Bioorganic Chemistry 99 (2020) 103774

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Benzimidazoquinazolines as new potent anti-TB chemotypes: Design, synthesis, and biological evaluation

Pradeep S. Jadhavar[a], Kshitij I. Patel[a], Tejas M. Dhameliya[a], Nirjhar Saha[a], Maulikkumar D. Vaja[a], Vagolu Siva Krishna[b], Dharmarajan Sriram[b], Asit K. Chakraborti[a,*]

[a] Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S.A.S. Nagar, Punjab 160062, India
[b] Department of Pharmacy, Birla Institute of Technology & Science – Pilani, Hyderabad Campus, Jawahar Nagar, Hyderabad 500 078, India

ARTICLE INFO

Keywords:
Polyheterocycle
Benzimidazoquinolines
New anti-TB chemotypes
Anti-TB (H37Rv) activity
INH resistant-Mtb

ABSTRACT

In search for new molecular entities as anti-TB agents, the benzimidazoquinazoline polyheterocyclic scaffold has been designed adopting the scaffold hopping strategy. Thirty-two compounds have been synthesized through an improved tandem decarboxylative nucleophilic addition cyclocondensation reaction of *o*-phenylenediamine with isatoic anhydride followed by further cyclocondensation of the intermediately formed 2-(*o*-aminoaryl) benzimidazole with trialkyl orthoformate/acetate. The resultant benzimidazoquinazolines were evaluated in vitro for anti-TB activity against *M. tuberculosis* $H_{37}Rv$ (ATCC27294 strain). Fourteen compounds exhibiting MIC values in the range of 0.4–6.25 μg/mL were subjected to cell viability test against RAW 264.7 cell lines and were found to be non-toxic (< 30% inhibition at 50 μg/mL). The active compounds were further evaluated against INH resistant Mtb strains. The most active compound **6x** [MIC (H37Rv) of 0.4 μg/mL] and the compound **6d** [MIC (H37Rv) of 0.78 μg/mL] were also found to be active against INH resistant Mtb strain with MIC values of 12.5 and 0.78 μg/mL, respectively.

1. Introduction

Tuberculosis (TB), a highly contagious and chronic infectious disease, responsible for the estimated death of 1.3 million TB infected and 300 000 TB-HIV co-infected patients in 2017 [1] has plagued the human being since ancient times. The path finding discovery by Robert Koch [2] on identification of *Mycobacterium tuberculosis* (Mtb) as the causative agent for this deadly infection has provided impetus to scientists to develop therapeutic agents to combat with TB. However, despite of the advances in our understanding of the disease pathogenesis of Mtb, it has been difficult to treat TB which continues to be the reason of high death toll of human lives. Recently bedaquiline and delamanid have been approved for treatment of multi-drug resistant tuberculosis (MDR-TB) independently. The clinical trials attempted in India, South Africa and Armenia to use both of these drugs in combination on TB patients resulted in a safe combination with low risk of cardiotoxicity and a few adverse side effects [3]. The emergence of resistance strains of Mtb such as the extensively drug resistant tuberculosis (XDR-TB), and total drug resistant tuberculosis (TDR-TB), the treatment and control of TB infection adopting the directly observed treatment short therapy (DOTS) using the first line and second line anti-TB drugs is being realized to be inadequate to combat with TB [4–9]. Therefore, there is pressing need for development of new anti-TB agents effective against drug sensitive and drug resistant strains of Mtb.

1.1. Design

Towards our endeavour in finding new anti-TB chemotypes [10–14] we realized that designing polyheterocyclic scaffold would offer new and more effective therapeutic agents to treat TB. We were attracted by the anti-TB potential of the 2-substituted benzimidazole core [15–20] and the quinazoline motif [21–24]. This, inspired us to adopt the scaffold hopping strategy [11,13,14,25–28] to design the benzimidazoquinazoline polyheterocyclic motif (Fig. 1) as new anti-TB scaffold. We observed that though there are limited reports on the biological activities of benzimidazoquinazolines such as anti-convulsant [29], anti-cancer [30–32], anti-inflammatory [33], anti-fungal [34], and anti-microbial [35,36] activities that are indicative of the pharmacophoric potential of the benzimidazoquinazoline scaffold, however, there has been no report on the anti-TB activity of this motif. Hence, we planned to synthesize alkylimidazoquinoline derivatives and evaluate their anti-TB activity.

* Corresponding author at: Department of Chemistry, Indian Institute of Technology- Ropar (IIT-Ropar), Rupnagar, Punjab 140001, India.
E-mail addresses: akchakraborti@niper.ac.in, chakrabortiak@iitrpr.ac.in (A.K. Chakraborti).

https://doi.org/10.1016/j.bioorg.2020.103774
Received 11 February 2020; Accepted 16 March 2020
Available online 19 March 2020

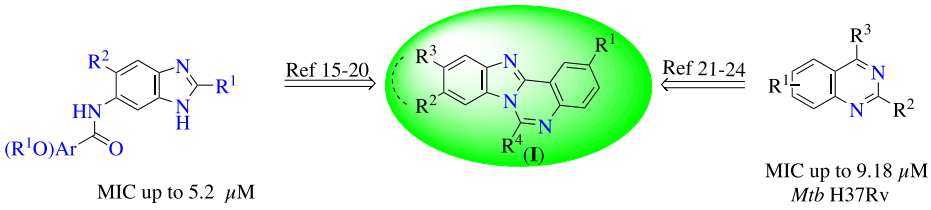
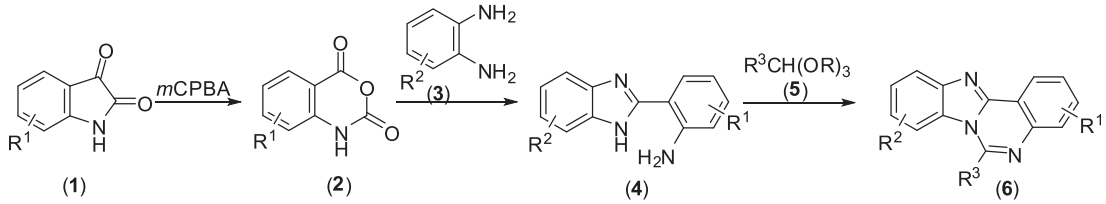


Fig. 1. Design of benzimidazoquinazoline motif as new anti-TB scaffold.



Scheme 1. Synthetic route for the preparation of 2-alkylbenzimidazoquinazolines.

2. Results and discussion

2.1. Chemistry

The target benzimidazoquinazoline derivatives (**6**) were synthesized following the route depicted in Scheme 1 that involved the tandem nucleophilic attack of the *o*-phenylenediamines (**3**) on the isatoic anhydrides (**2**), prepared from the corresponding isatins (**1**), and decarboxylative cyclocondensation to form the intermediate 2-(2′-aminophenyl)benzimidazoles (**4**) followed by cyclocondensation reaction with trialkyl orthoformate/acetate (**5**) derivatives.

