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Original article

Design, synthesis and antimycobacterial activity of some novel imidazo[1,2-*c*]pyrimidines

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ABSTRACT

Tuberculosis, due to its relentless nature, is now a major public health threat. The concomitant resurgence of TB with the MDR- or XDR-TB and HIV/AIDS pandemic has exposed the frailties of the current drug armatorium. Based on isosteric replacement and good 3D structural similarity between PA-824, a novel antimycobacterial agent undergoing clinical trials, and imidazo[1,2-*c*]pyrimidines, we have designed novel imidazo[1,2-*c*]pyrimidines. The designed molecules were synthesized by nucleophilic displacement of chloro group of various substituted 4-chloropyrimidines by ethanolamine followed by cyclisation of these 4-(2-hydroxyethyl)aminopyrimidines to imidazo[1,2-*c*]pyrimidines in good yield. All the compounds were screened for their antimycobacterial activity on *Mycobacterium tuberculosis* H37Rv strain by 1% proportion method. Some of the synthesized compounds exhibited potent antimycobacterial activity with MIC values in the range of 2–20 μg/mL.

1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is a disease rich in paradoxes. Currently, one third of the world population is latently infected with TB bacteria [1]. Despite the availability of the BCG vaccine and chemotherapy, TB still remains a leading infectious disease globally, especially in Third World countries. According to estimates of the World Health Organization (WHO), TB is now the leading infectious cause of death worldwide and there were an estimated 9.2 million new cases of TB every year [1] (afflicting mostly the young and productive adults). Because of relentless spread of TB throughout the world, WHO took the unprecedented step of declaring TB a global emergency in 1993 that has to be given prime importance [2]. The problem has worsened primarily due to the growing human immunodeficiency virus (HIV) epidemic and the emergence of drug resistance [3,4]. There were an estimated 1.5 million deaths from TB in HIV-negative people and 0.2 million among people infected with HIV [1].

The approach to chemotherapy of TB is very different from that for other bacterial infections. The organism has a long generation time and a capacity for dormancy, when its low metabolic activity makes it a difficult therapeutic target [5–7]. In addition, *M. tuberculosis* may be located in pulmonary cavities, empyema pus, or solid caseous material, where penetration of antibiotics is difficult or the pH is sufficiently low to inhibit the activity of most antibiotics [8,9]. Although TB can be cured by an optimized regimen comprising of various first line and second line drugs [10,11], the emergence of MDR-TB and extremely drug resistant TB (XDR-TB, first reported in November 2005 [12]) has created new challenges to control and defeat the disease. The concomitant resurgence of TB with the MDR- or XDR-TB and HIV/AIDS pandemic has exposed the frailties of the current drug armatorium. All these suggest that there is an urgent need of new potent therapeutic agents which can be effective against resistant strains of mycobacteria.

PA-824, an imidazooxazine derivative [13] has generated considerable excitement with its antitubercular potency and presently is undergoing clinical trials. It was thought of interest to replace the oxazine ring of PA-824 with its bioisoster pyrimidine ring (Fig. 1). Further, the 3D structural similarity between PA-824 and the designed imidazopyrimidines was checked by indirect type of molecular modeling studies. Low r.m.s.d. (root mean square distance) value suggested good 3D structural similarity between the designed molecule and PA-824. This prompted us to synthesize a series of ethyl 5-(un)substituted-7-(substituted amino)-2,3-dihydroimidazo[1,2-*c*]pyrimidine-8-carboxylates and check its antimycobacterial potential.

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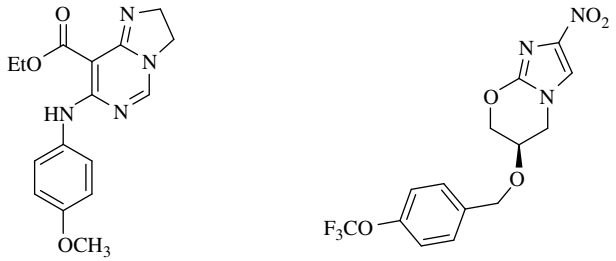


Fig. 1. Structures of Compound **7i** and PA-824.

2. Chemistry

The most common method for synthesis of imidazo[1,2-*c*]pyrimidines is the condensation of 4-aminopyrimidine with α-halogenated carbonyl compounds [14–28]. The 4-chloropyrimidines can also be used for the preparation of imidazo[1,2-*c*]pyrimidine [29–33]. Dihydroimidazo[1,2-*c*]pyrimidines have been prepared through the cyclization of the 4-β-chloroethylaminopyrimidines [29,34,35] and of 4-β-β-diethoxyethylaminopyrimidines [18,36] with phosphorus oxychloride.

Designed molecules were synthesized by nucleophilic displacement of chloro group of 4-chloropyrimidines with ethanolamine followed by cyclization in the presence of phosphorus oxychloride (Scheme 1). The 4-chloropyrimidines (**5**) were synthesized by cyclization of difficultly isolable vinyl amidine intermediate (**4**), which was synthesized by condensation of substituted amidine (**3**) with *S*,*N*-acetal (**2**) under controlled reaction conditions [37,38]. This vinyl amidines on reaction with dry hydrogen chloride gas get cyclized to 4-chloropyrimidines (**5**, Scheme 2).

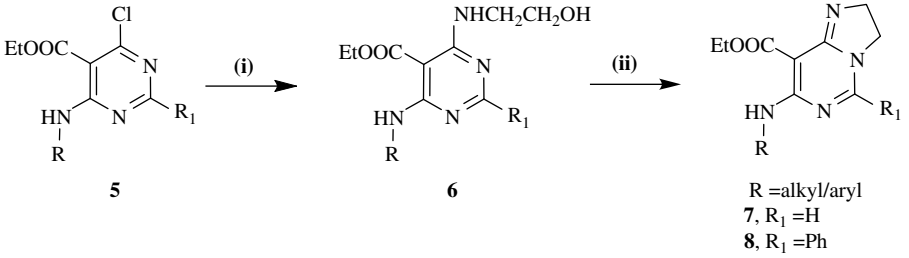
3. Results and discussion

3.1. Molecular modeling

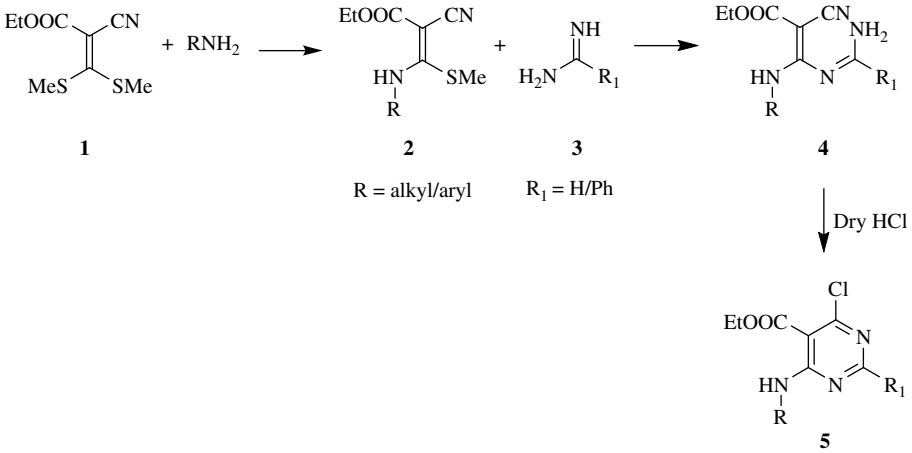
The 3D structural similarity between PA-824 and designed series of imidazo[1,2-*c*]pyrimidines was checked by indirect type of molecular modeling studies (Fig. 2). All the structures were generated, energy minimized and superimposed using PC based molecular modeling software ChemDraw Ultra (Version 11.0, Cambridge Soft Corporation, USA). All geometries were fully optimized by minimizing the energy with respect to geometrical variables without symmetry constraints, using a 0.01 Kcal/mol gradient. The r.m.s.d. observed was 0.202. The low r.m.s.d. value suggested good 3D similarity between PA-824 and imidazo[1,2-*c*]pyrimidines which prompted us to synthesize some imidazo[1,2-*c*]pyrimidine as novel potential antimycobacterial agents.

