



## AntiHIV, antitubercular and antibacterial activities of novel 1-substituted-3-(3-(4-methylphenyl)-4-oxo-3,4-dihydrobenzo pyrimidin-2-yl amino) isothioureas

Narendhar B<sup>1</sup>, Chitra K<sup>2</sup>, Alagarsamy V\*<sup>1</sup>

<sup>1</sup>Medicinal Chemistry Research Laboratory, MNR College of Pharmacy, Sangareddy, Hyderabad-502 294, Telangana, India

<sup>2</sup>Faculty of Pharmacy, Sri Ramachandra Institute of Higher education and Research (Deemed to be University), Porur, Chennai-600 116, Tamil Nadu, India



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### ABSTRACT

In this research, substituted thiosemicarbazide group was placed at 2<sup>nd</sup> position & 4-methylphenyl group was placed at 3<sup>rd</sup> position of condensed pyrimidine nucleus. Entire prepared title analogues were examined for its antibacterial, antitubercular, & anti HIV activities against selected bacteria & virus. The target compounds 1-substituted-3-(3-(4-methylphenyl)-4-oxo-3,4-dihydrobenzopyrimidin-2-yl amino)isothioureas (TTS01 – TTS10) were synthesized from 2-hydrazino-3-(4-methylphenyl)benzopyrimidin-4(3H)-one (5) by reacting with various alkyl/aryl isothiocyanates followed by methylation with dimethyl sulphate. Among the test compounds, 2-methyl-3-(3-(4-methylphenyl)-4-oxo-3,4-dihydrobenzopyrimidin-2-yl amino)-1-(3-chlorophenyl) isothiourea (TTS09) and 2-methyl-3-(3-(4-methylphenyl)-4-oxo-3,4-dihydrobenzopyrimidin-2-yl amino)-1-(4-nitrophenyl) isothiourea (TTS06) shown most potent activity against *S. epidermidis*, *S. Aureus*, and *P. vulgaris* 3 µg/ml MIC. Compounds TTS06 & TTS09 exhibited the antitubercular activity with 12.5 µg/ml MIC and antiHIV activity at 9.06 and 8.56 µg/ml, respectively against HIV1 and HIV2. Thus for further optimization & development of novel antitubercular and antiHIV drugs, compounds TTS06 & TTS09 may act as a pilot derivative.

### \*Corresponding Author

Name: Alagarsamy V

Phone: 8500056663

Email: drvalagarsamy@gmail.com

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### INTRODUCTION

The immune system is weakened by HIV (human immunodeficiency virus) & it also boosts the TB

(Tuberculosis) risks. TB is an opportunistic infection that affects more frequently / severely weakened immune systems people. Principally in resource-limited treatment option, the major challenge to control TB was co-infection with HIV. In 2015, about 10.4 million cases of TB were reported, among that 11 %, i.e., 1.2 million people live with HIV. According to WHO about 4,56,000 deaths were reported HIV-associated TB (WHO, 2018; Balcha *et al.*, 2015; Reid and Shah, 2009; WHO, 2019). Due to multi-drug-resistant (MDR-TB) to isoniazid, rifampicin, quinolones and aminoglycoside, the problem of TB still continues. Recently TB threat has an additional challenge with the appearance of both MDR-TB & extensively drug-resistant TB (XDR-TB) strains. It obviously indicates the imperative need to develop new "druggable" molecules for

the co-infection treatment and strains of XDR-TB & MDR-TB.

Recent year's pyrimidines and condensed pyrimidines gained great attention of pharmaceutical chemists and pharmacologist because of its potential druggable behaviour (Alagarsamy *et al.*, 2018). Among that antimicrobial potencies of 2,3-disubstituted benzopyrimidines were encouraging for further development. Recent literature is evident that the 2,3-disubstituted benzopyrimidine nucleus displayed significant antitubercular activity (Figure 1), (Alagarsamy *et al.*, 2018; Hameed *et al.*, 2018).