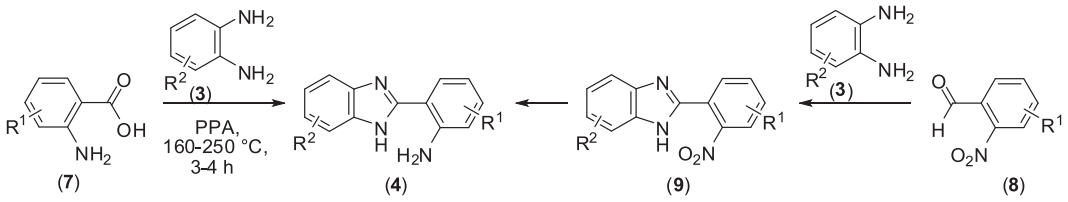
During our initial attempt towards the execution of the synthetic plan we realized that the literature reports for the preparation of the key intermediates 2-(2′-aminophenyl)-1*H*-benzimidazoles (**4**) involve either (i) direct condensation of 2-aminobenzoic acids (**7**) with *o*-phenylenediamines (**3**) in polyphosphoric acid (PPA) at 160–250 °C for 3–4 h [37–39] or (ii) a multi-step sequence involving the oxidative cyclocondensation of *o*-phenylenediamines (**3**) with *o*-nitrobenzaldehydes (**8**) to form the corresponding 2-(2′-nitrophenyl)-1*H*-benzimidazoles (**9**) followed by reduction of the nitro group [40–46] (Scheme 2).

The direct condensation approach is desirable compared to the two step oxidative cyclocondensation reduction process as it would avoid the use of large amount of transition metal-based reagents required as oxidizing and reducing agents. However, due to the poor electrophilicity of the carboxyl group in **7** it becomes necessary to perform the reaction in PPA at high temperature. Though the requirement to use such harsh reaction condition for benzazole ring formation can be avoided in performing the direct cyclocondensation under microwave heating [47,48] the electrophilic activation of the carboxylic acid to the aryl ester or acid chloride [49–51] would enable benzazole formation under milder conditions. Towards this, the isatoic anhydrides (**2**) are recognised as the synthetic equivalents of electrophilically activated masked 2-aminobenzoic acids (**7**).

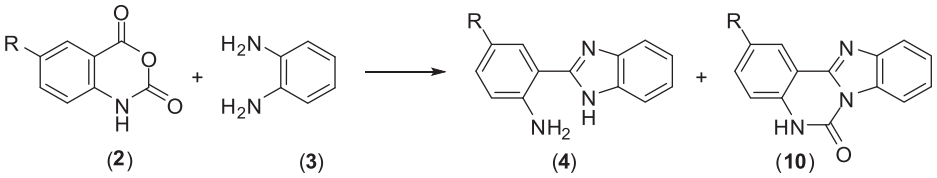
The decarboxylative cyclocondensation of **2** with **3** to from **4** has been reported in performing the reaction in HOAc at 90 °C for 1–3 h. [52] However, it requires elaborative workup procedure for product isolation from the reaction mixture followed by chromatographic purification to obtain the final product due to the use of large amount of HOAc which acts as the solvent as well as a protic acid catalyst. We reasoned that as **2** represents activated electrophilic species, the reaction of **2** with **3** may not require any catalytic assistance. However, it has been reported [53] that the reaction of **2** with **3** in aprotic polar solvents in the absence of any protic acid catalyst leads to the formation of the 2-(2′-aminophenyl)-1*H*-benzimidazole (**4**) and 6,7-dihydrobenzimidazo[1,2-*c*]quinazolin-6-ones (**10**) (Scheme 3).

We realized that as the isatoic anhydride **2** is a bis-electrophile the formation of the desired product **4** and the side product **10** is due to the initial competitive nucleophilic attack of one the NH_2 groups of **3** on the aroyl and imide carbonyl groups of **2**, respectively. Such type of differential product formation during the reaction of bis-electrophilic substrates with bis-nucleophilic agents has been reported [54]. We reasoned that solvent may play an important role in controlling the selectivity of the initial nucleophilic attack on the aroyl and imidic carbonyl group of **2** as the various physio-chemical properties (e.g., polarity, polarizing ability, hydrogen bond donor and acceptor ability etc.) are known to influence on nucleophilic substitution reaction [55–57]. Thus, the decarboxylative cyclocondensation of the unsubstituted isatoic anhydride **2a** with the unsubstituted *o*-phenylenediamine **3a** was performed in various aprotic, protic, ethereal, halogenated hydrocarbon, and hydrocarbon solvents (Table 1) at different temperature. Complete consumption of the starting material was observed in the case of PhMe. Performing the reaction in PhMe at 70 °C for 12 h afforded the unsubstituted 2-(2′-aminophenyl)-1*H*-benzimidazole **4a** in 77% yield without the necessity of any special/elaborative isolation and purification procedure. The product got precipitated when the reaction mixture was cooled to room temperature. Filtration and washing with PhMe gave the desired product **4a**. The use of DMSO under reflux for 20 min afforded **4a** in 68% yield along with the side product **10** in 17% yield [53].

The commercially available substituted isatin derivatives (**1**) were subjected to the Bayer-Villiger oxidation using *m*-chloroperoxybenzoic acid (*m*CPBA) in HOAc for 4 h at rt [58,59] to obtain the corresponding isatoic anhydride derivatives (**2**) (Table 2). The final products were

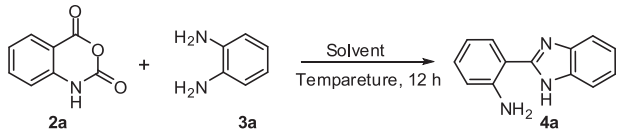


Scheme 2. Literature reported synthetic routes for the preparation of 2-(2′-aminophenyl)-1*H*-benzimidazoles.



Scheme 3. The reaction of isatoic anhydrides (**2**) with *o*-phenylenediamines (**3**) leading to 2-(2′-aminophenyl)-1*H*-benzimidazoles (**4**) and 6,7-dihydrobenzimidazo[1,2-*c*]quinazolin-6-ones (**10**).