3.2. Chemical synthesis

Various substituted 4-chloropyrimidines (**5**) were prepared from vinyl amidines (**4**) using dry hydrogen chloride gas as catalyst in 60–80% yield (Scheme 1). The 4-chloropyrimidines (**5**) were refluxed with ethanolamine in ethanol for 30 min to 2 h to obtain ethyl 4-(2-hydroxyethyl)amino-2-(un)substituted-6-(substituted amino)pyrimidine-5-carboxylates (**6**), which on cyclization by refluxing with phosphorous oxychloride in anhydrous toluene gave fluorescent 2,3-dihydroimidazo[1,2-*c*]pyrimidines (**7** and **8**) in good yield (Scheme 2, Table 1). All the synthesized compounds were freely soluble in chloroform, dichloromethane, DMF, DMSO and



Scheme 1. Synthesis of 2,3-dihydroimidazo[1,2-*c*]pyrimidines: (i) ethanolamine, EtOH, warm, 1/2–2 h; (ii) $POCl_3$, C_6H_6, reflux, 6–8 h.



Scheme 2. Synthesis of 4-chloropyrimidines.

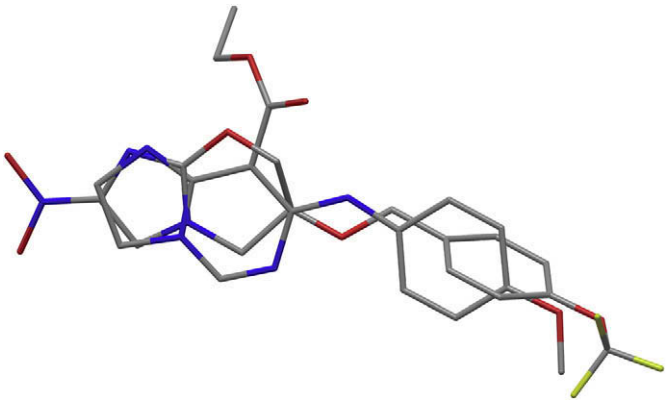
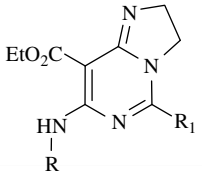


Fig. 2. 3D structure superimposition of compound **7i** and PA-824.

methanol but insoluble in non-polar solvents like *n*-hexane. The structures of the synthesized compounds were confirmed by IR, MS, ^{1}H NMR and elemental analysis.

It has been observed that the use of β-halogenoalkylamines is better instead of β-aminoalcohols in these reactions as the step involving conversion of the β-hydroxyalkylaminopyrimidine intermediate into corresponding cyclized β-chloro derivative can be omitted [18,29–33]. However, no such increase of reactivity was required in our reaction and the product could be isolated by a smooth reaction. As C-5 position is occupied by carbethoxy group the possible side reaction of alternative cyclization [21–23] could also be eliminated. Moreover, as the hydroxyl group of amino-ethanol is not sufficiently nucleophilic in nature to attack the carbethoxy group, the cyclization with the later cannot be expected (Scheme 3). Thus, various 2,3-dihydroimidazo[1,2-*c*]pyrimidines (**7** and **8**) were the only isolated products in the cyclocondensation reaction with phosphorus oxychloride. The possible intermediate **10** was not isolated.

Table 1
Physical data of ethyl 5-(un)substituted-7-(substituted amino)-2,3-dihydroimidazo[1,2-*c*]pyrimidine-8-carboxylates.



Compound	R	R_1	Mol. formula	M.P. (°C)	Yield[a] (%)
7a	CH_3	H	$C_{10}H_{14}N_4O_2$	178–180	48
7b	C_2H_5	H	$C_{11}H_{16}N_4O_2$	196–198	52
7c	$C_6H_5CH_2$	H	$C_{16}H_{18}N_4O_2$	128–130	54
7d	C_6H_5	H	$C_{15}H_{16}N_4O_2$	192–194	62
7e	2-CH_3–C_6H_4	H	$C_{16}H_{18}N_4O_2$	140–142	58
7f	3-CH_3–C_6H_4	H	$C_{16}H_{18}N_4O_2$	138–140	51
7g	4-CH_3–C_6H_4	H	$C_{16}H_{18}N_4O_2$	149–150	61
7h	2-CH_3O–C_6H_4	H	$C_{16}H_{18}N_4O_3$	178–180	60
7i	4-CH_3O–C_6H_4	H	$C_{16}H_{18}N_4O_3$	152–154	68
7j	2-F–C_6H_4	H	$C_{15}H_{15}FN_4O_2$	172–174	68
7k	4-F–C_6H_4	H	$C_{15}H_{15}FN_4O_2$	135–137	62
7l	3-CF_3–C_6H_4	H	$C_{16}H_{18}F_3N_4O_2$	178–180	35
7m	2-Cl–C_6H_4	H	$C_{15}H_{15}ClN_4O_2$	145–147	45
7n	3-Cl–C_6H_4	H	$C_{15}H_{15}ClN_4O_2$	115–117	51
7o	4-Cl–C_6H_4	H	$C_{15}H_{15}ClN_4O_2$	170–171	63
7p	4-Br–C_6H_4	H	$C_{15}H_{15}BrN_4O_2$	149–151	70
8a	CH_3	C_6H_5	$C_{16}H_{18}N_4O_2$	180–182	40
8b	C_2H_5	C_6H_5	$C_{17}H_{20}N_4O_2$	187–190	42
8c	$C_6H_5CH_2$	C_6H_5	$C_{22}H_{22}N_4O_2$	154–156	52
8d	C_6H_5	C_6H_5	$C_{21}H_{20}N_4O_2$	192–194	50
8e	2-CH_3–C_6H_4	C_6H_5	$C_{22}H_{22}N_4O_2$	182–184	50
8f	4-CH_3–C_6H_4	C_6H_5	$C_{22}H_{22}N_4O_2$	184–186	52
8g	2-CH_3O–C_6H_4	C_6H_5	$C_{22}H_{22}N_4O_3$	192–194	42
8h	4-CH_3O–C_6H_4	C_6H_5	$C_{22}H_{22}N_4O_3$	152–154	45
8i	2-F–C_6H_4	C_6H_5	$C_{21}H_{19}FN_4O_2$	160–162	55
8j	4-F–C_6H_4	C_6H_5	$C_{21}H_{19}FN_4O_2$	164–166	49
8k	2-Cl–C_6H_4	C_6H_5	$C_{21}H_{19}ClN_4O_2$	130–132	45
8l	3-Cl–C_6H_4	C_6H_5	$C_{21}H_{19}ClN_4O_2$	115–117	37
8m	4-Cl–C_6H_4	C_6H_5	$C_{21}H_{19}ClN_4O_2$	126–128	48
8n	4-Br–C_6H_4	C_6H_5	$C_{21}H_{19}BrN_4O_2$	128–130	51

[a] All the compounds were recrystallized from dichloromethane–*n*-hexane.