Thiosemicarbazones have been explored for various medicinal chemistry properties due to their widespread pharmacological potencies like anti-malarial antibacterial, antifungal, antimycobacterial, antineoplastic & antiviral. Thiosemicarbazones bind great coordination with target sites because of its versatility due to nitrogen and sulfur atoms. Thiosemicarbazone was well known for its iron-chelating properties using the azomethine nitrogen & sulfur atoms. The most considered prospective pharmacological behaviour of thiosemicarbazone was complex formation with metal ions by nitrogen and sulfur atoms. Recently several thiosemicarbazone analogs have been prepared & screened for its antimicrobial activity. The recent role of these moieties in microbial infections has led to the development of new antimicrobial agents (Figure 1, (Saripinar *et al.*, 1996; Milczarska *et al.*, 1999; Pandeya *et al.*, 2005; Sriram *et al.*, 2005; Karali *et al.*, 2007; Turan-Zitouni *et al.*, 2008; Guzel *et al.*, 2008; Sriram *et al.*, 2009; Pavan *et al.*, 2010).

This research effort is a continuation of our aims on the way to develop potent antimicrobial & antitubercular agents using the benzopyrimidine scaffold by a pharmacophore hybrid approach (Figure 1), (Meunier, 2008; Alagarsamy *et al.*, 2016). In this research, substituted thiosemicarbazide group was placed at 2<sup>nd</sup> position & 4-methylphenyl group was placed at 3<sup>rd</sup> position of benzopyrimidine nucleus. Entire prepared title analogues were examined for its antibacterial, antitubercular & antiHIV activities against selected bacteria & virus.

## 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 ( $\nu$ ,  $\text{cm}^{-1}$ ) was documented. At 300 MHz in  $\text{CDCl}_3$ , the  $^1\text{H-NMR}$  spectra were recorded using Bruker FT-NMR spectrom-

eter (Bruker, USA) using tetramethylsilane (TMS) as an internal standard as parts per million ( $\delta$ , 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, ready made silica gel plates, the progresses 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

### Preparation of 3-(4-methylphenyl)-2-thioxo-2,3-dihydro benzopyrimidin-4-one (3)

A mixture of 0.02 mole 4-methylaniline (1) in 10 ml DMSO were stirred energetically. To the above mixture over a period of 30 min, 1.6 ml of carbon disulphide & 1.2 ml of 20 M aqueous NaOH were drop wise added. To this 0.02-mole dimethyl sulphate was added & continued the stirring further for 2 h in a freezing mixture. After 2 h period, the solution was added into water (ice cold) with stirring. The product mass separated was filtered, washed with water, dried and recrystallized from ethanol. Latter, 0.02 mole of the synthesized *N*-(4-methylphenyl)-methyl dithiocarbamic acid, 0.02 mole of methyl anthranilate (2) were added to 20 ml ethanol. To this mixture about 100 mg anhydrous  $\text{K}_2\text{CO}_3$  was mixed & for 22 h the resultant solution was refluxed. The resultant solutions were cooled by adding ice-cold water & the product obtained was filtered. The resultant product (3) was dissolved in 10 % alcoholic NaOH solution for purification & using dilute hydrochloric acid the compound (3) was re-precipitated. The product formed were filtered, washed with water, dried & recrystallized from alcohol. Yield: 75 %; mp: 303-305 °C (Reported 302-305 °C) (Alagarsamy and Murugesan, 2007).

### Preparation of 2-methylthio-3-(4-methylphenyl) benzopyrimidin-4-one (4)

0.01 mole of compound 3 was taken in a reaction vessel. The above solid was dissolved by using 25 ml alcoholic NaOH mixture. To the above solution, 0.01 mole  $(\text{CH}_3)_2\text{SO}_4$  was added with stirring dropwise. After complete addition of dimethyl sulphate for 1 h stirring was continued. Then to the ice-cold water containing beaker, the reaction mixture was transferred and mixed well. The product separated were filtered, washed with water, and dried. The obtained solids were purified by crystallisation using alcohol. Yield: 76 %; mp: 160-162 °C (Reported 160-162°C) (Alagarsamy and Murugesan, 2007).