Table 1
Reaction of isatoic anhydride **2a** with *o*-phenylenediamines (**3a**) in different solvents under various conditions to form **4a**.[a]



Entry	Solvent	Temp (°C)	Yield (%)[b]
1	DMF	70	0
2	DMF	reflux	0
3	DMF	MW	0
4	NMP	reflux	0
5	NMP	70	0
6	DMA	reflux	0
7	DMA	70	0
8	Formamide	reflux	0
9	Formamide	70	0
10	MeCN	reflux	0
11	DMSO	reflux	52
12	DMSO	70	23
13	MeOH	reflux	30
14	MeOH	rt[c]	0
15	EtOH	reflux	32
16	EtOH	rt[c]	0
17	TFE	reflux	42
18	H_2O	reflux	0
19	H_2O[d]	reflux	0
20	**Toluene**	**reflux**	**76**
21	**Toluene**	**70**	**77**
22	Toluene	rt[c]	0
23	Chlorobenzene	reflux	70
24	Chlorobenzene	70	54
25	Chlorobenzene	rt[c]	trace
26	Neat	130	51
27	Neat	70	0
28	Dioxane	reflux	38
29	Dioxane	70	31
30	THF	reflux	25

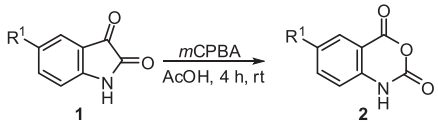
[a] The magnetically stirred mixture of **2a** (1 mmol) and **3a** (1 mmol, 1 equiv) in the specified solvent (1.5 mL) was treated at the indicated tempareture for 12 h.
[b] Isolated yield of **4a.**
[c] rt = 25–30 °C.
[d] The reaction was performed in the presence of 10 mol% SDOSS.

isolated by filtration in 70–87% yields and did not require further purification.

To bring about the variations in the final molecule it was thought to prepare the derivatives of the key intermediate. The substituted isatoic anhydrides **2** were treated with the various substituted *o*-phenylenediamines **3** in PhMe at 70 °C for 12 h to generate the various substituted 2-(2′-aminophenyl)-1*H*-benzimidazole derivatives (**4a-h**, Table 3). In each case the desired product **4** was obtained by cooling the reaction mixture to rt wherein the products precipitated out as solid that were filtered out and washed with PhMe to obtain the pure products.

Thirty two benzimidazoquinazoline derivatives (**6**) were synthesized in 30–96% yields (Table 4) by treating the 2-(2′-aminophenyl)-1*H*-benzimidazoles (**4a-h)** with ethyl ortho esters (**5**) in DMF at 100 °C. [60]

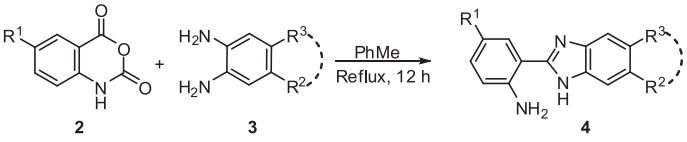
Table 2
Synthesis of the isatoic anhydride derivatives (**2**) from substituted isatins (**1**).[a]



Entry	R^1	Product	Yield (%)[b]
1	Br	**2a**	87
2	Cl	**2b**	75
3	F	**2c**	80
4	Me	**2d**	71
5	OMe	**2e**	70

[a] The solution of isatin (**1**) (1 mmol) and *m*CPBA (1.5 mmol, 1.5 equiv) in HOAc (2 mL) was stirred magnetically at rt for 4 h.
[b] Isolated yield of **2.**

Table 3
Synthesis of the 2-(2′-aminophenyl)benzimidazole derivatives (**4**) from substituted isatoic anhydrides (**2**) and *o*-phenylenediamines (**3**).[a]



Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1	H	H	H	**4a**	81
2	F	H	H	**4b**	66
3	Cl	H	H	**4c**	68
4	Br	H	H	**4d**	75
5	CH_3	H	H	**4e**	55
6	OMe	H	H	**4f**	48
7	H	$R^2 = R^3 = (CH)_4$		**4g**	62
8	H	Cl	Cl	**4h**	58

[a] The mixture of isatoic anhydride (**2**) (1 mmol) and *o*-phenylene diamine (**3**) (1 mmol, 1 equiv) in PhMe (2 mL) was heated under reflux for 12 h.
[b] Isolated yield of **4**.

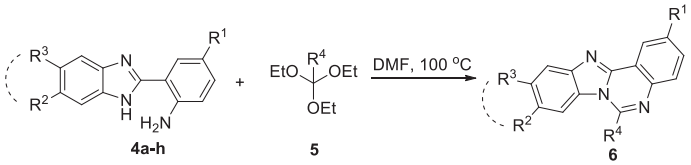
2.2. Biological evaluation

2.2.1. Determination of MIC against *M. tuberculosis* $H_{37}Rv$

The synthesized alkylbenzimidazoquinazolines (**6**) were subjected to in vitro anti-TB activity against *M. tuberculosis* $H_{37}Rv$ (ATCC 27294 strain) (Table 5, Fig. 2) [61]. The minimum inhibitory concentration (MIC), minimum concentration in μg/mL of the compound required for 99% inhibition of bacterial growth, of **6** and those of the standard drugs such as isoniazid (INH), rifampicin (R), ethambutol (E), pyrazinamide (Z) and ciprofloxacin (Cfx) were determined in triplicate at pH 7.4. All of these synthesized compounds showed MIC values in the micromolar range (0.40– > 25 μg/mL). Out of these, eleven compounds exhibited MIC in the range of 1.56–6.25 μg/mL, two compounds **6d** and **6v** were active at 0.78 μg/mL and compound **6x** was the most active (MIC 0.40 μg/mL or 1.45 μM) from this series of compounds.

Further, we screened the total nine active compounds with

Table 4
The cyclocondensation of the 2-(2′-aminophenyl)-1*H*-benzimidazoles (**4a-h**) with the ortho esters (**5**) to forme the benzimidazoquinazoline derivatives **6**.[a]



Entry	4	R^1	R^2	R^3	R^4	Product	Yield 6 (%)[b]
1	**4a**	H	H	H	H	**6a**	96
2	**4a**	H	H	H	Me	**6b**	92
3	**4a**	H	H	H	Et	**6c**	89
4	**4a**	H	H	H	*n*-Pr	**6d**	87
5	**4a**	H	H	H	*n*-Bu	**6e**	90
6	**4b**	F	H	H	H	**6f**	86
7	**4b**	F	H	H	Me	**6g**	84
8	**4b**	F	H	H	Et	**6h**	82
9	**4b**	F	H	H	*n*-Pr	**6i**	76
10	**4b**	F	H	H	*n*-Bu	**6j**	81
11	**4c**	Cl	H	H	H	**6k**	79
12	**4c**	Cl	H	H	Me	**6l**	81
13	**4c**	Cl	H	H	Et	**6m**	84
14	**4c**	Cl	H	H	*n*-Pr	**6n**	80
15	**4c**	Cl	H	H	*n*-Bu	**6o**	81
16	**4d**	Br	H	H	H	**6p**	79
17	**4d**	Br	H	H	Me	**6q**	81
18	**4d**	Br	H	H	Et	**6r**	87
19	**4d**	Br	H	H	*n*-Pr	**6s**	71
20	**4d**	Br	H	H	*n*-Bu	**6t**	80
21	**4e**	CH_3	H	H	H	**6u**	83
22	**4e**	CH_3	H	H	Me	**6v**	78
23	**4e**	CH_3	H	H	Et	**6w**	77
24	**4e**	CH_3	H	H	*n*-Pr	**6x**	72
25	**4e**	CH_3	H	H	*n*-Bu	**6y**	79
26	**4f**	OMe	H	H	Me	**6z**	65
27	**4g**	H	$R^2 = R^3 = (CH)_4$		H	**6aa**	81
28	**4g**	H	$R^2 = R^3 = (CH)_4$		Me	**6ab**	87
29	**4g**	H	$R^2 = R^3 = (CH)_4$		Et	**6ac**	80
30	**4g**	H	$R^2 = R^3 = (CH)_4$		*n*-Pr	**6ad**	76
31	**4g**	H	$R^2 = R^3 = (CH)_4$		*n*-Bu	**6ae**	79
32	**4h**	H	Cl	Cl	Me	**6af**	30

