053 (Ar-CH), 2946 (CH_3 -CH), 1731 (C=O), 1655 (C=N), 1602 (C=C); ^1H NMR (CDCl_3) d: 1.85 (s, 3H, SCH_3), 6.82-8.08 (m, 9H, Ar-H), 9.64 (s, 1H, C=NH); MS (m/z): 295 [M⁺]; Anal. Calcd. for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{OS}$: C, 65.06; H, 4.44; N, 14.23. Found: C, 64.83; H, 4.46; N, 14.28.

Preparation of 2-hydrazino-3-substituted-3H-quinazolin-4-one (4)

It was prepared by adopting our earlier reported methods (Alagarsamy *et al.*, 2005).

Preparation of 4-Oxo-N-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl amino)-2-phenylquinazoline-3(4H)-carboxamide (BQC1)

A solution of 0.01 mole 3-(phenyl)-2-hydrazinoquinazolin-4(3H)-one (**4**) & 0.01 mole 3-(methylthiocarbamido)-2-phenylquinazolin-4(3H)-one (**3**) was mixed with dimethyl formamide. The obtained mixture was then refluxed for 16 h & added into ice (crushed). The solid formed was filtered washed with water, dried and recrystallized to obtain the title derivative. Yield: 80%; mp: 205-206 °C; IR (KBr) cm⁻¹: 3375, 3314 & 3279 (NH), 3051 (Ar-CH), 1727 (C=O), 1650 (C=N), 1602 (C=C); ¹H NMR (CDCl₃) δ: 2.54 (s, 1H, NHNH), 5.69 (s, 1H, Ar-NH), 7.13-8.37 (m, 18H, Ar-H), 9.21 (s, 1H, C=NH); MS (*m/z*): 499 [M⁺]; Anal. Calcd. for C₂₉H₂₁N₇O₂: C, 69.73; H, 4.24; N, 19.63. Found: C, 70.00; H, 4.22; N, 19.56. Adopting this procedure compounds BQC2- BQC10 were prepared.

Pharmacology

Antitubercular activity

Into 7H11 agar slants (Middle brook) every investigated drug/compound (10 fold serial dilutions) were incorporated with OADC growth supplement. OADC growth supplement in fresh Middle brook 7H11 agar slants was used to prepare inoculums of *M. tuberculosis* H37R_V. Approximately 10⁷ cfu/mL concentrate *M. tuberculosis* was prepared by final dilution to 10⁻² using 0.05 % W/V Tween 80 saline (1 mg/ml). The bacterial suspension (5 μl) was spotted per ml of the drug (10 fold serial dilutions) in 7H11 agar tubes. At 37 °C the tubes were incubated, and after 28 days the final readings were recorded. Medium alone incubated control tubes with H37RV were used to compare tubes having the compounds. Active concentration of test compound was taken from entire colonies inhibition concentration. The minimum concentration of drug necessary to inhibit bacterial growth completely was taken as MIC (Kuneš *et al.*, 2000; Sriram *et al.*, 2006; Shanmugavelan *et al.*, 2011). The MIC of reference drug isoniazid, rifampicin and ethambutol were compared with test derivatives.

AntiHIV activity

In MT-4 cells against replication of HIV-1 (III B) & HIV-2 (ROD), anti-HIV potencies of test analogs (BQC1-BQC10) was examined (Pauwels *et al.*, 1987). The MT-4 cells were supplemented with 10% v/v fetal calf serum (heat-inactivated) & gentamicin (20 mg/ml; E. Merck, Darmstadt, Germany) & grown in

RPMI-1640 DM (Dutch modification) medium (Flow Laboratories, Irvine, Scotland). HIV-1 (III B) & HIV-2 (ROD) was obtained from the MT-4 cell lines (HIV-1 infected culture supernatant) and until use at -70 °C the virus stocks were stored. Anti-HIV assay was performed by microtiter plates by filling with 25 ml of drugs & 100 ml of medium (triplicate) in order to allow concurrent screening of its ability on infected cells. To the microtiter tray, either infected/mock-infected part HIV (50 ml) at 100 CCID₅₀ medium was added. In a 5 % CO₂ in air humidified atmosphere, the cell cultures were incubated at 37 °C. By the MTT method, after five days of infection, spectrophotometrically examined the viability of mock & HIV infected cells. Against the cytopathic effect, the successful concentration of drugs attaining 50 % protection of MT-4 cells (cell death/degeneration was takes place in culture caused by a virus, which can be examined microscopically). Certain pathological changes manifest the cell degeneration of HIV (EC₅₀) & the cytotoxic concentration of drugs, necessary to decrease the viability of ordinary uninfected MT-4 cells by 50% (CC₅₀) were estimated.