**Table 1: Antitubercular, antiHIV & antibacterial potency of title derivatives (TTS01 - TTS10)**

Microbes	MIC of test compounds/Standard ( $\mu\text{g/ml}$ )											STD 1	STD 2	STD 3
	TTS-1	TTS-2	TTS-3	TTS-4	TTS-5	TTS-6	TTS-7	TTS-8	TTS-9	TTS-10	TTS-11			
MTB	25	25	25	25	25	12.5	25	25	12.5	25	0.05	0.1	1.56	
HIV-1	100	43.95	100	100	100	9.06	26.95	43.52	8.56	9.21	0.0012	-	-	
HIV-2	100	43.95	100	100	100	9.06	26.95	43.52	8.56	9.21	0.0006	42	-	
S. typhi	25	50	50	50	25	25	25	25	25	50	4	-	-	
E. coli	50	50	25	25	25	25	25	25	6	50	1	-	-	
B. subtilis	50	50	50	25	50	13	13	25	25	50	1	-	-	
K. pneumonia	50	50	50	25	25	25	25	25	6	25	1	-	-	
P. vulgaris	25	25	25	25	25	3	13	25	3	25	1	-	-	
P. aeruginosa	50	25	25	25	50	25	13	13	13	25	1	-	-	
S. aureus	50	25	50	25	13	3	25	13	3	50	1	-	-	
M. luteus	25	50	25	25	50	25	25	13	13	25	1	-	-	
S. epidermidis	50	13	13	13	13	3	25	25	3	25	1	-	-	
S. albus	25	13	25	25	25	25	25	25	13	25	1	-	-	

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

### Preparation of 2-hydrazino-3-(4-methylphenyl) benzopyrimidin-4-one (5)

Using 25 ml ethanol dissolved the 0.01 mole of compound 4. 0.1 moles of 99 % hydrazine hydrate & 100 mg potassium carbonate (anhydrous) were mixed to the above solution & refluxed for 33 h. To a room temperature, the obtained solution was cooled & mixed with well stirring into ice-cold water. The resultant product mass so obtained were filtered, washed with water, dried and recrystallized from alcohol to obtain the compound (5). Yield: 72 %; mp: 170-171 °C (Reported 170 °C (Alagarsamy and Murugesan, 2007)).

### Preparation of 4-methyl-1-(4-oxo-3-(4-methylphenyl)-3,4-dihydrobenzopyrimidin-2-yl)thiosemicarbazide (6A)

0.01 mole of compound 5, 0.01 mole of alkyl/ aryl isothiocyanate & 25 ml dioxan was taken in RBF & for the period of 6 h the mixture were refluxed. The resultant solutions were concentrated & the product separated was filtered, dried & recrystallised from dioxan. Yield: 78 %; mp: 191-192 °C; IR (KBr) cm<sup>-1</sup>: 3356, 3271 & 3224 (NH), 3019 (Ar-CH), 2982 (CH<sub>3</sub>-CH), 1730 (C=O), 1658 (C=N), 1615 (C=C), 1273 (C=S); <sup>1</sup>H NMR (CDCl<sub>3</sub>) d: 1.74 (s, 3H, CH<sub>3</sub>), 1.94 (s, 3H, CH<sub>3</sub>), 5.62 (s, 1H, Ar-NH), 7.18-8.20 (m, 8H, Ar-H), 8.73 (s, 1H, CSNH), 9.36 (s, 1H, CSNH); MS (m/z): 339 [M<sup>+</sup>]; Elemental analysis Calcd (C<sub>17</sub>H<sub>17</sub>N<sub>5</sub>OS): C, 60.16; H, 5.05; N, 20.63. Found: C, 59.94; H, 5.07; N,