[a] To the magnetically stirred solution of **4** (1 mmol) in DMF (2 mL) was added the triethyl ortho ester (**5**) (1 mmol, 1.5 equiv) and the mixture was heated at 100 °C for 12 h. [b]Isolated yield of **6**.

MIC ≤ 3.125 μg/mL (**6a**, **6b**, **6d**, **6p**, **6s**, **6t**, **6v**, **6x**, and **6ae**) against INH resistant Mtb strain, and found **6d** as the potent compound with MIC of 0.78 μg/mL (Table 5). Two compounds (**6b** and **6v**) displayed good activity with MIC of 1.56 μg/mL and compounds **6a** and **6t** were also found potent against INH resistant strain with MIC of 1.56 and 3.125 μg/mL.

2.2.2. *In vitro cell viability test*

The in vitro cell viability of a few selected benzimidazoquinazolines (**6a**, **6b**, **6d**, **6f**, **6m**, **6p**, **6s**, **6t**, **6v**, **6x**, **6ab**, **6ad**, **6ae** and **6af**) with MIC ≤ 6.25 μg/mL was determined against RAW 264.7 cell lines using MTT assay at 50 μg/mL (Table 5, Fig. 3) that revealed the non-cytotoxic nature of these compounds. The most active compounds **6d**, **6v** (MIC of 0.78 μg/mL) and **6x** (MIC of 0.40 μg/mL) exhibited selectivity index of 64, 64 and 125 respectively and emerged as the most promising anti-TB leads.

2.2.3. *Structure activity relationship (SAR)*

The structure activity relationship (SAR) of the benzimidazoquinazolines could be drawn by correlating the MIC (μg/mL) values of the compounds with the specific changes in the structure made by various substitution on the core moieties. General structure for this class of compounds can be written as shown in Fig. 4.

Table 5
The anti-TB activity and in vitro cell viability of alkylbenzimidazoquinazolines **6** and a few standard anti-TB drugs against *M. tuberculosis* H37Rv (ATCC 27294).

Entry	Compd. No.	MIC[a] Against drug sensitive Mtb (μg/mL)	MIC[a] Against drug sensitive Mtb (μM)[a,b]	Cytotoxicity (%)[c]	MIC (μg/mL)[d] Against INH resistant Mtb
1	**6a**	1.56	7.12	14.67	3.125
2	**6b**	1.56	6.69	14.56	1.56
3	**6c**	25	101.10	ND	ND
4	**6d**	0.78	2.98	21.70	0.78
5	**6e**	> 25	ND	ND	ND
6	**6f**	6.25	26.35	19.70	ND
7	**6g**	25	99.50	ND	ND
8	**6h**	> 25	ND	ND	ND
9	**6i**	25	89.51	ND	ND
10	**6j**	12.5	42.61	ND	ND
11	**6k**	> 25	ND	ND	ND
12	**6l**	> 25	ND	ND	ND
13	**6m**	6.25	22.18	32.12	ND
14	**6n**	> 25	ND	ND	ND
15	**6o**	25	80.70	ND	ND
16	**6p**	3.125	10.48	10.16	12.5
17	**6q**	12.5	40.04	ND	ND
18	**6r**	12.5	38.32	ND	ND
19	**6s**	1.56	4.59	22.13	> 25
20	**6t**	3.125	8.82	30.12	6.25
21	**6u**	> 25	ND	ND	ND
22	**6v**	0.78	3.15	21.82	1.56
23	**6w**	25	95.67	ND	ND
24	**6x**	0.40	1.45	12.65	12.5
25	**6y**	25	86.39	ND	ND
26	**6z**	12.5	47.48	ND	ND
27	**6aa**	> 25	ND	ND	ND
28	**6ab**	6.25	22.06	23.42	ND
29	**6ac**	25	84.08	ND	ND
30	**6ad**	6.25	20.07	18.88	ND
31	**6ae**	1.56	4.79	18.46	12.5
32	**6af**	6.25	20.68	23.00	ND
33	**INH**	0.098	ND	ND	0.72
34	**R**	0.197	ND	ND	0.24
35	**E**	1.56	ND	ND	7.64
36	**Z**	6.25	ND	ND	50.77
37	**Cfx**	1.56	ND	ND	4.71

[a] For 99% inhibition of *M. tuberculosis* $H_{37}Rv$ ATCC 27294 strain. [b]Conversion of the MIC value of μg/mL determined as under foot note 'a' into μM. [c]% inhibition at 50 μg/mL concentration determined against RAW 264.7 cell lines. [d]For 99% inhibition of *M. tuberculosis* $H_{37}Rv$ ATCC 27294 strain resistant to INH. ND: Not determined.

2.2.3.1. Effect of C ring substitution. In our first attempt we tried to introduce sp^3 hybridization on the flat benzimidazoquinazoline core by substitution of the alkyl group at the C6 position. The introduction of sp^3 hybridization increases the drug likeness of the molecule by affecting its physicochemical properties and binding to the target protein [62,63]. The effect of alkyl group substitution on C-ring of benzimidazoquinazoline is seen on the MIC values.

Compound **6a** having no alkyl group was active at 1.56 μg/mL. When the methyl group is placed at the C-6 position the anti-TB activity was found to be retained in resultant compound **6b** which was equipotent to **6a**. However, the introduction of the ethyl (**6c**) or butyl (**6e**) group at this position (C-6) led to decrease in anti-TB activity. The propyl group substitution at C-6 led to the compound **6d** with much superior anti-TB activity with MIC of 0.78 μg/mL (Table 6).

