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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

7-chloro-3-(substituted benzylidene/phenyl ethylidene amino)-2-phenylquinazolin-4(3*H*)-ones: synthesis, antimicrobial and antitubercular evaluation

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Abstract In this study, a series of 7-chloro-3-(substituted benzylidene/phenyl ethylidene amino)-2-phenyl quinazolin-4(3*H*)-ones (**1–10**) were prepared and evaluated for antitubercular activity against *Mycobacterium tuberculosis* (MTB). The antitubercular screening results indicated that 7-chloro-3-(4-(dimethylamino)benzylidene amino)-2-phenylquinazolin-4(3*H*)-one (**10**) was the most potent one (MIC = 0.78×10^{-3} μM) and exhibited activity equivalent to the standard compound isoniazid (MIC = 0.80×10^{-3} μM). Further, the synthesized compounds were tested for their antibacterial activity against Gram positive and Gram negative bacteria. The comparison of antibacterial and antimycobacterial results indicated that different structural requirements are necessary for a compound to be effective against bacterial and mycobacterial targets.

Keywords Quinazolinones · Synthesis · Antitubercular · Antibacterial

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Introduction

According to WHO global report, there were an estimated 9.2 million new cases of tuberculosis (TB) and 1.5 million deaths from TB in HIV-negative people. Keeping in view of above statistics, WHO declared TB as a global health emergency and aimed at saving 14 million lives between 2006 and 2015 (Abdel-Aziz and Abdel-Rahman, 2010).

First-line drugs for TB control includes streptomycin, isoniazid, rifampin (RMP), ethambutol, and pyrazinamide, while second-line treatments are based on use of *p*-amino salicylic acid, ethionamide, cycloserine, and macrolide antibiotics, such as azithromycin and clarithromycin, as well fluoroquinolones. However, the main problem associated with antitubercular drugs is poor compliance with prolonged treatment, and especially with the regimens used to treat TB that are badly tolerated, expensive, relatively ineffective, and must be taken for at least 2 years (Gemma *et al*., 2009). Hence, there is a need to develop newer antimycobacterial agents acting by novel mode of action with minimal chances of cross resistance to existing drugs.

Quinazoline nucleus has attracted attention of medicinal chemists because of their wide spectrum of biological activities *Viz.* anticonvulsant (Ochiai and Ishida, 1982), antiphlogistic (Alagarsamy *et al*., 2006), muscle-relaxant (Maggio *et al*., 2001), antimalarial, antihistamine (Ghorab *et al*., 2000), anti-inflammatory (Jantova *et al*., 2000), antimicrobial, and antitubercular activities (Kidwai *et al*., 2005; Pandeya *et al*., 1999; Caroll *et al*., 1994; Farghaly and Moharram, 1999; Kunes *et al*., 2000; Pattan *et al*., 2006).

There are two basic approaches to develop a new drug for tuberculosis: (a) synthesis of analogue, modifications or derivatives of existing compounds for shortening and improving TB treatment; and (b) searching for novel

structures that TB organism has never been presented with before (Kumar *et al*., 2010).

By observing the biological potential of quinazolinone and in continuation of our research on the development of antitubercular agents (Kumar *et al*., 2010; Narasimhan *et al*., 2011), we have decided to follow the second approach of drug design, i.e., searching for novel structures that TB organism has never been presented with before, and we hereby report the synthesis and antitubercular evaluation of 7-chloro-3-(substituted benzylidene/phenyl ethylidene amino)-2-phenylquinazolin-4(3*H*)-ones (**1**–**10**).

Experimental

The melting points were taken in open capillary tubes and are uncorrected. The IR spectra of the compounds were recorded in the region, 4000–400 cm^{-1} using KBr disks on JASCO 4100 FTIR, and the NMR spectral study was done using DMSO as solvent on DSX-300/AV-700 transform-NMR spectrometer. Mass spectra studies were done in JEOL GC mate. Elemental analysis was performed on a Perkin-Elmer 2400 C, H, and N analyzer (Perkin Elmer, Beaconsfield, UK).