20.70. Adopting this procedure, compounds 6B to 6J were prepared and characterised.

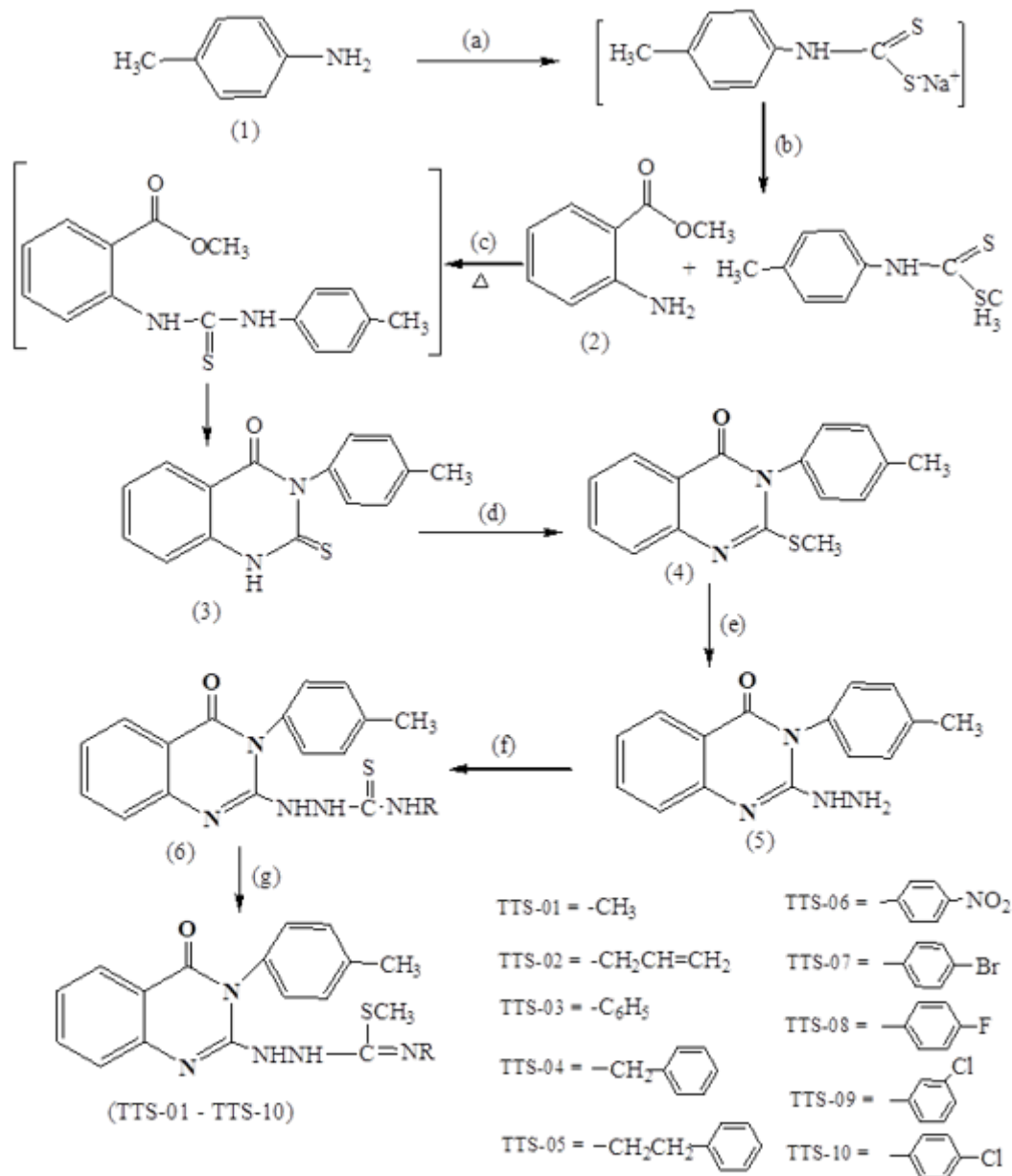
### 1,2-Dimethyl-3-(4-oxo-3-(4-methylphenyl)-3,4-dihydrobenzopyrimidin-2-yl amino) isothiourea (TTS01)