2.2.3.2. Effect of D ring substitution. The substitution on D ring has also shown influence on the anti-TB activity of these compounds. Halogen

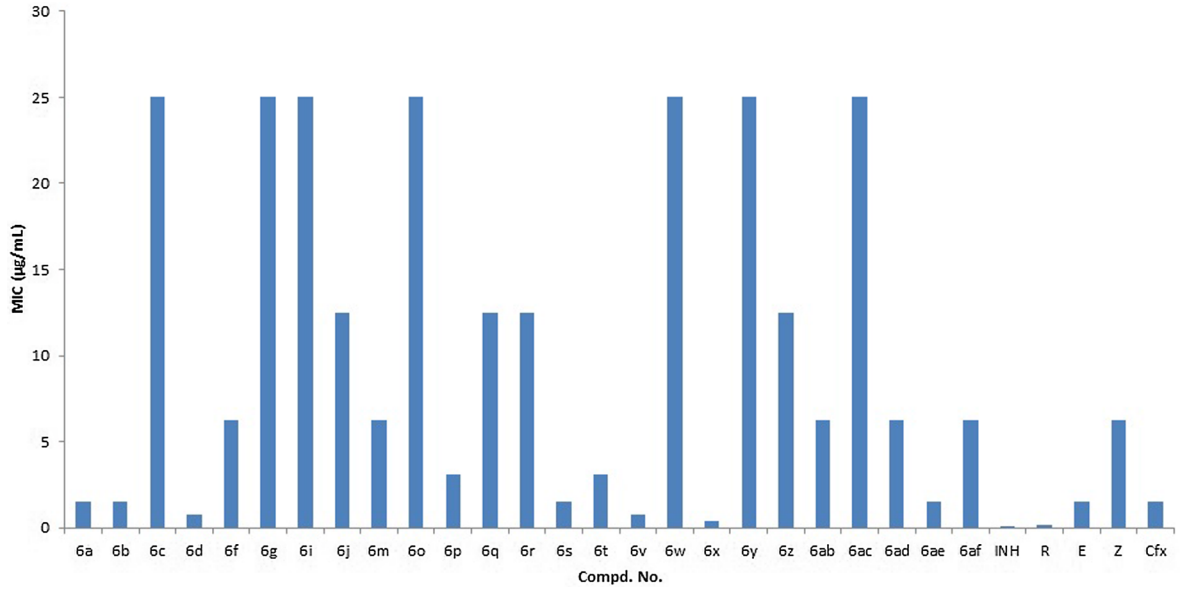


Fig. 2. The anti-TB activity data profile of the synthesized compounds in comparison with that of the standard anti-TB drugs.

substitution has a varied effect on the anti-TB activity. When the fluorine group is substituted at C-2 position of ring D, the resultant compound **6f** showed a decrease in the anti-TB activity compared to that of **6a**. A similar trend is observed in the corresponding compounds bearing alkyl substituent at the C-6 position in ring C (e.g., **6g-6j** as compared to **6b-e**). The incorporation of chloro or bromine at the C-2 position in the D ring also in general showed an overall decrease in the anti-TB activity except for the bromo derivative **6s** which though was equipotent to **6a** with MIC of 1.56 µg/mL but exhibits inferior activity compared to the parent compound **6d** bearing a ^{n}Pr substituent at the C-6 position in ring C (Table 7).

The methyl group substitution at C-2 position on the D ring leads to the most potent anti-TB compound **6x** with the MIC of 0.40 µg/mL. This compound also has C-6 ^{n}Pr substitution in ring C which further confirms the earlier observation of the importance of the ^{n}Pr group at this position for anti-Mtb activity (Table 8).

2.2.3.3. Effect of fusion on ring A. The fusion of **A** ring with the six membered aromatic ring in general appears to be detrimental to the anti-TB potential as except for the compound **6ae** that retains the anti-TB activity (with MIC value of 1.56 µg/mL comparable to that of **6a**) (Table 9).

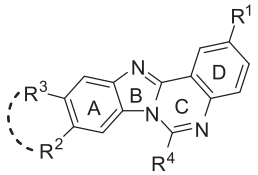


Fig. 4. General structure of 2-alkylbenzimidazoquinazolines.

2.3. Evaluation of drug-like properties of the active compounds

These active compounds with MIC ≤ 6.25 µg/mL were also tested for amenability to the Lipinski rule of five. According to this rule, the

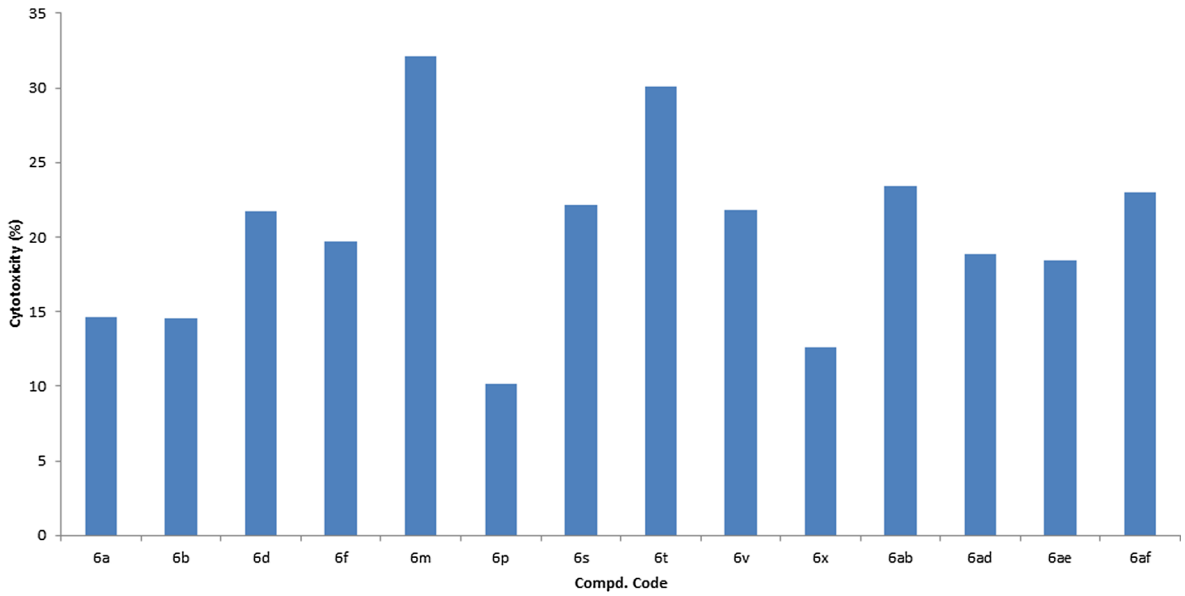
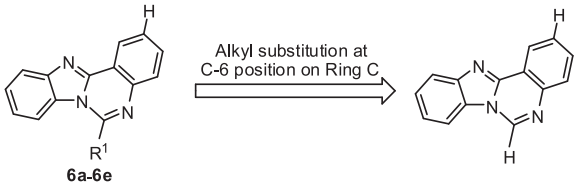


Fig. 3. In vitro cytotoxicity profile of active compounds with MIC ≤ 6.25 µg/mL.

Table 6
Effect of substitutions at Ring C on the anti-TB activity.