General procedure for synthesis of 7-chloro-3-(substituted benzylidene/phenyl ethylidene amino)-2-phenylquinazolin-4(3*H*)-ones (**1**–**10**)

2-Amino-4-chlorobenzoic acid (0.1 mol) was dissolved in 30 ml of dry pyridine by slow stirring at room temperature. This solution was cooled to 0°C, and a solution of a benzoyl chloride (0.2 mol) in 30 ml of dry pyridine was added slowly with constant stirring. After this addition, the reaction mixture was further stirred for half an hour at room temperature and set aside for 1 h. The pasty mass thus obtained was diluted with 50 ml of water and treated with aqueous sodium bicarbonate solution. When the effervescence ceased, the resultant precipitate was filtered and washed with water, and recrystallized from ethanol. To a cold solution of 7-chloro-2-phenyl-4H-benzo[d][1,3]oxazin-4-one (0.05 mol) (synthesized above) in anhydrous pyridine (20 ml) was added drop-wise a solution of hydrazine hydrate (0.1 mol) in anhydrous pyridine (25 ml) with constant stirring. When the addition was completed, the reaction mixture was stirred vigorously for 30 min at room temperature and subsequently refluxed for 6 h under anhydrous reaction conditions. The reaction mixture was then allowed to cool to room temperature and poured into ice cold water containing diluted hydrochloric acid. The precipitated 3-amino-7-chloro-2-phenylquinazolin-4(3*H*)-one was filtered, washed repeatedly with water, dried, and recrystallized from ethanol. 3-amino-7-chloro-2-phenylquinazolin-4(3*H*)-one (0.01 mol) synthesized above was dissolved in ethanol (20 ml) and added slowly to an ethanolic solution of corresponding aromatic carbonyl compound (0.01 mol). The reaction mixture was acidified with 5 ml of glacial acetic acid and refluxed for half an hour. The precipitate obtained was filtered and washed with the mixture of ether and water and dried, and recrystallized from 95% ethanol.

Compound **1**: IR (cm^{-1}): C=O—1660, C=N—1574; ^{1}H NMR (δ ppm): Ar (13H) 7.5–8.813, CH=N—8.819; MS: *m*/*z* 359.0921 (M^+); Anal. Calculated for $C_{21}H_{14}ClN_3O$: C, 70.10; H, 3.92; N, 11.68, Found: C, 70.18; H, 3.98; N, 11.60.

Compound **2**: IR (cm^{-1}): C=O—1668, C=N—1588, NO_2——1515, 1348; ^{1}H NMR (δ ppm): 7.59–8.06 (m, 12H, Ar–H), 8.81 (s, 1H, CH=N); MS: *m*/*z* 404.1391 (M^+); Anal. Calculated for $C_{22}H_{13}ClN_4O_3$: C, 62.31; H, 3.24; N, 13.84, Found: C, 62.24; H, 3.19; N, 13.78.

Compound **3**: IR (cm^{-1}): OH—3500–3100, C=O—1665, C=N—1587; ^{1}HNMR (δ ppm): 7.60–8.84 (m, 12H, Ar–H), 8.84 (s, 1H, CH=N), 10.59 (s, 1H, OH); MS: *m*/*z* 375.08 (M^+); Anal. Calculated for $C_{21}H_{14}ClN_3O_2$: C, 67.12; H, 3.75; N, 11.18, Found: C, 67.19; H, 3.75; N, 11.21.

Compound **4**: IR (cm^{-1}): OH—3500–3100, C=O—1672, C=N—1590, CH. Str. 3000–2800; ^{1}H NMR (δ ppm): 7.57–8.67 (m, 12H, Ar–H), 8.811 (s, 1H, CH=N), 10.25 (s, 1H, OH); MS: *m*/*z* 375.3051 (M^+); Anal. Calculated for $C_{21}H_{14}ClN_3O_2$: C, 67.12; H, 3.75; N, 11.18, Found: C, 67.08; H, 3.79; N, 11.23.

Compound **5**: IR (cm^{-1}): OH—3500–3100, C=O—1668, C=N—1588, CH. Str.—3000–2800; ^{1}H NMR (δ ppm): 7.57–8.80 (m, 11H, Ar–H), 8.81 (s, 1H, CH=N), 10.23 (s, 1H, OH), 3.82 (s, 1H, OCH_3); MS: *m*/*z* 405.12 (M^+); Anal. Calculated for $C_{22}H_{16}ClN_3O_3$: C, 65.11; H, 3.97; N, 10.35, Found: C, 65.16; H, 3.99; N, 10.41.

Compound **6**: IR (cm^{-1}): C=O—1662, C=N—1571; ^{1}H NMR (δ ppm): 7.57–8.8 (m, 12H, Ar–H), 8.81 (s, 1H, CH=N), 3.47 (s,1H, OCH_3); MS: *m*/*z* 389.0875 (M^+); Anal. Calculated for $C_{22}H_{16}ClN_3O_2$: C, 67.78; H, 4.14; N, 10.78, Found: C, 67.72; H, 4.16; N, 10.80.