In 20 ml of 0.01 mole NaOH mixture (alcoholic) 0.01 mole compound 6A was dissolved. To this mixture drop wise with stirring 0.01 mole dimethyl sulphate was added. The stirring was continued for 3 h & mixed in to water (ice). The solid obtained were filtered, dried & recrystallized from alcohol. Yield: 78 %; mp: 165-166 °C; IR (KBr) cm<sup>-1</sup>: 3351 & 3204 (NH), 3027 (Ar-CH), 2942 (CH<sub>3</sub>-CH), 1731 (C=O), 1659 (C=N), 1616 (C=C), 683 (C-S-C); <sup>1</sup>H NMR (CDCl<sub>3</sub>) d: 1.52 (s, 3H, CH<sub>3</sub>), 1.71 (s, 3H, CH<sub>3</sub>), 2.15 (s, 3H, SCH<sub>3</sub>), 5.39 (s, 1H, Ar-NH), 5.72 (s, 1H, C=N-NH), 6.86-7.94 (m, 8H, Ar-H); MS (m/z): 353 [M<sup>+</sup>]; Elemental analysis Calcd (C<sub>18</sub>H<sub>19</sub>N<sub>5</sub>OS): C, 61.17; H, 5.42; N, 19.81. Found: C, 60.98; H, 5.44; N, 19.85. Adopting this procedure, compounds TTS02 to TTS10 were prepared and characterised Scheme 1.

### 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



Scheme 1: Synthesis of 1-substituted-3-(3-(4-methylphenyl)-4-oxo-3,4-dihydro benzopyrimidin-2-yl amino) isothiourreas

7H11 agar slants was used to prepare inoculums of *M. tuberculosis* H37R<sub>V</sub>. Approximately 10<sup>7</sup> cfu/mL concentrate *M. tuberculosis* was prepared by final dilution to 10<sup>-2</sup> using 0.05 % W/V Tween 80 saline (1 mg/ml). The bacterial suspension (5 μl) was spotted per ml of 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 H37R<sub>V</sub> 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 (Kunes *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 (TTS01-TTS10) 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. The 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 CCID<sub>50</sub> medium was added. In a 5 % CO<sub>2</sub> 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 manifests the cell degeneration of HIV (EC<sub>50</sub>) & the cytotoxic concentration of drugs, necessary to decrease the viability of ordinary uninfected MT-4 cells by 50% (CC<sub>50</sub>) were estimated.

#### Antibacterial activity

Agar dilution technique was used to estimate 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.