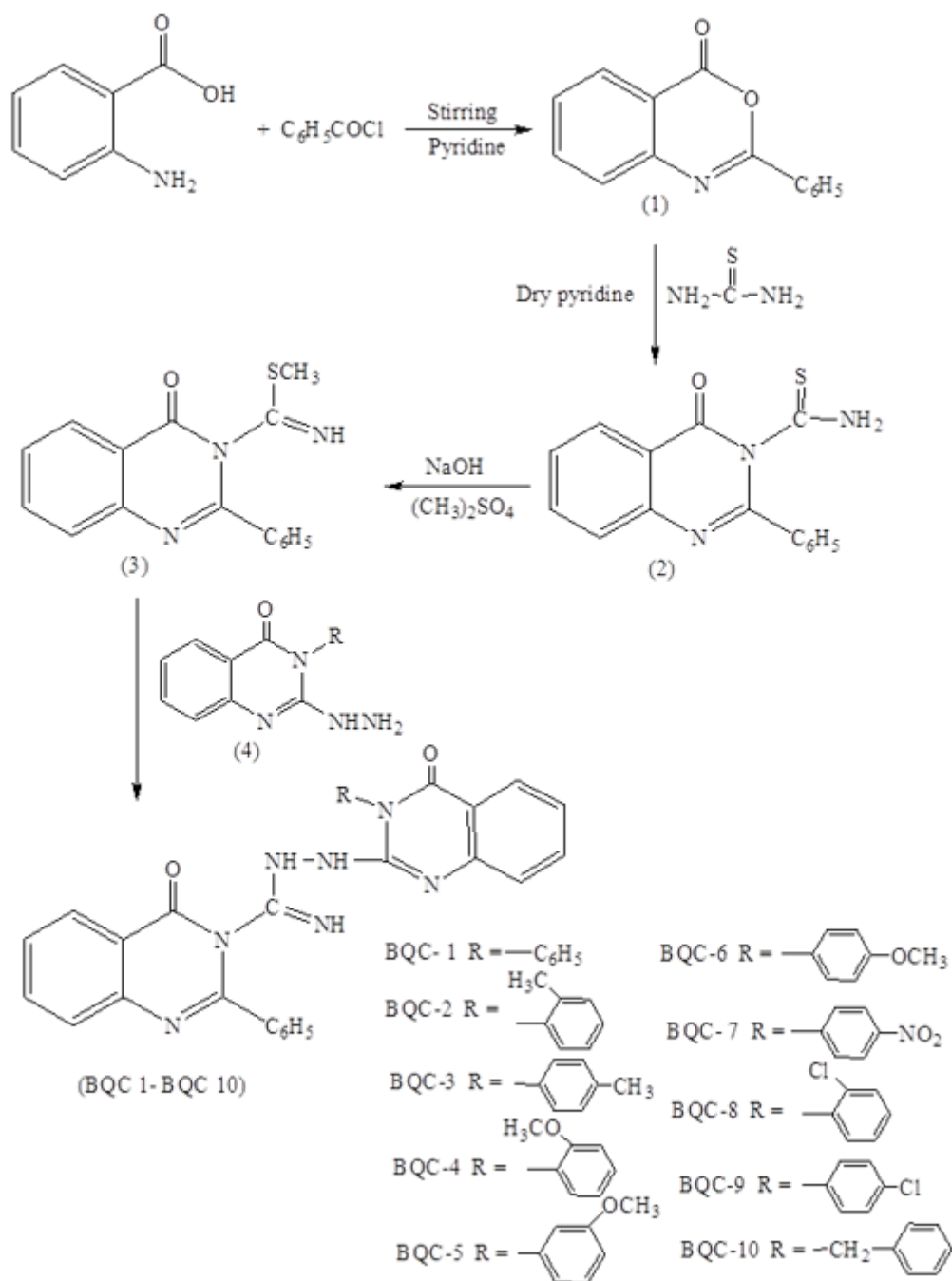
Antibacterial activity

Agar dilution technique was used to estimate the antibacterial activity of derivatives (Barry, 1991; Pandeya *et al.*, 1999). Procured the standard strains were from the ATCC (American type culture collection), Rockville, USA & the pathological strains were procured from the department of microbiology, MNR medical college, Sangareddy, India. The antibacterial potency of the prepared derivatives were tested against the below mentioned bacteria strains: *E. coli* ATCC 25922, *S. typhimurium* ATCC 33068, *B. subtilis* ATCC 6051, *K. pneumoniae* ATCC 13883, *P. vulgaris* ATCC 9484, *P. aeruginosa* ATCC 2853, *S. Aureus* ATCC25923, *M. Luteus* ATCC 10240, *S. Epidermidis* ATCC 35984 & *S. Albus* ATCC 17900. Hi-media Muller-Hinton Agar plates were used (37 °C, 24 h) for bacterial growth. On agar plates, the lowest concentration of drugs that totally inhibit the bacterial growth was considered as MIC, ignoring a faint haze / single colony caused by the inoculums. Ciprofloxacin was employed as a standard drug for comparing MIC of synthesized derivatives. MICs of standard & test drugs are tabulated in Table 1, which is estimated from as a minimum of 3 different experiments in duplicate.

RESULTS AND DISCUSSION

Chemistry

The 2-phenyl-3,1-benzoxazin-4-one (**1**) was prepared by treating a mixture of benzoyl chloride & anthranilic acid in pyridine. Compound 3-



Scheme 1: Synthesis of 4-oxo-N-(4-oxo-3-substituted-3,4-dihydroquinazolin-2-yl amino)-2-phenylquinazoline-3(4H)-carboxamides (BQC1- BQC 10)