3.3. Antimycobacterial activity

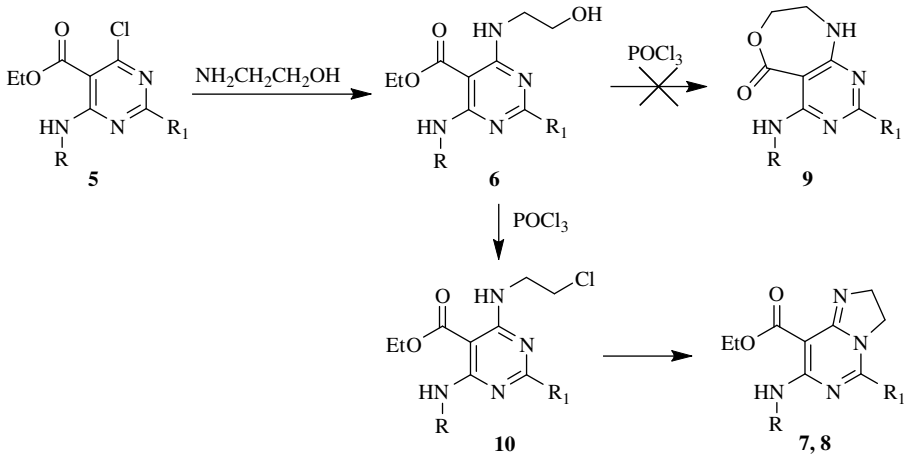
In the present investigation, various 2,3-dihydroimidazo[1,2-*c*]pyrimidines were evaluated for their antimycobacterial activity against H37Rv strain of *M. tuberculosis*. The minimum inhibitory concentration (MIC) was determined by the serial dilution technique on Lowenstein–Jensen (L–J) medium, added with Gruft mycobacterial supplement [39]. Rifabutin and amikacin were used as standards for antimycobacterial activity. Some of the compounds exhibited remarkable activity against *M. tuberculosis* H37Rv strain as indicated by their MIC values (Table 2). It was observed that the compounds unsubstituted at C-5 have exhibited significant antimycobacterial activity as compared to the other substitution. Compounds **7c**, **7d**, **7g**, **7i**–**k**, **7o**, **8h**, **8j** and **8m** have shown potent antimycobacterial activity after 21 days with MIC values in the range of 2–20 μg/mL. An interesting fact observed was that the compounds with *para*-substitution on the benzene ring at C-7 (**7g**, **7i**, **k**, **7o**, **8h**, **8j** and **8m**) have shown potent activity after 21 days (Table 2). However, compounds **7d** and **7j** were also found equally active. Compounds **8d**, **8f** and **8i** were failed to exhibit significant effect on the mycobacteria.

Additionally, it was observed that in a group of compounds without any substitution at C-5, substitution on the *para*-position of the benzene ring at C-7 was influencing the antimycobacterial activity significantly. The presence of electron-withdrawing halogen atoms (**7j**–**l** and **7o**) or methoxy group (**7i**) improved potency. However, a methyl group (**7g**) was also equally permissible at that position. Other substitutions on the benzene ring at C-7 decreased the antimycobacterial activity. Alkyl groups at C-7 remarkably reduce the potency of the test compounds.

The most potent compound **7i** has exhibited MIC of 2 μg/mL which is comparable to the MIC value of amikacin and less potent than rifabutin. As per the reported MIC range of PA-824 (0.015–0.25 μg/mL) [13], compound **7i** has exhibited less potency.

4. Conclusion

Synthesis and antimycobacterial activity of certain novel imidazo[1,2-*c*]pyrimidines have been carried out. Some of the synthesized compounds showed significant activity against *M. tuberculosis* H37Rv strain. Compounds **7g**, **7i**, **7j**, **7k**, **7o**, **8h** and **8j** have exhibited potent antimycobacterial activity as indicated by their low MIC values (≤5 μg/mL). Thus the present investigation suggests that the bioisosteric replacement of imidazooxazine ring of PA-824 with fused imidazopyrimidine can result into promising compounds with good antimycobacterial potential. In comparison with the antibiotics commonly used in the therapy, test compounds were found significantly potent, forcing us to explore the potential of the projected series to be developed as promising candidates for antimycobacterial therapy to treat various clinical conditions associated with multiple infectious diseases and drug resistant TB.



Scheme 3. Cyclization of 4-(2-hydroxyethyl)aminopyrimidines.

5. Experimental

5.1. General

Melting points were determined in open capillaries using microprocessor based melting point apparatus, Model VMP-D (Veego India Ltd., Mumbai, India) and are uncorrected. Purity of the compounds synthesized was checked by thin layer chromatography (TLC) performed on microscopic slides, 2 × 7.5 cm, coated with silica gel G as stationary phase and the spots were visualized by exposure to iodine vapors or in the UV light. IR spectra were recorded using KBr on 8400S Shimadzu Fourier Transform Spectrophotometer (V_{max} in cm^{-1}). ^1H NMR spectra were recorded in DMSO-d_6/$CDCl_3$ on a Bruker Evance 400 MHz Spectrophotometer using TMS as internal standard. Chemical shift values are reported in ppm downfield on δ scale. Mass spectra were recorded on Perkin–Elmer LC-MS PE Sciex API/65 Spectrophotometer. The elemental analyses were done on Elementar Vario EL III Carlo Erba 1108 and were in well accordance with the structures assigned to the compounds.

Synthetic grade chemicals procured from SD fine Chemicals, Baroda, India, were used for the synthesis of the target compounds, only after purification. All the starting materials were prepared according to the literature procedures with some minor modifications. General synthetic procedures used for the preparation of the target compounds **7a–p** and **8a–n** are as follows:

Table 2
Antimycobacterial activity of ethyl 5-(un)substituted-7-(substituted amino)-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylates.

Compound	MIC (μg/mL)		
	14th Day	21st Day	30th Day
7a	>200	>200	>200
7b	>200	>200	>200
7c	20	20	100
7d	20	20	50
7e	>200	>200	>200
7f	>200	>200	>200
7g	5	5	50
7h	>200	>200	>200
7i	2	2	20
7j	5	5	50
7k	5	5	20
7l	100	100	>200
7m	>200	>200	>200
7n	>200	>200	>200
7o	5	5	20
7p	50	50	100
8a	>200	>200	>200
8b	>200	>200	>200
8c	>200	>200	>200
8d	50	50	100
8e	100	100	>200
8f	100	100	>200
8g	>200	>200	>200
8h	5	5	50
8i	>200	>200	>200
8j	5	5	20
8k	>200	>200	>200
8l	>200	>200	>200
8m	20	20	50
8n	100	100	>200
Rifabutin	0.05	0.05	0.05
Amikacin	2	2	2

5.2. General method for synthesis of ethyl 4-(2-hydroxyethyl)amino-2-(un)substituted-6-(substituted amino)pyrimidine-5-carboxylate (**6**)

A mixture of ethyl 4-chloro-2-(substituted amino)pyrimidine-5-carboxylate [38] (0.01 mol) and ethanolamine (0.61 g, 0.01 mol) was refluxed in ethanol (40 mL) for 30 min to 2 h. The completion of reaction was monitored through TLC. After the completion of reaction, the reaction content was poured into ice–water mixture with constant stirring. The content was allowed to stand at 20 °C overnight and the solid crystals obtained were filtered, washed with cold water, dried and recrystallized from ethanol–water mixture (50:50).