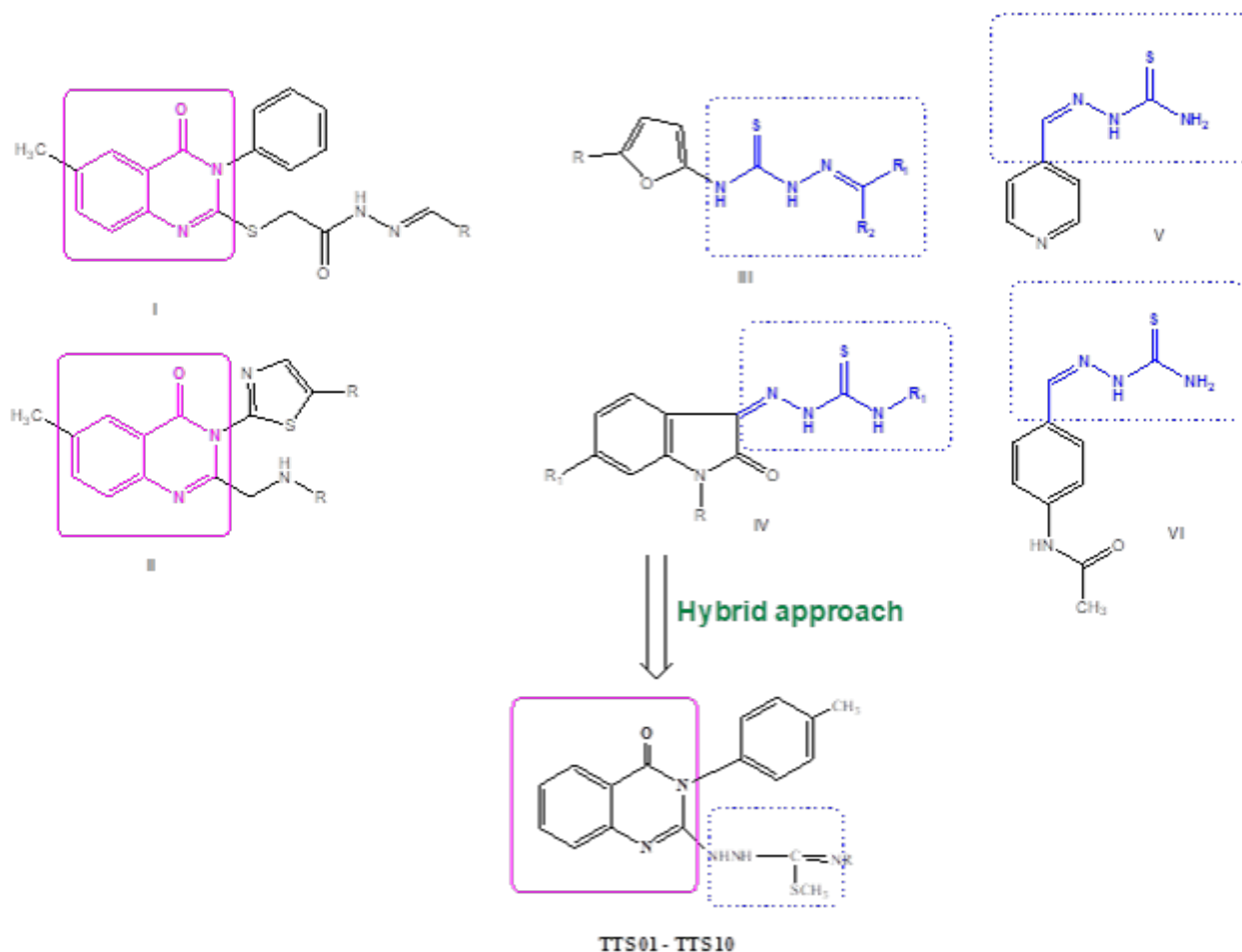
## RESULTS AND DISCUSSION

### Chemistry

Initially, the major intermediate compound 3-(4-methylphenyl)-2-thioxo-2,3-dihydro-1*H*-benzopyrimidine-4-one (3) were prepared. In which 4-amino toluene (1) was treated with CS<sub>2</sub> & NaOH in DMSO to produce sodium dithiocarbamate, which was further undergoes methylation by reacting with dimethyl sulphate to produce the methyl esters of dithiocarbamic acid. The desired 3-(4-methylphenyl)-2-thioxo-2,3-dihydro-1*H*-benzopyrimidine-4-one (3) were synthesized by refluxing the methyl esters of dithiocarbamic acid in ethanol with methyl anthranilate (2). Compound 3 was dissolved in 2 % alcoholic NaOH solution & methylated at room temperature by treating with dimethyl sulphate to produce 2-methylsulfanyl-3-(4-methylphenyl)-3*H*-benzopyrimidine-4-one 4. Using ethanol as solvent 2-hydrazino-3-(4-methylphenyl)-3*H*-benzopyrimidine-4-one 5 was synthesized by nucleophilic displacement of -SCH<sub>3</sub> moiety of 4 with NH<sub>2</sub>NH<sub>2</sub>. The analogs 1-(3-(4-methylphenyl)-4-oxo-3*H*-dihydrobenzopyrimidin-2-yl)-4-(substituted) thiosemicarbazides (6A - 6J) are prepared treating the amino group of compound (5) with a several of alkyl/aryl isothiocyanates. The structure of desired products was confirmed from IR & 1H NMR spectrum of entire derivatives (6A - 6J) by the vanishing of NH & NH<sub>2</sub> peak of the parent compound. The IR & 1H NMR spectrum of these derivatives displayed the thiosemicarbazides, carbonyl (C=O), NH and aryl groups absorption peaks. The target analogs 1-substituted-3-(3-(4-methylphenyl)-4-oxo-3,4-dihydrobenzopyrimidin-2-yl amino) isothioureas (TTS01 - TTS10) were obtained by the methylation of the thiosemicarbazides (6A - 6J) using dimethyl sulphate. Disappearance of NH and C=S peak of the starting material in IR & 1H NMR spectrum indicates the formation of entire title products TTS01 - TTS10. The IR & 1H NMR spectrum of this derivatives displayed the presence of methyl thioureas, carbonyl (C=O), NH and aryl groups 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 TTS01 - TTS10 corresponds to 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 assigned structure.