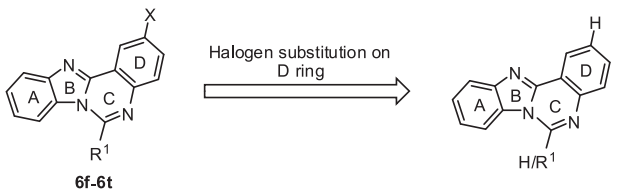


6a-6e

Compd. No.	R^1	MIC (μg/mL)[a]
6a	H	1.56
6b	Me	1.56
6c	Et	25
6d	*n*-Pr	0.78
6e	*n*-Bu	> 25

[a] For 99% inhibition of growth of *M. tuberculosis* H37Rv (ATCC 27294 strain).

Table 7
Effect of halogen substitutions at Ring D on the anti-TB activity.

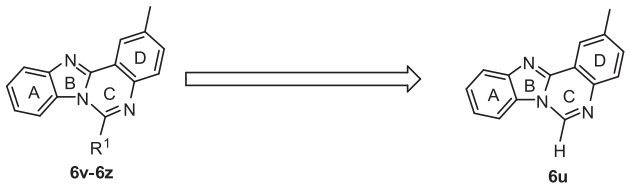


6f-6t

Compd. No.	R^1	MIC (μg/mL)	Compd. No.	R^1	MIC (μg/mL)[a]
6f (X = F)	H	6.25	**6n** (X = Cl)	*n*-Pr	> 25
6g (X = F)	Me	25	**6o** (X = Cl)	*n*-Bu	25
6h (X = F)	Et	> 25	**6p** (X = Br)	H	3.125
6i (X = F)	*n*-Pr	25	**6q** (X = Br)	Me	12.5
6j (X = F)	*n*-Bu	12.5	**6r** (X = Br)	Et	12.5
6k (X = Cl)	H	> 25	**6s** (X = Br)	*n*-Pr	1.56
6l (X = Cl)	Me	> 25	**6t** (X = Br)	*n*-Bu	3.125
6m(X = Cl)	Et	6.25			

[a] For 99% inhibition of growth of *M. tuberculosis* H37Rv (ATCC 27294 strain).

Table 8
Effect of substitutions on Ring C on the anti-TB activity of **6u**.



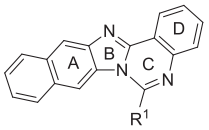
6v-6z 6u

Compd. No.	R^1	MIC (μg/mL)[a]
6u	H	> 25
6v	Me	0.78
6x	Et	25
6y	*n*-Pr	0.40
6z	*n*-Bu	25

[a] For 99% inhibition of growth of *M. tuberculosis* H37Rv (ATCC 27294 strain).

drug likeliness of a molecule to be an orally active drug is characterized by the non-violation of more than one of the following four criteria: should not have more than five hydrogen bond (HB) donors, should not possess more than 10 HB acceptors, molecular weight (MW) should not be greater than 500 Da, and the octanol–water partition coefficient (cLogP) should not be greater than 5 [64]. These properties have been computed by using the Molinspiration Online Software v2016.10 [65] (Table 10) that reveal that these compounds **6a**, **6b**, **6d**, **6f**, **6p**, **6v** and **6ab** followed the Lipinski rule and showed no violation of the above criteria. Therefore, these active ligands are likely to have the potential to be an active drug candidate.

Table 9
Effect of substitutions at Ring C on the anti-TB activity of **6ab**.



Compd. No.	R^1	MIC (μg/mL)
6ab	H	> 25
6ac	Me	6.25
6ad	Et	25
6ae	*n*-Pr	6.25
6af	*n*-Bu	1.56

[a]99% inhibition of growth of *M. tuberculosis* H37Rv (ATCC 27294 strain).

3. Conclusions

In this study alkylbenzimidazoquinazolines have been revealed as new anti-TB chemotypes. Thirty two compounds have been synthesized and tested for anti-TB activity. Fourteen compounds displayed good in vitro anti-mycobacterial activity, with MIC in low micromolar range against replicating TB. The most potent compound **6x** exhibited MIC of 0.40 μg/mL more than that of the standard drugs E, Z and Cfx against drug sensitive Mtb strain and compound **6d** was found as the potent compound with MIC of 0.78 μg/mL against INH resistant Mtb strain. The early SAR for this class of compounds has been established. The in vitro cell viability of a few benzimidazoquinazolines with MIC of ≤6.25 μg/mL against RAW 264.7 cell lines revealed the non-cytotoxic nature of these compounds. The major improvements in activity were observed when the C-6 substitution is propyl group and the D ring substitution has methyl group. Compounds **6a**, **6b**, **6d**, **6f**, **6p**, **6v** and **6ab** followed the Lipinski rule and showed no violation of the above criteria. In conclusion, this study has provided a novel scaffold for the anti-TB drug discovery process.

4. Experimental section

4.1. General chemistry

The glass wares were thoroughly washed and dried in an oven. Chemicals and all solvents were commercially available (Aldrich Chemical, Merck AG, Fluka and S-D Fine Chemicals) and used without further purification. The $^1H/^{13}C$ NMR spectra were recorded on a Bruker Advance 400/100 MHz NMR spectrometer in $CDCl_3$ with residual undeuterated solvent ($CDCl_3$: 7.26/77.0) using TMS as an internal standard. Chemical shifts (δ) are given in ppm and J values are given in Hz. ^{13}C NMR spectra were fully decoupled and were referenced to the middle peak of the solvent $CDCl_3$ at 77.0 ppm. Splitting pattern were designated as s, singlet; br s, broad singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; qnt, quintet; sxt, sixtet; m, multiplet. Mass spectra were recorded on mass spectrometer (ESI). Infra-red (IR) spectra were recorded on Perkin Elmer FT-IR spectrometer in the range 4000–600 cm^{-1} either as neat samples for liquids or using KBr for preparing pellets for solid samples. Compounds were routinely checked

Table 10
Calculated Lipinski properties of compounds with anti-TB activity (MIC ≤ 6.25 μg/mL).

Entry	Compd No.	MIC (μg/mL)[a]	nViol[b]	cLogP[c,d]	Mol. Wt.[c,e]	No. of HBA[f,g]	No. of HBD[f,h]	No. of RB[f,i]
Acceptable Range				≤5	≤500	≤10	≤5	≤5
1	**6a**	1.56	0	3.27	219.24	3	0	0
2	**6b**	1.56	0	3.77	233.27	3	0	0
3	**6d**	0.78	0	4.83	261.32	3	0	2
4	**6f**	6.25	0	3.42	237.23	3	0	0
5	**6m**	6.25	1	5.02	281.74	3	0	1
6	**6p**	3.125	0	4.14	298.14	3	0	0
7	**6s**	1.56	1	5.70	340.22	3	0	2
8	**6t**	3.125	1	6.23	354.24	3	0	3
9	**6v**	0.78	0	4.27	247.29	3	0	0
10	**6x**	0.40	1	5.33	275.35	3	0	2
11	**6ab**	6.25	0	4.95	283.33	3	0	0
12	**6ad**	6.25	1	6.00	311.38	3	0	2
13	**6ae**	1.56	1	6.53	325.41	3	0	3
14	**6af**	6.25	1	5.08	302.16	3	0	0