5.2.1. Ethyl 4-(2-hydroxyethyl)amino-6-phenylaminopyrimidine-5-carboxylate (**6d**)

IR (KBr, cm^{-1}): 3367 (OH), 3226 (NH), 1680 (C=O); ^1H NMR ($CDCl_3$, δ ppm): 1.33–1.41 (t, 3H, OCH_2CH_3, $J = 7.04$ Hz); 4.28–4.31 (t, 2H, $NHCH_2CH_2$, $J = 7.68$ Hz); 4.65–4.67(t, 2H, $NHCH_2CH_2$, $J = 7.68$ Hz); 4.68–4.72 (q, 2H, OCH_2CH_3, $J = 14.12$ Hz); 5.35–5.42 (b, 1H, $NHCH_2CH_2$); 7.20–7.36 (m, 5H, NHAr*H*); 8.11–8.23 (t, 1H, O*H*, $J = 5.24$ Hz); 8.46 (s, 1H, NC*H*N); 11.38 (s, 1H, N*H*Ar); MS: *m*/*z* 302 (M^+), 303 (M + 1); Anal. calcd for $C_{15}H_{18}N_4O_3$: C, 59.60; H, 5.96; N, 18.54; Found: C, 59.88; H, 6.12; N, 18.62.

5.2.2. Ethyl 4-(2-hydroxyethyl)amino-6-(4-methylphenyl)aminopyrimidine-5-carboxylate (**6g**)

IR (KBr, cm^{-1}): 3375 (OH), 3234 (NH), 1674 (C=O); ^1H NMR ($CDCl_3$/DMSO-d_6, δ ppm): 1.29 (s, 3H, ArCH_3); 1.32–1.41 (t, 3H, OCH_2CH_3, $J = 7.04$ Hz); 4.12–4.24 (t, 2H, $NHCH_2CH_2$, $J = 7.68$ Hz);

4.42–4.55 (t, 2H, $NHCH_2CH_2$, $J = 7.68$ Hz); 4.65–4.75 (q, 2H, OCH_2CH_3, $J = 14.12$ Hz); 5.66–5.79 (b, 1H, $NHCH_2CH_2$); 6.89–7.17 (m, 4H, NHAr*H*); 8.10–8.22 (t, 1H, O*H*, $J = 5.24$ Hz); 8.31 (s, 1H, NC*H*N); 11.45 (s, 1H, N*H*Ar); MS: *m*/*z* 316 (M^+), 317 (M + 1); Anal. calcd for $C_{16}H_{20}N_4O_3$: C, 60.76; H, 6.33; N, 17.72; Found: C, 60.42; H, 6.41; N, 17.63.

5.2.3. Ethyl 4-(2-hydroxyethyl)amino-6-(4-methoxyphenyl)aminopyrimidine-5-carboxylate (**6i**)

IR (KBr, cm^{-1}): 3377 (OH), 3226 (NH), 1672 (C═O); ^1H NMR ($CDCl_3$/DMSO-d_6, δ ppm): 1.35–1.47 (t, 3H, OCH_2CH_3, $J = 7.04$ Hz); 3.80 (s, 3H, $ArOCH_3$); 4.28–4.35 (t, 2H, $NHCH_2CH_2$, $J = 7.68$ Hz); 4.62–4.67 (t, 2H, $NHCH_2CH_2$, $J = 7.68$ Hz); 4.71–4.78 (q, 2H, OCH_2CH_3, $J = 14.12$ Hz); 5.37–5.47 (b, 1H, $NHCH_2CH_2$); 7.08–7.32 (m, 4H, NHAr*H*); 8.15–8.28 (t, 1H, O*H*, $J = 5.24$ Hz); 8.52 (s, 1H, NC*H*N); 11.45 (s, 1H, N*H*Ar); MS: *m*/*z* 332 (M^+), 333 (M + 1); Anal. calcd for $C_{16}H_{20}N_4O_4$: C, 57.83; H, 6.02; N, 16.87; Found: C, 58.02; H, 6.30; N, 17.03.

5.3. General method for synthesis of ethyl 2-(un)substituted-7-(substituted amino)-2,3-dihydoimidazo[1,2-c]pyrimidine-8-carboxylate (**7a**–**p** and **8a**–**n**)

To a solution of ethyl 4-(2-hydroxyethyl)amino-2-(un) substituted-6-(substituted amino)pyrimidine-5-carboxylate (0.01 mol) in anhydrous toluene (40 mL), was added phosphorous oxychloride (1.68 g, 0.01 mol) and the resultant reaction mixture was refluxed for 6–8 h. The excess of solvent was removed under reduced pressure to obtain sticky mass, which was poured into ice–water mixture with constant stirring. It was allowed to stand for 6 h at room temperature and neutralized with saturated solution of sodium bicarbonate. The solid product obtained was washed with cold water, dried and recrystallized from dichloromethane–*n*-hexane.

5.3.1. Ethyl 7-(methylamino)-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**7a**)

IR (KBr, cm^{-1}): 3375 (NH), 1676 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.30–1.34 (t, 3H, $-CO_2CH_2CH_3$, $J = 7.04$ Hz); 2.23–2.27 (d, 3H, $NHCH_3$, $J = 6.25$ Hz); 3.49–3.59 (b, 1H, $NHCH_3$); 3.90–3.95 (t, 2H, $=NCH_2CH_2N-$, $J = 7.68$ Hz); 4.06–4.11 (t, 2H, $=NCH_2CH_2N-$, $J = 7.68$ Hz); 4.34–4.40 (q, 2H, $-CO_2CH_2CH_3$, $J = 14.68$ Hz); 7.87 (s, 1H, NC*H*N), MS: *m*/*z* 222 (M^+), 223 (M + 1); Anal. calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21; Found: C, 53.73; H, 6.49; N, 25.07.

5.3.2. Ethyl 7-(ethylamino)-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**7b**)

IR (KBr, cm^{-1}): 3360 (NH), 1680 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.21–1.26 (t, 3H, $NHCH_2CH_3$, $J = 7.06$ Hz); 1.32–1.40 (t, 3H, $-CO_2CH_2CH_3$, $J = 7.68$ Hz); 2.23–2.37 (m, 2H, $NHCH_2CH_3$); 3.49–3.59 (b, 1H, NHC_2H_5); 3.90–3.95 (t, 2H, $=NCH_2CH_2N-$, $J = 7.68$ Hz); 4.06–4.11 (t, 2H, $=NCH_2CH_2N-$, $J = 7.68$ Hz); 4.34–4.40 (q, 2H, $-CO_2CH_2CH_3$, $J = 14.68$ Hz); 7.87 (s, 1H, NC*H*N), MS: *m*/*z* 236 (M^+), 237 (M + 1); Anal. calcd for $C_{11}H_{16}N_4O_2$: C, 55.92; H, 6.83; N, 23.71; Found: C, 55.78; H, 6.98; N, 23.75.