Compound **7**: IR (cm^{-1}): C=O—1668, C=N—1574; ^{1}H NMR (δ ppm): 7.57–8.06 (m, 12H, Ar–H), 8.81 (s, 1H, CH=N), 2.49 (s,1H, CH_3); MS: *m*/*z* 373.33 (M^+); Anal. Calculated for $C_{22}H_{16}ClN_3O$: C, 70.68; H, 4.31; N, 11.24, Found: C, 70.72; H, 4.29; N, 11.30.

Compound **8**: IR (cm^{-1}): OH—3500–3100, C=O—1667, C=N—1575, CH. Str.—3000–2800; ^{1}H NMR (δ ppm): 7.58–8.82 (m, 11H, Ar–H), 8.81 (s, 1H, CH=N), 10.29 (s, 1H, OH), 2.49 (s,1H, CH_3); MS: *m*/*z* 389.09 (M^+); Anal. Calculated for $C_{22}H_{16}ClN_3O_2$: C, 67.78; H, 4.14; N, 10.78, Found: C, 67.84; H, 4.14; N, 10.75.

Compound **9**: IR (cm^{-1}): C=O—1679, C=N—1583; ^{1}H NMR (δ ppm): 7.59–8.59 (m, 11H, Ar–H), 8.81 (s, 1H,

CH=N), 2.52 (s,1H, CH_3); MS: *m/z* 406.9873 (M^+); Anal. Calculated for $C_{22}H_{15}Cl_2N_3O$: C, 64.72; H, 3.70; N, 10.29, Found: C, 64.77; H, 3.75; N, 10.34.

Compound **10**: IR (cm^{-1}): C=O—1661, C=N—1591; ^1H NMR (δ ppm): 6.76–7.68 (m, 12H, Ar–H), 9.65 (s, 1H, CH=N), 3.03 (s,6H, $N(CH_3)_2$; MS: *m/z* 402.606 (M^+); Anal. Calculated for $C_{23}H_{19}ClN_4O$: C, 68.57; H, 4.750; N, 13.19, Found: C, 68.56; H, 4.77; N, 13.13.

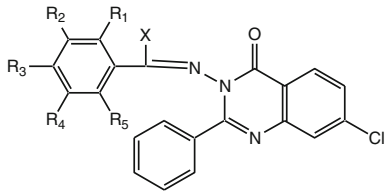
Antitubercular activity

The synthesized compounds were screened for their antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ using micro plate Alamar Blue assay (MABA) (Table 1). This methodology is a nontoxic one which uses thermally stable reagent and shows good correlation with proportional and BACTEC radiometric methods (Reis *et al*., 2004). In brief, 200 ml of sterile deionized water was added to all outer-perimeter wells of sterile 96-well plates to minimize the evaporation of medium in test wells during incubation. The 96 plates received 100 ml of the Middlebrook 7H9 broth. The serial dilution of synthesized compounds was made directly on the plates. Plates were covered and sealed with parafilm, and incubated at 37°C for 5 days. Afterward, 25 ml of a freshly prepared 1:1 mixture of Alamar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth, and a pink color was scored as growth. The MIC (minimal inhibition concentration) was defined as the lowest drug concentration, which prevented a color change from blue to pink.

Antibacterial screening by Kirby–Bauer Method

Diffusion Disk Method (Kirby–Bauer) was used to evaluate the antimicrobial activity of synthesized quinalzolinone derivatives. *Staphylococcus aureus* (ATCC 6538), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeroginosa* (ATCC 27853) were inoculated in Mueller–Hinton, MacConkey, and Cetrimide agar, respectively, and incubated at 37°C for 24 h. After incubation, each culture was diluted in sterile saline solution (0.9% NaCl) according to 0.5 MacFarland scale, to obtain a bacterial density of 1.0×10^8 cfu/ml approximately. A sample of this suspension was inoculated homogeneously in petri dishes, and the synthesized compounds were deposited aseptically in disk forms over the inoculated medium and the petri dishes were incubated at 37°C for 24 h. After incubation, the zone of inhibition was measured.