thiocarbamido-2-phenyl quinazolin-4(3H)-ones (2) was obtained by treating a mixture of 2-phenyl-3-benzoxazin-4-one (1) & thiourea in dry pyridine. The compound methyl-4-oxo-2-phenylquinazoline-3(4H)-carbthioimide (3) was obtained by the methylation of compound 2 with dimethyl sulphate. The synthesis of thiomethyl derivative was pointed out by vanishing of thiocarbonyl moiety peak of compound 2 in IR & ^1H NMR spectrum of derivative 3. The title analogs 4-oxo-N-(4-oxo-3-

substituted-3,4-dihydroquinazolin-2-yl amino)-2-phenylquinazoline-3(4H)-carboxamide (BQC1-BQC10) were prepared from the reaction of methyl 4-oxo-2-phenylquinazoline-3(4H)-carbthioimide (3) & 3-(substituted)-2-hydrazinoquinazolin-4(3H)-ones (4), which in turn was synthesized from aniline. Formation of compounds BQC1-BQC10 was confirmed from the disappearance of $-\text{NH}_2$ peak in IR & ^1H NMR spectrum of the starting material. The IR & ^1H NMR spectrum of these derivatives

Table 1: Antitubercular, antiHIV and antibacterial activity of title compounds (BQC1- BQC10)

Microbes	MIC of test compounds/ Standards(mg/ml)										STD 1	STD 2	STD 3
	BQC	BQC:	BQC3	BQC4	BQC5	BQC6	BQC7	BQC8	BQC9	BQC10			
MTB	25	25	25	25	25	25	12.5	25	12.5	25	0.05	0.1	1.56
HIV-1	22.7758.55	100	44.76	50.82	50.79	8.53	13.30	13.24	100	0.0012	-	-	
HIV-2	22.7758.55	100	44.76	50.82	50.79	8.53	13.30	13.24	50	0.000642	-	-	
S. typhi	50	50	50	50	50	50	25	13	25	50	4	-	-
E. coli	6	50	25	25	25	25	6	13	6	50	1	-	-
B. subtilis	25	25	50	50	25	50	3	50	3	00	1	-	-
K. pneumoniae	13	50	100	25	50	25	25	25	25	50	1	-	-
P. vulgaris	25	50	50	25	25	25	13	25	25	50	1	-	-
P. aeruginosa	13	50	100	25	25	50	6	13	13	100	1	-	-
S. aureus	6	25	100	13	13	50	3	13	3	100	1	-	-
M. luteus	6	25	50	25	50	25	6	50	6	25	1	-	-
S. epidermidis	25	50	50	13	25	25	3	13	3	100	1	-	-
S. albus	50	50	50	50	50	13	25	13	25	100	1	-	-