[a] For 99% Inhibition of the growth of *M. tuberculosis* H37Rv (ATCC 27294 strain).
[b] nViol, no. of violations.
[c] Calculated using ChembioDraw Ultra 12.0.
[d] cLog P, octanol-water partition co-efficient.
[e] MW, molecular weight.
[f] Calculated using Molinspiration property engine v 2016.10.
[g] HBA, no. of hydrogen bond acceptors.
[h] HBD, no. of hydrogen bond donors.
[i] RB, no. of rotatable bonds.

for their purity on the silica gel GF-254 and visualized under UV at wavelength 254 nm. Melting points were measured with Gupta scientific melting point apparatus and were uncorrected. Evaporation of solvents was performed at reduced pressure, using a rotary evaporator. HPLC (model SCL-10AVP, Shimadzu, Japan) of all the target compounds has been performed using Qualisil Gold C18 column (4.6 × 250 mm, 5 μm, LCGC Chromatography Solution Pvt. Ltd) and acetonitrile:water (70:30) as the mobile phase at 30 °C utilizing 20 μL of the sample with flow rate of 1 mL min^{-1} using binary pump. Photo diode array detector was used for variable wavelength ranging from 200 to 800 nM. For interpretation of the results of HPLC, Class VP software was used. Elemental analyses were performed on organic element analyzer (Thermo SCIENTIFIC FLASH 2000) and, indicated by the symbols of the elements or functions were within ± 0.4% of the theoretical values. For interpretation of the results of elemental analysis, Eager Xperience software was used.

*4.1.1. Typical procedure for the preparation of isatoic anhydride. Preparation of **2a** [58,59]*

To the magnetically stirred solution of the 5-bromoisatin (**1**) (0.22 g, 1 mmol) in HOAc (2 mL) was added of *m*CPBA (2.5 g, 1.5 mmol, 1.5 equiv) and the resultant mixture was stirred magnetically for another 4 h (TLC). The crude reaction mixture was filtered and washed with aq $NaHCO_3$ to afford **2a** as light red solid (0.21 g, 87%).

*4.1.2. Typical procedure for the preparation of 2-(2′-aminophenyl) benzimidazole. Synthesis of **4a***

The mixture of **2a** (0.16 g, 1 mmol) and **3a** (0.11 g, 1 mmol) in PhMe (2 mL) was heated under reflux for 12 h. The reaction mixture was cooled to rt, filtered, and the solid residue washed with hexane to afford **4a** as white solid (0.17 g, 81%); mp 213–216 °C; IR (KBr, cm^{-1}) 3442, 1676, 1545, 1472, 1258, 1132; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.30 (d, J = 7.9 Hz, 1H), 7.97 (d, J = 15.5 Hz, 1H), 7.79 (d, J = 3.4 Hz, 2H) 7.53–7.61 (m, 3H), 7.47–7.50 (m, 1H), 7.28–7.34 (m, 7H), 6.39 (d, J = 15.5 Hz, 1H); MS (APCI) m/z: 325.21 $(M+H)^+$.

*4.1.3. Typical experimental procedure for the synthesis of benzimidazoquinazoline. Synthesis of **6a** [60]*

The magnetically stirred mixture of **4a** (0.41 g, 2.5 mmol) and triethyl orthoformate (0.3 g, 5 mmol, 2 equiv) in DMF (2.5 mL) was treated at 100 °C (oil bath) for 12 h. The crude reaction mixture was poured into crushed ice (10 g) and the precipitated solid was filtered to obtain **6a** as white solid (210.5 mg, 96%); mp > 220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.15 (s, 1H), 8.69 (d, J = 7.9 Hz, 1H), 8.04–7.97 (m, 3H), 7.83–7.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 146.36, 144.03, 142.57, 136.13, 131.79, 128.67, 128.52, 128.15, 126.17, 124.22, 123.29, 120.32, 119.32, 110.08; MS (ESI) m/z: 219.98 $(M+H)^+$. HPLC analysis: retention time = 3.267 min; peak area, 100%.

*4.1.4. 6-Methylbenzo[4,5]imidazo[1,2-c]quinazoline (**6b**): [66]*

White solid (214.6 mg, 92%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.69–8.67 (m, 1H), 8.06–8.03 (m, 2H), 7.90–7.89 (m, 1H), 7.79–7.75 (m, 1H), 7.67–7.63 (m, 1H), 7.60–7.56 (m, 1H), 7.48–7.44 (m, 1H), 3.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 147.67, 144.37, 142.26, 131.74, 129.45, 127.70, 127.35, 125.60, 124.11, 123.07, 120.23, 118.09, 114.02, 24.13; HPLC analysis: retention time = 4.133 min; peak area, 100%.

*4.1.5. 6-Ethylbenzo[4,5]imidazo[1,2-c]quinazoline (**6c**): [67]*

White solid (220.1 mg, 89%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.71 (d, J = 7.9 Hz, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.95–7.93 (m, 1H), 7.80–7.76 (m, 1H), 7.67–7.63 (m, 1H), 7.61–7.57 (m, 1H), 7.51–7.46 (m, 1H), 3.52 (q, J = 7.3 Hz, 2H), 1.66 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 151.58, 148.02, 144.45, 142.26, 131.65, 129.01, 127.62, 125.47, 124.12, 123.07, 120.24, 118.17, 114.44, 29.38, 10.30; HPLC analysis: retention time = 4.417 min; peak area, 92.37%.

*4.1.6. 6-Propylbenzo[4,5]imidazo[1,2-c]quinazoline (**6d**): [68]*

White solid (227.3 mg, 87%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.70 (d, J = 7.8 Hz, 1H), 8.06–7.91 (m, 3H), 7.78 (t, J = 7.6 Hz, 1H), 7.67–7.57 (m, 2H), 7.50–7.47 (m, 1H), 3.44 (t, J = 7.6 Hz, 2H), 2.18–2.08 (m, 2H), 1.26 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.64, 148.06, 144.46, 142.21, 131.66, 129.02, 127.61, 127.58, 125.47, 124.11, 123.08, 120.27, 118.17, 114.30, 37.87, 19.35, 13.87; HPLC analysis: retention time = 4.850 min; peak area, 100%.

*4.1.7. 6-Butylbenzo[4,5]imidazo[1,2-c]quinazoline **(6e)**: [60]*

Light grey solid (247.8 mg, 90%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.72 (d, J = 7.8 Hz, 1H), 8.05 (q, J = 9.2 Hz, 2H), 7.94 (d, J = 8.0 Hz, 1H), 7.79 (t, J = 7.6 Hz, 1H), 7.69–7.59 (m, 2H), 7.53–7.49 (m, 1H), 3.49 (t, J = 13.9 Hz, 2H), 2.13–2.05 (m, 2H), 1.74–1.63 (m, 2H), 1.10 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.90, 144.51, 142.25, 131.67, 129.06, 127.61, 127.58, 125.49, 124.13, 123.10, 120.31, 118.19, 114.33, 35.82, 27.94, 22.54, 13.97; HPLC analysis: retention time = 5.600 min; peak area, 96.77%.