Table 1 Physicochemical characteristics and antitubercular activity of synthesized 7-chloro-3-(substituted benzylidene/phenyl ethylidene amino)-2-phenyl quinazolin-4(3*H*)-ones



(1-10)

Comp.	X	R_1	R_2	R_3	R_4	R_5	Molecular formula	Molecular weight	% Yield	M.P. (°C)	Rf value[a]	MIC ($\mu M \times 10^{-3}$)
1	H	H	H	H	H	H	$C_{21}H_{14}ClN_3O$	359.81	92	166	0.72	3.47
2	H	H	H	NO_2	H	H	$C_{21}H_{13}ClN_4O_3$	404.81	80	164	0.62	3.08
3	H	H	H	OH	H	H	$C_{21}H_{14}ClN_3O_2$	375.81	89	136	0.61	1.66
4	H	OH	H	H	H	H	$C_{21}H_{14}ClN_3O_2$	375.81	88	176	0.48	3.32
5	H	H	OCH_3	OH	H	H	$C_{22}H_{16}ClN_3O_3$	405.83	84	139	0.41	6.16
6	H	H	H	OCH_3	H	H	$C_{22}H_{16}ClN_3O_2$	389.83	94	185	0.63	6.41
7	CH_3	H	H	H	H	H	$C_{22}H_{16}ClN_3O$	373.83	96	170	0.60	6.68
8	CH_3	H	H	OH	H	H	$C_{22}H_{16}ClN_3O_2$	389.83	96	160	0.51	6.38
9	CH_3	H	H	Cl	H	H	$C_{22}H_{15}Cl_2N_3O$	408.28	82	156	0.42	12.2
10	H	H	H	$N(CH_3)_2$	H	H	$C_{23}H_{19}ClN_4O$	402.88	88	98	0.52	0.78
Isoniazid												0.8
Ethambutol												7.6
Ciprofloxacin												6.4

[a] TLC mobile phase : Benzene: chloroform (80:20)

Results and discussion

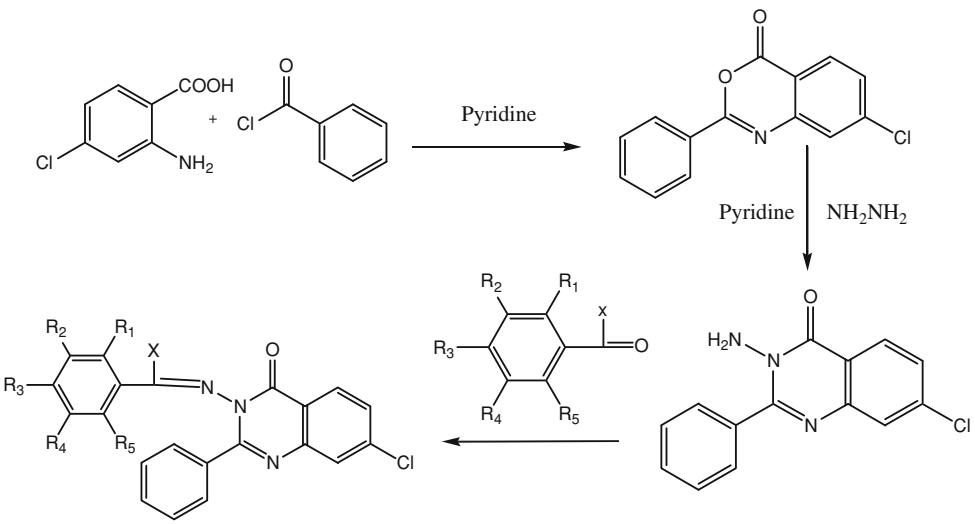
The synthesis of 7-chloro-3-(substituted benzylidene/ethylidene amino)-2-phenylquinazolin-4(3*H*)-ones (**1–10**) was carried out as outlined in Scheme 1. The reaction of 2-amino-4-chlorobenzoic acid with benzoyl chloride resulted in the formation of 7-chloro-2-phenyl-4*H*-benzo[d]-[1,3]oxazin-4-one which on treatment with hydrazine hydrate yielded 3-amino-7-chloro-2-phenylquinazolin-4(3*H*)-one which on reaction with corresponding aromatic carbonyl compounds yielded the title compounds, 7-chloro-3-(substituted benzylidene/ethylidene amino)-2-phenylquinazolin-4(3*H*)-ones (**1–10**)**.** The physicochemical characteristics of the synthesized compounds are presented in Table 1. The synthesized compounds were characterized by IR, ^{1}H-NMR, and mass spectral as well by elemental analysis studies, and the results were found to be in agreement with the assigned molecular structures.