Antitubercular standard: STD 1 - Isoniazid, STD 2 - Rifampicin, STD 3 - Ethambutol; Anti-HIV standard: STD 1 - AZT; Antibacterial standard: STD 1 - Ciprofloxacin; "-":Not applicable

displayed the presence of NH, carbthioimidate, aryl & carbonyl (C=O) moieties peak. Corresponding to their molecular formula, the mass spectra of the title derivatives displayed molecular ion peaks. A common peak at m/z 144 in mass spectra of compounds BQC1 - BQC10 corresponds to the benzopyrimidine-4-one nucleus was emerged in all mass spectrums of the derivatives. A micro analyses value was found agreement with the theoretical values of the assigned structure.

Pharmacology

Antitubercular activity

Against *M. tuberculosis* (H37R_V strain) entire title derivatives was screened for its antimycobacterial (*in vitro*) activity. The MIC of all derivatives was determined to study its antitubercular potency & the obtained outcomes are presented in Table 1. Results indicated that the title derivatives inhibited the growth of *M. tuberculosis* at the minimum microgram of 12.5 to 25 $\mu\text{g}/\text{mL}$ concentration. Among the title derivatives, BQC7 and BQC9 displayed the most potent antitubercular activity at 12.5 $\mu\text{g}/\text{mL}$ concentration.

Anti-HIV activity

The anti-HIV activity results (Table 1) indicated entire derivatives displayed mild to moderate anti-HIV activity; whereas compounds BQC7 containing aryl ring with electron-withdrawing group exhibited potent anti-HIV activity at 8.53 $\mu\text{g}/\text{mL}$ concentration against HIV1 and HIV2. While the test compounds with other substituent's showed mild to moderate anti-HIV activity against HIV1 and HIV2.

Antibacterial activity

Out of various substituents tested at N-3 of quinoxaline, compared to aliphatic & cyclic substituents, aryl & heteroaryl substituents showed superior activity. Similarly, compared to analogs having unsubstituted or electron-donating moiety, analogs possessing electron-withdrawing moiety like chloro and nitro on aryl ring displayed superior activity. Among the series, N-(3-(4-nitrophenyl)-4-oxo-3,4-dihydroquinazolin-2-ylamino)-4-oxo-2-phenylquinazoline-3(4H)-carboxamide (BQC7) and N-(3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl amino)-4-oxo-2-phenylquinazoline-3(4H)-carboxamide (BQC9)

displayed very good potency against *S. epidermidis*, *S. aureus* & *B. subtilis* with a MIC of 3 µg/mL. Derivatives BQC7 and BQC9 came out as the lead derivative of this sequence.

CONCLUSION

A series of novel 4-oxo-N-(4-oxo-3-substituted-3,4-dihydroquinazolin-2-yl amino)-2-phenylquinazoline-3(4H)-carboxamides have been synthesized. Test compounds have displayed significant antibacterial potency against a variety of gram "+"ve & "-"ve bacteria including *M. tuberculosis*; and significant activity against HIV1 and HIV2 strains. Among the series, N-(3-(4-nitrophenyl)-4-oxo-3,4-dihydroquinazolin-2-ylamino)-4-oxo-2-phenylquinazoline-3(4H)-carboxamide (BQC7) and N-(3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-ylamino)-4-oxo-2-phenylquinazoline-3(4H)-carboxamide (BQC9) shown most potent activity against *S. epidermidis*, *S. aureus* & *B. subtilis* with the MIC of 3 µg/mL. The compound BQC7 displayed the antitubercular potency at 12.5 µg/mL and anti-HIV activity at 8.53 µg/mL against HIV1 and HIV2 and they can act as a lead for future development of novel antitubercular and anti-HIV drugs.