5.3.3. Ethyl 7-(benzylamino)-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**7c**)

IR (KBr, cm^{-1}): 3361 (NH), 1680 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.36–1.40 (t, 3H, $-CO_2CH_2CH_3$, $J = 7.04$ Hz); 3.90–3.95 (t, 2H, $=NCH_2CH_2N-$, $J = 9.08$ Hz); 4.06–4.11 (t, 2H, $=NCH_2CH_2N-$, $J = 9.08$ Hz); 4.34–4.40 (q, 2H, $-CO_2CH_2CH_3$, $J = 14.16$ Hz); 4.73–4.75 (d, 2H, $NHCH_2Ar$); 7.24–7.35 (m, 5H, CH_2ArH); 7.73 (s, 1H, NC*H*N); 10.09 (b, 1H, $NHCH_2Ar$), MS: *m*/*z* 298 (M^+), 299 (M + 1); Anal. calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78; Found: C, 64.31; H, 6.02; N, 18.34.

5.3.4. Ethyl 7-(phenylamino)-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**7d**)

IR (KBr, cm^{-1}): 3305 (NH), 1676 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.47–1.51 (t, 3H, $-CO_2CH_2CH_3$, $J = 7.04$ Hz); 4.28–4.31 (t, 2H, $=NCH_2CH_2N-$, $J = 8.08$ Hz); 4.65–4.67 (t, 2H, $=NCH_2CH_2N-$, $J = 8.08$ Hz); 4.68–4.72 (q, 2H, $-CO_2CH_2CH_3$, $J = 14.12$ Hz); 7.20–7.36 (m, 5H, NHAr*H*); 8.46 (s, 1H, NC*H*N); 11.38 (s, 1H, N*H*Ar), MS: *m*/*z* 284 (M^+), 285 (M + 1); Anal. calcd for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71; Found: C, 63.78; H, 5.25; N, 19.55.

5.3.5. Ethyl 7-[(2-methylphenyl)amino]-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**7e**)

IR (KBr, cm^{-1}): 3307 (NH), 1641 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.41–1.50 (t, 3H, $-CO_2CH_2CH_3$, $J = 7.04$ Hz); 2.43 (s, 3H, $ArCH_3$); 4.28–4.31 (t, 2H, $=NCH_2CH_2N-$, $J = 8.08$ Hz); 4.63–4.67 (t, 2H, $=NCH_2CH_2N-$, $J = 8.08$ Hz); 4.68–4.72 (q, 2H, $-CO_2CH_2CH_3$, $J = 14.12$ Hz); 7.21–7.35 (m, 4H, NHAr*H*); 8.49 (s, 1H, NC*H*N); 11.35 (s, 1H, N*H*Ar), MS: *m*/*z* 298 (M^+), 299 (M + 1); Anal. calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78; Found: C, 64.38; H, 5.89; N, 18.62.

5.3.6. Ethyl 7-[(3-methylphenyl)amino]-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**7f**)

IR (KBr, cm^{-1}): 3394 (NH), 1668 (C═O); ^1H NMR ($CDCl_3$, δ ppm): 1.48–1.52 (t, 3H, $-CO_2CH_2CH_3$, $J = 7.04$ Hz); 3.81 (s, 3H, $ArCH_3$); 4.27–4.32 (t, 2H, $=NCH_2CH_2N-$, $J = 9.08$ Hz); 4.49–4.54 (t, 2H, $=NCH_2CH_2N-$, $J = 9.08$ Hz); 4.65–4.71 (q, 2H, $-CO_2CH_2CH_3$, $J = 14.12$ Hz); 7.41–7.71 (m, 4H, NHAr*H*); 10.01 (s, 1H, NC*H*N); 11.49 (s, 1H, N*H*Ar), MS: *m*/*z* 298 (M^+), 299 (M + 1); Anal. calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78; Found: C, 63.99; H, 5.72; N, 18.35.

5.3.7. Ethyl 7-[(4-methylphenyl)amino]-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**7g**)

IR (KBr, cm^{-1}): 3300 (NH), 1680 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.47–1.51 (t, 3H, $-CO_2CH_2CH_3$, $J = 7.04$ Hz); 2.37 (s, 3H, $ArCH_3$); 4.28–4.31 (t, 2H, $=NCH_2CH_2N-$, $J = 8.08$ Hz); 4.65–4.67 (t, 2H, $=NCH_2CH_2N-$, $J = 8.08$ Hz); 4.68–4.72 (q, 2H, $-CO_2CH_2CH_3$, $J = 14.12$ Hz); 7.20–7.36 (m, 4H, NHAr*H*); 8.46 (s, 1H, NC*H*N); 11.38 (s, 1H, N*H*Ar), MS: *m*/*z* 298 (M^+), 299 (M + 1); Anal. calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78; Found: C, 64.18; H, 5.76; N, 18.70.

5.3.8. Ethyl 7-[(2-methoxyphenyl)amino]-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**7h**)

IR (KBr, cm^{-1}): 3300 (NH), 1680 (C═O); ^1H NMR (DMSO-d_6, δ ppm): 1.35–1.41 (t, 3H, OCH_2CH_3, $J = 7.04$ Hz); 2.13 (s, 3H, $ArOCH_3$); 3.92–3.98 (t, 2H, $=NCH_2CH_2N-$, $J = 8.08$ Hz); 4.04–4.12 (t, 2H, $=NCH_2CH_2N-$, $J = 8.08$ Hz); 4.41–4.47 (q, 2H, OCH_2CH_3, $J = 14.12$ Hz); 7.12–7.29 (m, 4H, NHAr*H*); 7.72(s, 1H, NC*H*N); 11.35–11.42 (s, 1H, N*H*Ar); MS: *m*/*z* 314 (M^+), 315 (M + 1); Anal. calcd for $C_{16}H_{18}N_4O_3$: C, 61.13; H, 5.77; N, 17.82; Found: C, 61.55; H, 5.38; N, 17.81.

5.3.9. Ethyl 7-[(4-methoxyphenyl)amino]-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**7i**)

IR (KBr, cm^{-1}): 3336 (NH), 1645 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.41–1.47 (t, 3H, $-CO_2CH_2CH_3$, $J = 7.04$ Hz); 3.82 (s, 3H, $ArOCH_3$); 3.92–3.98 (t, 2H, $=NCH_2CH_2N-$, $J = 8.08$ Hz); 4.08–4.12 (t, 2H, $=NCH_2CH_2N-$, $J = 8.08$ Hz); 4.40–4.45 (q, 2H, $-CO_2CH_2CH_3$, $J = 14.12$ Hz); 7.27–7.32 (m, 4H, NHAr*H*); 7.73 (s, 1H,

NC*H*N); 11.35–11.42 (s, 1H, N*H*Ar), MS: *m*/*z* 314 (M^+), 315 (M + 1); Anal. calcd for $C_{16}H_{18}N_4O_3$: C, 61.13; H, 5.77; N, 17.82; Found: C, 60.82; H, 5.81; N, 17.59.

*5.3.10. Ethyl 7-[(4-fluorophenyl)amino]-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**7k**)*

IR (KBr, cm^{-1}): 3292 (NH), 1678 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.29–1.37 (t, 3H, $-CO_2CH_2CH_3$, *J* = 7.04 Hz); 3.85–3.92 (t, 2H, $=NCH_2CH_2N-$, *J* = 8.08 Hz); 3.99–4.10 (t, 2H, $=NCH_2CH_2N-$, *J* = 8.08 Hz); 4.35–4.47 (q, 2H, $-CO_2CH_2CH_3$, *J* = 14.12 Hz); 7.59–7.76 (m, 4H, NHAr*H*); 8.21 (s, 1H, NC*H*N); 11.21(s, 1H, N*H*Ar), MS: *m*/*z* 302 (M^+), 303 (M + 1); Anal. calcd for $C_{15}H_{15}FN_4O_2$: C, 59.60; H, 5.00; N, 18.53; Found: C, 59.67; H, 5.01; N, 18.45.