The characteristic absorption peaks were observed for all relevant groups in the IR spectra of the synthesized compounds. The absorption peaks around 1600 cm^{-1} indicated the formation of C=N ring atoms of quinazoline. Amide C=O stretching vibration was observed near 1640–1690 cm^{-1}. Aromatic and imine protons were observed at 6.68–8.13 and 8.0–9.5 δ ppm, respectively, for all the synthesized compounds. Molecular ion peak in mass spectra confirmed the molecular weight of the synthesized compounds.

Antimycobacterial activity

The antimycobacterial activity of 7-chloro-3-(substituted benzylidene/ethylidene amino)-2-phenylquinazolin-4(3*H*)-ones (**1–10**) was assessed against *Mycobacterium tuberculosis* $H_{37}Rv$ using microplate alamar blue assay (MABA) (Franzblau *et al*., 1998), and the results are presented in Table 1. At the commencement of this study, we have synthesized quinazolinone with an unsubstituted phenyl ring on the benzylidene portion (**1**) and tested for its antimycobacterial activity. The promising antitubercular activity of compound **1** (MIC = 3.47 × 10^{-3} μM, which is greater than the reference standards, ethambutol and ciprofloxacin) created interest among us to go for further optimization taking compound **1** as a prototype compound.

It was known from the literature that the presence of strongly deactivating electron-withdrawing nitro group on the phenyl ring improved antimycobacterial activity (Sriram *et al*., 2007). In view of the above, we decided to introduce electron-withdrawing nitro group into the phenyl ring, and accordingly synthesized 7-chloro-3-[(4-nitrobenzylidene)-amino]-2-phenyl-3*H*-quinazolin-4-one (**2**). However, as expected, the electron-withdrawing nitro group did not improve the antitubercular activity significantly (MIC = 3.08 × 10^{-3} μM). Hence, we have dropped the idea of introducing electron-withdrawing groups further and planned to introduce electron-donating groups and synthesized compounds, **3** and **4** with an electron-donating hydroxy group at para and ortho positions of phenyl ring. This idea resulted in significant improvement of antitubercular activity of quinazolinone derivatives especially in case of 7-chloro-3-(4-hydroxybenzylideneamino)-2-phenylquinazolin-4(3*H*)-one (**3**) which showed activity at 1.66 × 10^{-3} μM which was almost two times more potent than compound **1** (MIC—3.47 × 10^{-3} μM). However, the presence of OH group at ortho position did not improve the antimycobacterial activity significantly. From the above results, we have decided to introduce an additional electron-donating group by keeping the hydroxyl group intact at



Scheme 1 Synthesis of 7-chloro-3-(substituted benzylidene/phenyl ethylidene amino)-2-phenyl quinazolin-4(3*H*)-ones

(1-10)

para position and accordingly synthesized 7-chloro-3-(4-hydroxy-3-methoxybenzylideneamino)-2-phenylquinazolin-4(3*H*)-one (**5**). This idea did not give fruitful result as evidenced by the MIC value of compound **5** (MIC—6.16×10^{-3} μM) which was almost four times more than compound **3**. The above results confirmed that the presence of electron-donating group at para position was essential for antitubercular activity of quinazolinones. Keeping this fact in mind and in order to know the antimycobacterial spectrum of the electron-releasing methoxy group, we have synthesized compound **6**. This modification also produced the same result as in case of compound **5**, which ruled out the effectiveness of methoxy substituent to bind with the antimycobacterial target. By viewing the structure, we remembered that there was a possibility to go for alkylation of CH of benzylidene group, and accordingly we have synthesized compounds **7**–**9** with H, OH, and Cl groups attached to the phenyl ring of benzylidene moiety. This idea of introducing alkyl group did not give fruitful results as none of these compounds (**7**–**9**) exhibited appreciable antimycobacterial activity (Table 1). It was observed that alkylation of CH group significantly decreased the antitubercular activity as evidenced by the antimycobacterial activity of compound **8** with para hydroxy group, MIC of which was almost four times more than the MIC of compound **3** with the same substitution on phenyl ring. The aforementioned results led us to conclude that the presence of electron-donating group at para position is a must for antitubercular activity of quinazolinones, and we have planned to search for the better electron-donating group than the hydroxyl group at para position of phenyl ring of synthesized quinazolinones. During the course of this study, we came across the recent study of Eswaran *et al*. (Eswaran *et al*., 2010) who identified that addition of (3R)-3-amino-*N,N*-dimethyl-4-(phenylthio)butanamide to positions 3 and 4 of quinoline skeleton has tremendously enhanced antitubercular activity of quinoline-3-carbohydrazones. This motivated us to replace the para hydroxy group of compound **3** with *N,N*-dimethylamino group, and accordingly we synthesized 7-chloro-3-(4-(dimethylamino) benzylidene amino)-2-phenylquinazolin-4(3*H*)-one (**10**) which showed excellent antitubercular activity (MIC—0.78×10^{-3} μM) equivalent to standard, isoniazid (MIC = 0.80×10^{-3} μM).