REFERENCES

- Alagarsamy, V., Chitra, K., Saravanan, G., Solomon, V. R., Sulthana, M. T. 2018. An overview of quinazolines: Pharmacological significance and recent developments. *European Journal of Medicinal Chemistry*, 151:628–685.
- Alagarsamy, V., Giridhar, R., Yadav, M. R. 2005. Synthesis and pharmacological investigation of novel 1-substituted-4-phenyl-1,2,4-triazolo[4,3-a]quinazolin-5(4H)-ones as a new class of H1-antihistaminic agents. *Bioorganic & Medicinal Chemistry Letters*, 15(7):1877–1880.
- Barry, A. 1991. Antibiotics in Laboratory Medicine. volume 1. William and Wilkins, Baltimore, MD.
- Hameed, A., Al-Rashida, M., Uroos, M., Ali, S. A., Arshia, M. I. 2018. Quinazoline and quinazolinone as important medicinal scaffolds: a comparative patent review. *Expert Opinion on Therapeutic Patents*, 28(4):281–297.
- Hogale, M. B. D., Deshmukh, D. S. 1995. Synthesis and biological activity of some new quinazolinyl thiazolidinones and azetidiones. *Journal of the Indian Chemical Society*, 72(12):847–848.
- Karali, N., Gürsoy, A., Kandemirli, F., Shvets, N., Kaynak, F. B. 2007. Synthesis and structure-antituberculosis activity relationship of 1H-indole-2,3-dione derivatives. *Bioorganic & Medicinal Chemistry*, 15(17):5888–5904.
- Kuneš, J., Bažant, J., Pour, M., Waisser, K., Šlosárek, M. 2000. Quinazoline derivatives with antitubercular activity. *Il Farmaco*, 55(11–12):725–729.
- Pandeya, S., Sriram, D., Nath, G., De Clercq, E. 1999. Synthesis and antimicrobial activity of Schiff and Mannich bases of isatin and its derivatives with pyrimidine. *Il Farmaco*, 54(9):624–628.
- Pandeya, S. N., Smitha, S., Jyoti, M., Sridhar, S. K. 2005. Biological activities of isatin and its derivatives. *Acta Pharmaceutica*, 55:27–46.
- Pauwels, R., De Clercq, E., Desmyter, J., Balzarini, J., Goubau, P. 1987. Sensitive and rapid assay on MT-4 cells for detection of antiviral compounds against the AIDS virus. *Journal of Virological Methods*, 16:171–185.
- Reid, M. J., Shah, N. S. 2009. Approaches to tuberculosis screening and diagnosis in people with HIV in resource-limited settings. *The Lancet Infectious Diseases*, 9(3):173–184.
- Saripinar, E., Guzel, Y., Patat, S., Yildirim, I., Akçamur, Y. 1996. Electron-topological investigation of structure-antitubercular activity relationship of thiosemicarbazone derivatives. *Arzneimittel-Forschung*, 46(8):824–828.
- Shanmugavelan, P., Nagarajan, S., Sathishkumar, M., Ponnuswamy, A., Yogeewari, P. 2011. Efficient synthesis and in vitro antitubercular activity of 1,2,3-triazoles as inhibitors of Mycobacterium tuberculosis. *Bioorganic & Medicinal Chemistry Letters*, 21(24):7273–7276.
- Sriram, D., Yogeewari, P., Dhakla, P., Senthilkumar, P., Banerjee, D. 2009. 5-Nitrofuranyl derivatives: Synthesis and inhibitory activities against growing and dormant mycobacterium species. *Bioorganic & Medicinal Chemistry Letters*, 19(4):1152–1154.
- Sriram, D., Yogeewari, P., Thirumurugan, R., Pavana, R. K. 2006. Discovery of New Antitubercular Oxazolyl Thiosemicarbazones. *Journal of Medicinal Chemistry*, 49(12):3448–3450.
- Turan-Zitouni, G., Özdemir, A., Kaplancikli, Z. A., Benkli, K., Chevallet, P. 2008. Synthesis and antituberculosis activity of new thiazolylhydrazones derivatives. *European Journal of Medicinal Chemistry*, 43(5):981–985.
- WHO 2018. Global Tuberculosis Report 2018 World Health Organization.
- WHO 2019. Tuberculosis. 17.