*5.3.11. Ethyl 7-[(3-trifluoromethylphenyl)amino]-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**7l**)*

IR (KBr, cm^{-1}): 3361 (NH), 1689 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.41–1.47 (t, 3H, $-CO_2CH_2CH_3$, *J* = 7.04 Hz); 3.92–4.01 (t, 2H, $=NCH_2CH_2N-$, *J* = 8.08 Hz); 4.08–4.15 (t, 2H, $=NCH_2CH_2N-$, *J* = 8.08 Hz); 4.45–4.52 (q, 2H, $-CO_2CH_2CH_3$, *J* = 14.12 Hz); 6.92–7.08 (m, 4H, Ar*H*); 8.47 (s, 1H, NC*H*N); 11.68 (s, 1H, N*H*Ar), MS: *m*/*z* 352 (M^+); Anal. calcd for $C_{16}H_{15}F_3N_4O_2$: C, 54.55; H, 4.29; N, 15.90; Found: C, 54.11; H, 3.99; N, 15.52.

*5.3.12. Ethyl 7-[(2-chlorophenyl)amino]-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**7m**)*

IR (KBr, cm^{-1}): 3394 (NH), 1668 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.21–1.34 (t, 3H, $-CO_2CH_2CH_3$, *J* = 7.04 Hz); 3.67–3.85 (t, 2H, $=NCH_2CH_2N-$, *J* = 8.08 Hz); 3.93–4.00 (t, 2H, $=NCH_2CH_2N-$, *J* = 8.08 Hz); 4.26–4.32 (q, 2H, $-CO_2CH_2CH_3$, *J* = 14.12 Hz); 7.39–7.51 (m, 4H, NHAr*H*); 8.13 (s, 1H, NC*H*N); 11.19 (s, 1H, N*H*Ar), MS: *m*/*z* 318 (M^+), 320 (M + 2); Anal. calcd for $C_{15}H_{15}ClN_4O_2$: C, 56.52; H, 4.74; N, 17.58; Found: C, 56.24; H, 4.51; N, 17.50.

*5.3.13. Ethyl 7-[(3-chlorophenyl)amino]-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**7n**)*

IR (KBr, cm^{-1}): 3365 (NH), 1676 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.28–1.39 (t, 3H, $-CO_2CH_2CH_3$, *J* = 7.04 Hz); 3.62–3.80 (t, 2H, $=NCH_2CH_2N-$, *J* = 8.08 Hz); 3.95–4.08 (t, 2H, $=NCH_2CH_2N-$, *J* = 8.08 Hz); 4.31–4.45 (q, 2H, $-CO_2CH_2CH_3$, *J* = 14.12 Hz); 7.31–7.52 (m, 4H, NHAr*H*); 8.25 (s, 1H, NC*H*N); 11.20 (s, 1H, N*H*Ar), MS: *m*/*z* 318 (M^+), 320 (M + 2); Anal. calcd for $C_{15}H_{15}ClN_4O_2$: C, 56.52; H, 4.74; N, 17.58; Found: C, 56.24; H, 4.42; N, 17.19.

*5.3.14. Ethyl 7-[(4-chlorophenyl)amino]-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**7o**)*

IR (KBr, cm^{-1}): 3304 (NH), 1653 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.20–1.31 (t, 3H, $-CO_2CH_2CH_3$, *J* = 7.04 Hz); 3.67–3.85 (t, 2H, $=NCH_2CH_2N-$, *J* = 8.08 Hz); 3.92–4.01 (t, 2H, $=NCH_2CH_2N-$, *J* = 8.08 Hz); 4.35–4.47 (q, 2H, $-CO_2CH_2CH_3$, *J* = 14.12 Hz); 7.35–7.50 (m, 4H, NHAr*H*); 8.15 (s, 1H, NC*H*N); 11.25 (s, 1H, N*H*Ar), MS: *m*/*z* 318 (M^+), 320 (M + 2); Anal. calcd for $C_{15}H_{15}ClN_4O_2$: C, 56.52; H, 4.74; N, 17.58; Found: C, 56.61; H, 4.59; N, 17.24.

*5.3.15. Ethyl 7-[(4-bromophenyl)amino]-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**7p**)*

IR (KBr, cm^{-1}): 3400 (NH), 1680 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.21–1.34 (t, 3H, $-CO_2CH_2CH_3$, *J* = 7.04 Hz); 3.77–3.84 (t, 2H, $=NCH_2CH_2N-$, *J* = 8.08 Hz); 3.93–4.00 (t, 2H, $=NCH_2CH_2N-$, *J* = 8.08 Hz); 4.16–4.27 (q, 2H, $-CO_2CH_2CH_3$, *J* = 14.12 Hz); 7.39–7.51 (m, 4H, NHAr*H*); 8.09 (s, 1H, NC*H*N); 11.17 (s, 1H, N*H*Ar), MS: *m*/*z* 363 (M^+), 365 (M + 2); Anal. calcd for $C_{15}H_{15}BrN_4O_2$: C, 49.60; H, 4.16; N, 15.43. Found: C, 49.36; H, 3.78; N, 14.98.

*5.3.16. Ethyl 7-(methylamino)-5-phenyl-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**8a**)*

IR (KBr, cm^{-1}): 3228 (NH), 1672 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.23–1.28 (t, 3H, $-CO_2CH_2CH_3$, *J* = 7.04 Hz); 1.49–1.54 (d, 3H, $NHCH_3$); 3.40–3.48 (b, 1H, $NHCH_3$); 3.51–3.55 (q, 2H, $-CO_2CH_2CH_3$, *J* = 14.08 Hz); 3.97–4.02 (t, 2H, $=NCH_2CH_2N-$, *J* = 7.68 Hz); 4.22–4.29 (t, 2H, $=NCH_2CH_2N-$, *J* = 7.68 Hz); 7.40–7.48 (m, 5H, Ar*H*), MS: *m*/*z* 298 (M^+), 299 (M + 1); Anal. calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78; Found: C, 64.22; H, 6.02; N, 18.51.

*5.3.17. Ethyl 7-(ethylamino)-5-phenyl-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**8b**)*

IR (KBr, cm^{-1}): 3340 (NH), 1695 (C═O); ^1H NMR ($CDCl_3$/DMSO-d_6, δ): 1.11–1.15 (t, 3H, $NHCH_2CH_3$, *J* = 7.06 Hz); 1.29–1.31 (t, 3H, OCH_2CH_3, *J* = 7.04 Hz); 3.21–3.26 (m, 2H, $NHCH_2CH_3$); 3.31–3.36 (b, 1H, NHC_2H_5); 3.97–4.02 (t, 2H, $=NCH_2CH_2N-$, *J* = 7.68 Hz); 4.22–4.29 (t, 2H, $=NCH_2CH_2N-$, *J* = 7.68 Hz); 4.51–4.55 (q, 2H, OCH_2CH_3, *J* = 14.08 Hz); 7.49–7.59 (m, 5H, Ar*H*); MS: *m*/*z* 312 (M^+), 313 (M + 1); Anal. calcd for $C_{17}H_{20}N_4O_2$: C, 65.37; H, 6.45; N, 17.94; Found: C, 65.04; H, 6.25; N, 17.83.