Antibacterial activity

The synthesized quinazolinone derivatives were tested for their antibacterial activity by Kirby–Bauer Method (Bauer *et al*., 1966) using ciprofloxacin as a standard. None of the synthesized compounds showed appreciable antibacterial activity except compounds **5**, **8,** and **9** which demonstrated activity comparable to ciprofloxacin against *E. coli* and *S. aureus* (Table 2).

Table 2 Antibacterial activity of synthesized compounds

Compound	Zone of inhibition (mm)		
	E. Coli	*P. aeruginosa*	*S. aureus*
5	21	05	15
8	22	04	15
9	22	04	15
Ciprofloxacin	25	18	17

From the results of antimycobacterial and antibacterial studies, the following SAR may be drawn.

1. The presence of electron-withdrawing group on phenyl ring of benzylidene moiety attached to the 3rd position of quinazolinone decreases the antimycobacterial activity whereas the presence of electron-donating substituent increases the antimycobacterial activity. This is contrary to the observations of Sriram *et al*. (Sriram *et al*., 2007) and our previous studies (Kumar *et al*., 2010; Narasimhan *et al*., 2011).
2. Among the different electron-donating groups tried, the methoxy group failed to improve the antitubercular activity, and hydroxy and dimethyl amino groups significantly improved the antitubercular activity. This indicates the fact that electron-donating hydroxy and dimethyl amino groups may interact with electron deficient portion of mycobacterial target.
3. The comparison of antitubercular and antimicrobial activities of the synthesized quinazolinones revealed that the presence of hydrogen on CH of benzylidene moiety is essential for hydrogen bonding of the synthesized compounds with electronegative region at mycobacterial target whereas this is not true in the case of antibacterial studies where the alkylated compounds **8** and **9** have shown appreciable antibacterial activity. This indicated that different structural requirements are necessary for a drug to bind with mycobacterial and bacterial targets. This is in accordance with the studies of Sortino *et al*. (2007).
4. It is worthwhile to note that compound **5** containing electron-donating groups OH and OCH_3 has shown poor antitubercular activity and appreciable antibacterial activity. The appreciable antibacterial activity of compound **5** may be attributed to the presence of methoxy group as observed in one of our previous studies (Sharma *et al*., 2009), where we found that presence of electron-donating methoxy group also improved the antimicrobial activity of imidazole derivatives against *S. aureus*, *B. subtilis* and *C. albicans* along with the imidazole derivatives containing electron-withdrawing substituents. The above findings are summarized in Fig. 1.

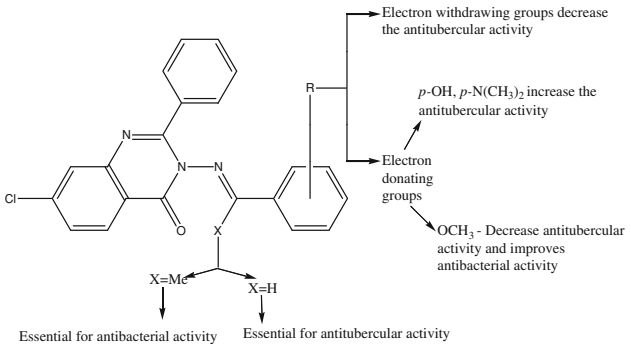


Fig. 1 Structural requirements for the antimycobacterial and antibacterial activity of 7-chloro-3-(substituted benzylidene/phenyl ethylidene amino)-2-phenyl quinazolin-4(3*H*)-ones

Conclusion

In conclusion, 7-chloro-3-(substituted benzylidene/phenyl ethylidene amino)-2-phenylquinazolin-4(3*H*)-ones (**1–10**) were prepared, characterized, and evaluated in vitro for their antitubercular and antibacterial activities. The antitubercular screening results indicated that 7-chloro-3-(4-(dimethylamino)benzylidene amino)-2-phenylquinazolin-4(3*H*)-one (**10**) was the most potent one with MIC value of 0.78×10^{-3} μM which is equivalent to isoniazid (MIC = 0.80×10^{-3} μM). The comparison of antibacterial and antimycobacterial results indicated that different structural requirements are necessary for a compound to be effective against bacterial and mycobacterial targets.

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