### Antitubercular activity

Against *M. tuberculosis* (H37R<sub>v</sub> strain) entire title derivatives were screened for its antimy-



**Figure 1: Designing of 1-substituted-3-(3-(4-methylphenyl)-4-oxo-3,4-dihydrobenzopyrimidin-2-yl amino) isothioureas by hybrid approach**

cobacterial (*in vitro*) activity. MIC of all derivatives was determined to study its antitubercular potency & the obtained outcomes are presented in Table 1. From the study, it was found that in varying degree, the growth of *Mycobacterium* was inhibited by title derivatives. Compared to aryl and heteroaryl substituents derivatives having aliphatic substituents displayed lesser antitubercular activity. Likewise, compared to analogs having unsubstituted or electron-donating moiety, analogs possessing electron-withdrawing moiety on aryl ring displayed superior activity. Among the title derivatives, 2-methyl-3-(3-(4-methylphenyl)-4-oxo-3,4-dihydrobenzopyrimidin-2-yl amino)-1-(3-chlorophenyl)isothiourea (TTS09) and 2-methyl-3-(3-(4-methylphenyl)-4-oxo-3,4-dihydrobenzopyrimidin-2-yl amino)-1-(4-nitrophenyl)isothiourea (TTS06) showed most potent antitubercular activity at minimum microgram concentration (MIC: 12.5  $\mu\text{g/ml}$ ).

#### AntiHIV activity

The results of anti-HIV activity pointed out that

entire test analogs displayed mild to moderate anti-HIV potency; whereas compounds TTS06 & TTS09 containing aryl ring with electron-withdrawing group exhibited anti-HIV activity at 9.06 & 8.56  $\mu\text{g/ml}$  concentration against HIV1 and HIV2 (Table 1). While the test compounds with other substituent's showed moderate anti-HIV activity against HIV1 and HIV2 with the MIC in the range of 26 to 100  $\mu\text{g/ml}$ .

#### Antibacterial activity

Out of various substituents tested at N-3 of benzopyrimidine-2-yl, 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, compound 2-methyl-3-(3-(4-methylphenyl)-4-oxo-3,4-dihydrobenzopyrimidin-2-yl amino)-1-(4-nitrophenyl) isothiourea (TTS06) and 2-methyl-3-(3-(4-methyl phenyl)-4-oxo-

3,4-dihydrobenzopyrimidin-2-yl amino)-1-(3-chlorophenyl) isothioureas (TTS09) showed very good activity against *S. Aureus*, *P. vulgaris* & *S. epidermidis* with an MIC of 3 µg/ml. Compounds TTS06 and TTS09 were promising as the most active analogs of this sequence.

## CONCLUSION

A series of 1-substituted-3-(3-(4-methylphenyl)-4-oxo-3,4-dihydrobenzopyrimidin-2-yl amino) isothioureas TTS01 – TTS10 have been synthesized. These compounds displayed significant antibacterial potency against a variety of gram "+"ve & "-"ve bacteria including *M. tuberculosis*; and moderate activity against HIV1 and HIV2 strains. The substituents at the thiosemicarbazide shown varied antimicrobial activity, aryl substituents with an electron-withdrawing group showed most potent and the allyl, alkyl/aryl substituents showed moderate activity, and the aryl substituents possessing electron-donating groups displayed the least activity. Among the series, compound 2-methyl-3-(3-(4-methyl phenyl)-4-oxo-3,4-dihydrobenzopyrimidin-2-yl amino)-1-(3-chlorophenyl) isothioureas (TTS09) and 2-methyl-3-(3-(4-methylphenyl)-4-oxo-3,4-dihydrobenzopyrimidin-2-yl amino)-1-(4-nitrophenyl) isothioureas (TTS06) showed very good potency against *S. epidermidis*, *S. aureus* & *P. vulgaris* with an MIC of 3 µg/ml. Compounds TTS06 and TTS09 showed the antitubercular potency at the least 12.5 µg/ml concentration of and antiHIV activity at 9.06 and 8.56 µg/ml respectively against HIV1 and HIV2 & proffers lead molecule for further optimization & development of novel antitubercular and antiHIV drugs.

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