*5.3.18. Ethyl 7-(benzylamino)-5-phenyl-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**8c**)*

IR (KBr, cm^{-1}): 3240 (NH), 1680 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.19–1.22 (t, 3H, $-CO_2CH_2CH_3$, *J* = 7.04 Hz); 3.22–3.29 (b, 1H, $NHCH_2Ar$); 4.17–4.22 (t, 2H, $=NCH_2CH_2N-$, *J* = 7.68 Hz); 4.55–4.60 (t, 2H, $=NCH_2CH_2N-$, *J* = 7.68 Hz); 4.63–4.68 (q, 2H, $-CO_2CH_2CH_3$, *J* = 14.08 Hz); 4.72–4.77 (d, 2H, $NHCH_2Ar$, *J* = 6.24 Hz); 7.23–7.41 (m, 5H, CH_2ArH); 7.56–7.79 (m, 5H, Ar*H*), MS: *m*/*z* 374 (M^+), 375 (M + 1); Anal. calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96; Found: C, 70.27; H, 5.63; N, 15.23.

*5.3.19. Ethyl 7-(phenylamino)-5-phenyl-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**8d**)*

IR (KBr, cm^{-1}): 3215 (NH), 1677 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.49–1.52 (t, 3H, $-CO_2CH_2CH_3$, *J* = 7.06 Hz); 4.17–4.22 (t, 2H, $=NCH_2CH_2N-$, *J* = 9.68 Hz); 4.58–4.62 (t, 2H, $=NCH_2CH_2N-$, *J* = 9.68 Hz); 4.63–4.68 (q, 2H, $-CO_2CH_2CH_3$, *J* = 14.08 Hz); 7.23–7.41 (m, 5H, Ar*H*); 7.55–7.79 (m, 5H, NHAr*H*); 11.42(s, 1H, N*H*Ar), MS: *m*/*z* 360 (M^+), 361 (M + 1); Anal. calcd for $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.55; Found: C, 69.71; H, 5.48; N, 15.82.

*5.3.20. Ethyl 7-[(2-methylphenyl)amino]-5-phenyl-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**8e**)*

IR (KBr, cm^{-1}): 3302 (NH), 1676 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.42–1.46 (t, 3H, $-CO_2CH_2CH_3$, *J* = 7.04 Hz); 1.88 (s, 3H, $ArCH_3$); 3.95–3.99 (t, 2H, $=NCH_2CH_2N-$, *J* = 10.80 Hz); 4.05–4.08 (t, 2H, $=NCH_2CH_2N-$, *J* = 10.80 Hz); 4.45–4.51 (q, 2H, $-CO_2CH_2CH_3$, *J* = 14.24 Hz); 6.86–7.01 (m, 4H, NHAr*H*); 7.49–7.67 (m, 5H, Ar–*H*); 11.81 (s, 1H, N*H*Ar), MS: *m*/*z* 374 (M^+), 375 (M + 1); Anal. calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96; Found: C, 70.35; H, 5.57; N, 14.73.

*5.3.21. Ethyl 7-[(4-methylphenyl)amino]-5-phenyl-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**8f**)*

IR (KBr, cm^{-1}): 3334 (NH), 1645 (C═O); ^1H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.50–1.54 (t, 3H, $-CO_2CH_2CH_3$, *J* = 7.04 Hz); 2.35 (s, 3H, $ArCH_3$); 4.28–4.33 (t, 2H, $=NCH_2CH_2N-$, *J* = 10.56 Hz); 4.53–4.58

(t, 2H, =NCH_2CH_2N–, J = 10.56 Hz); 4.70–4.75 (q, 2H, –CO_2CH_2CH_3, J = 14.12 Hz); 7.16–7.43 (m, 4H, NHAr*H*); 7.55–7.75 (m, 5H, Ar*H*); 11.50 (s, 1H, N*H*Ar), MS: m/z 374 (M^+), 375 (M + 1); Anal. calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96; Found: C, 70.55; H, 5.97; N, 14.75.

*5.3.22. Ethyl 7-[(2-methoxyphenyl)amino]-5-phenyl-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**8g**)*

IR (KBr, cm^{-1}): 3352 (NH), 1668 (C=O); ^{1}H NMR ($CDCl_3$/DMSO-d_6, δ ppm): 1.48–1.52 (t, 3H, OCH_2CH_3, J = 7.04 Hz); 3.80 (s, 3H, ArOCH_3); 4.27–4.32 (t, 2H, =NCH_2CH_2N–, J = 10.56 Hz); 4.49–4.54 (t, 2H, =NCH_2CH_2N–, J = 10.56 Hz); 4.65–4.71 (q, 2H, OCH_2CH_3, J = 14.12 Hz); 7.41–7.44 (m, 4H, NHAr*H*); 7.54–7.72 (m, 5H, Ar*H*); 11.42 (s, 1H, N*H*Ar); MS: m/z 390 (M^+), 391 (M + 1); Anal. calcd for $C_{22}H_{22}N_4O_3$: C, 67.68; H, 5.68; N, 14.35; Found: C, 67.65; H, 5.52; N, 13.98.

*5.3.23. Ethyl 7-[(4-methoxyphenyl)amino]-5-phenyl-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**8h**)*

IR (KBr, cm^{-1}): 3315 (NH), 1676 (C=O); ^{1}H NMR ($CDCl_3$/DMSO-d_6, δ ppm): 1.45–1.52 (t, 3H, –CO_2CH_2CH_3, J = 7.04 Hz); 3.08 (s, 3H, ArOCH_3); 3.97–4.02 (t, 2H, =NCH_2CH_2N–, J = 10.56 Hz); 4.39–4.45 (t, 2H, =NCH_2CH_2N–, J = 10.56 Hz); 4.61–4.67 (q, 2H, –CO_2CH_2CH_3, J = 14.12 Hz); 7.35–7.49 (m, 4H, NHAr*H*); 7.55v7.67 (m, 5H, Ar*H*); 11.55 (s, 1H, N*H*Ar), MS: m/z 390 (M^+), 391 (M + 1); Anal. calcd for $C_{22}H_{22}N_4O_3$: C, 67.68; H, 5.68; N, 14.35; Found: C, 67.39; H, 5.25; N, 14.21.

*5.3.24. Ethyl 7-[(2-fluorophenyl)amino]-5-phenyl-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**8i**)*

IR (KBr, cm^{-1}): 3226 (NH), 1647 (C=O); ^{1}H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.42–1.46 (t, 3H, –CO_2CH_2CH_3, J = 7.04 Hz); 3.94–4.00 (t, 2H, =NCH_2CH_2N–, J = 8.88 Hz); 4.06–4.11 (t, 2H, =NCH_2CH_2N–, J = 8.88 Hz); 4.45–4.51 (q, 2H, –CO_2CH_2CH_3, J = 14.24 Hz); 7.01–7.10 (m, 5H, Ar*H*); 7.47–7.66 (m, 3H, NHAr*H*); 11.68 (s, 1H, N*H*Ar), MS: m/z 378 (M^+), 379 (M + 1); Anal. calcd for $C_{21}H_{19}FN_4O_2$: C, 66.66; H, 5.06; N, 14.81; Found: C, 66.62; H, 4.86; N, 14.54.

*5.3.25. Ethyl 7-[(4-fluorophenyl)amino]-5-phenyl-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**8j**)*

IR (KBr, cm^{-1}): 3348 (NH), 1658 (C=O); ^{1}H NMR ($CDCl_3$/DMSO-d_6, δ ppm): 1.41–1.50 (t, 3H, OCH_2CH_3, J = 7.04 Hz); 4.01–4.11 (t, 2H, =NCH_2CH_2N–, J = 8.88 Hz); 4.15–4.22 (t, 2H, =NCH_2CH_2N–, J = 8.88 Hz); 4.42–4.52 (q, 2H, OCH_2CH_3, J = 14.24 Hz); 7.21–7.41 (m, 5H, Ar*H*); 7.48–7.55 (m, 4H, NHAr*H*); 11.72 (s, 1H, N*H*Ar); MS: m/z 378 (M^+), 379 (M + 1); Anal. calcd for $C_{21}H_{19}FN_4O_2$: C, 66.66; H, 5.06; N, 14.81; Found: C, 66.75; H, 5.14; N, 14.88.

*5.3.26. Ethyl 7-[(2-chlorophenyl)amino]-5-phenyl-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**8k**)*

IR (KBr, cm^{-1}): 3375 (NH), 1678 (C=O); ^{1}H NMR ($CDCl_3$/DMSO-d_6, δ ppm): 1.32–1.37 (t, 3H, OCH_2CH_3, J = 7.04 Hz); 4.17–4.22 (t, 2H, =NCH_2CH_2N–, J = 8.88 Hz); 4.58–4.62 (t, 2H, =NCH_2CH_2N–, J = 8.88 Hz); 4.63–4.68 (q, 2H, OCH_2CH_3, J = 14.24 Hz); 7.23–7.41 (m, 5H, Ar*H*); 7.55–7.79 (m, 4H, NHAr*H*); 11.37 (s, 1H, N*H*Ar); MS: m/z 395 (M^+), 397 (M + 2), 396 (M + 1); Anal. calcd for $C_{21}H_{19}ClN_4O_2$: C, 63.88; H, 4.85; N, 14.19; Found: C, 63.97; H, 4.82; N, 13.83.

*5.3.27. Ethyl 7-[(3-chlorophenyl)amino]-5-phenyl-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**8l**)*

IR (KBr, cm^{-1}): 3274 (NH), 1660 (C=O); ^{1}H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.41–1.52 (t, 3H, –CO_2CH_2CH_3, J = 7.04 Hz); 4.11–4.23 (t, 2H, =NCH_2CH_2N–, J = 8.88 Hz); 4.45–4.51 (t, 2H, =NCH_2CH_2N–, J = 8.88 Hz); 4.62–4.70 (q, 2H, –CO_2CH_2CH_3, J = 14.24 Hz); 7.21–7.45 (m, 5H, Ar*H*); 7.55–7.71 (m, 4H, NHAr*H*); 11.52 (s, 1H, N*H*Ar), MS: m/z 395 (M^+), 397 (M + 2), 396 (M + 1); Anal. calcd for $C_{21}H_{19}ClN_4O_2$: C, 63.88; H, 4.85; N, 14.19; Found: C, 63.58; H, 4.56; N, 14.01.

*5.3.28. Ethyl 7-[(4-chlorophenyl)amino]-5-phenyl-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**8m**)*

IR (KBr, cm^{-1}): 3361 (NH), 1670 (C=O); ^{1}H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.49–1.52 (t, 3H, –CO_2CH_2CH_3, J = 7.04 Hz); 4.17–4.22 (t, 2H, =NCH_2CH_2N–, J = 8.88 Hz); 4.55–4.59 (t, 2H, =NCH_2CH_2N–, J = 8.88 Hz); 4.62–4.69 (q, 2H, –CO_2CH_2CH_3, J = 14.24 Hz); 7.23–7.41 (m, 5H, Ar*H*); 7.51–7.69 (m, 4H, NHAr*H*); 11.51 (s, 1H, N*H*Ar), MS: m/z 395 (M^+), 397 (M + 2), 396 (M + 1); Anal. calcd for $C_{21}H_{19}ClN_4O_2$: C, 63.88; H, 4.85; N, 14.19; Found: C, 63.95; H, 4.89; N, 14.22.

*5.3.29. Ethyl 7-[(4-bromophenyl)amino]-5-phenyl-2,3-dihydroimidazo[1,2-c]pyrimidine-8-carboxylate (**8n**)*

IR (KBr, cm^{-1}): 3380 (NH), 1666 (C=O); ^{1}H NMR (DMSO-d_6/$CDCl_3$, δ ppm): 1.39–1.42 (t, 3H, –CO_2CH_2CH_3, J = 7.04 Hz); 4.28–4.31 (t, 2H, =NCH_2CH_2N–, J = 8.88 Hz); 4.58–4.62 (t, 2H, =NCH_2CH_2N–, J = 8.88 Hz); 4.68–4.72 (q, 2H, –CO_2CH_2CH_3, J = 14.24 Hz); 7.35–7.48 (m, 5H, Ar*H*); 7.55–7.79 (m, 4H, NHAr*H*); 11.45 (s, 1H, N*H*Ar), MS: m/z 439 (M^+), 441 (M + 2), 440 (M + 1); Anal. calcd for $C_{21}H_{19}BrN_4O_2$: C, 57.41; H, 4.36; N, 12.75; Found: C, 57.49; H, 4.41; N, 12.86.

5.4. Antimycobacterial activity

All the test compounds were evaluated against *M. tuberculosis* H37Rv strain. The sensitivity testing for *M. tuberculosis* H37Rv strain was performed by 1% proportion method [39]. The MIC values were determined by the serial dilution technique using L–J medium, added with Gruft mycobacterial supplement. *M. tuberculosis* H37Rv strain was obtained from New Delhi TB Centre, New Delhi and was maintained on L–J medium at 37 °C. All experiments were performed in triplicate. The MIC values were obtained from the lowest concentration where the tubes remained clear indicating complete inhibition of the bacterial growth at that concentration. The MIC values for antimycobacterial activity are presented in Table 2.

The inoculum was prepared from master culture by transferring several spadesful of growth to a sterilized screw cap bottle containing 6–8 glass beads and 3 mL of Tween-albumin liquid medium (Middlebrook 7H9) and the content of the bottle was homogenized. Large particles were allowed to settle and the supernatant suspension was withdrawn. The suspension was adjusted to 3×10^8 CFU using McFarland turbidity standard (incubation at 37 °C for 7 days) and the number of CFU per mL of the final inoculum was confirmed by plating serial dilutions on L–J medium. The compounds were dissolved in DMSO to prepare a solution of 3 mg/mL so that when 1 mL of this stock solution is diluted to 15 mL, a final concentration of 200 μg/mL in the culture medium is obtained. From this, a series of consecutive double fold dilutions (100, 50, 20, 10, 5, 2 μg/mL) was prepared for all the compounds and tested against *M. tuberculosis* H37Rv strain. *M. tuberculosis* H37Rv culture inoculum (0.1 mL), as prepared above was added in L–J medium slants (15 mL) previously containing a specified concentration of the test compounds. Rifabutin and amikacin were used as standard drugs. The inoculated L–J medium slants were incubated at 37 °C for 30 days and results were observed at 14th, 21st and 30th day for the growth of mycobacteria. MIC values were determined for H37Rv strain of *M. tuberculosis* as described above.

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