*4.1.8. 2-Fluorobenzo[4,5]imidazo[1,2-c]quinazoline **(6f)**: [66]*

Yellow solid (204.0 mg, 86%); mp 190–193 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.12 (s, 1H), 8.32 (dd, J = 8.4, 2.8 Hz, 1H), 8.04–7.98 (m, 3H), 7.62–7.58 (m, 1H), 7.54–7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.68, 143.93, 139.21, 135.48, 131.01, 130.92, 126.39, 123.69, 120.51, 120.32, 120.08, 115.76, 112.55, 110.22, 109.69, 109.45; HPLC analysis: retention time = 3.225 min; peak area, 100%.

*4.1.9. 2-Fluoro-6-methylbenzo[4,5]imidazo[1,2-c]quinazoline **(6g)**:*

White solid (211.1 mg, 84%); mp 196–197 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.35 (dd, J = 8.35, 2.4 Hz, 1H), 8.09 (q, J = 7.7 Hz, 2H), 7.92 (q, J = 4.6, Hz, 1H), 7.63–7.61 (m, 1H), 7.55–7.50 (m, 2H), 3.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 154.30, 141.00, 138.80, 137.70, 136.00, 134.00, 129.73, 125.82, 123.4, 120.48, 120.05, 114.13, 109.21, 24.02; HRMS (ESI) m/z calcd for $C_{15}H_{11}FN_3$ [M + H], 252.0937; Found 252.0937. HPLC analysis: retention time = 4.225 min; peak area, 100%.

*4.1.10. 6-Ethyl-2-fluorobenzo[4,5]imidazo[1,2-c]quinazoline **(6h)***

White solid (217.5 mg, 82%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.32 (dd, J = 8.6, 2.8 Hz, 1H), 8.06–8.03 (m, 2H), 7.94–7.91 (m, 1H), 7.61–7.57 (m, 1H), 7.51–7.45 (m, 2H), 3.50 (q, J = 7.3 Hz, 2H), 1.63 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 151.10, 148.58, 144.36, 140.93, 138.95, 130.05, 129.96, 129.01, 125.67, 123.44, 120.44, 119.94, 119.41, 114.54, 109.41, 109.16, 29.28, 10.23; HRMS (ESI) m/z calcd for $C_{16}H_{13}FN_3$ [M + H], 266.1094; Found 266.1100. HPLC analysis: retention time = 4.467 min; peak area, 100%.

*4.1.11. 2-Fluoro-6-propylbenzo[4,5]imidazo[1,2-c]quinazoline **(6i)***

White solid (212.3 mg, 76%); mp 202–205 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.81 (s, 1H), 7.99 (dd, J = 8.0, 2H), 7.82–7.80 (m, 1H), 7.76–7.73 (m, 1H), 7.60–7.56 (m, 1H), 7.50–7.46 (m, 1H), 3.39 (t, J = 7.6 Hz, 2H), 2.10 (sxt, J = 7.5 Hz, 2H), 1.23 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 151.03, 146.7, 144.39, 140.9, 134.76, 129.3, 128.99, 126.7, 125.74, 123.51, 120.48, 114.37, 37.84, 19.20, 13.84; HRMS (ESI) m/z calcd for $C_{17}H_{15}FN_3$ 280.1250 [M + H$^+$], Found 280.1247. HPLC analysis: retention time = 5.375 min; peak area, 100%.

*4.1.12. 6-Butyl-2-fluorobenzo[4,5]imidazo[1,2-c]quinazoline **(6j)***

White solid (237.6 mg, 81%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.34–8.32 (m, 1H), 8.07–8.01 (m, 2H), 7.93–7.89 (m, 1H), 7.61–7.59 (m, 1H), 7.54–7.48 (m, 2H), 3.47 (t, J = 7.7 Hz, 2H), 2.08–2.05 (m, 2H), 1.71–1.66 (m, 2H), 1.10 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.53, 150.15, 144.35, 138.85, 129.98, 129.89, 129.00, 125.66, 123.44, 120.45, 120.18, 119.94, 119.48, 114.41, 109.40, 109.16, 35.66, 29.71, 27.85, 13.96; HRMS (ESI) m/z calcd for $C_{18}H_{17}FN_3$ [M + H$^+$], 294.1407; Found 294.1400. HPLC analysis: retention time = 5.758 min; peak area, 100%.

*4.1.13. 2-Chlorobenzo[4,5]imidazo[1,2-c]quinazoline **(6k)**: [69]*

White solid (200.4 mg, 79%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.17 (s, 1H), 8.69 (d, J = 2.4 Hz, 1H), 8.06–8.00 (m, 2H), 8.69 (d, J = 2.4 Hz, 1H), 7.8 (dd, J = 8.7, 2.4 Hz, 1H), 7.66–7.61 (m, 1H), 7.57–7.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 145.22, 143.97, 140.93, 136.27, 134.58, 132.19, 130.03, 128.11, 126.47, 123.76, 123.72, 120.55, 120.42, 110.21; HPLC analysis: retention time = 4.158 min; peak area, 100%.

*4.1.14. 2-Chloro-6-methylbenzo[4,5]imidazo[1,2-c]quinazoline **(6l)**: [70]*

White solid (216.8 mg, 81%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.67 (d, J = 2.3 Hz, 1H), 8.09–8.04 (m, 2H), 7.84–7.82 (m, 1H), 7.71–7.69 (m, 1H), 7.63–7.59 (m, 1H), 7.53–7.49 (m, 1H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 147.92, 146.58, 144.32, 140.64, 133.45, 132.12, 129.41, 128.93, 125.89, 123.54, 123.52, 120.46, 119.18, 114.10, 24.15; MS (ESI) m/z: 268.18 (M + H)$^+$; HPLC analysis: retention time = 4.608 min; peak area, 100%.

*4.1.15. 2-Chloro-6-ethylbenzo[4,5]imidazo[1,2-c]quinazoline **(6m)***

Yellow solid (236.7 mg, 84%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.84 (d, J = 2.08 Hz, 1H), 8.06–8.03 (m, 2H), 7.85–7.77 (m, 2H), 7.61–7.58 (m, 1H), 7.52–7.47 (m, 1H), 3.49 (q, J = 6.7 Hz, 2H), 1.63 (t, J = 8.00 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 151.98, 146.65, 144.39, 140.95, 134.76, 129.34, 128.99, 126.66, 125.74, 123.51, 121.18, 120.46, 119.62, 114.51, 29.40, 10.25; HRMS (ESI) m/z calcd for $C_{16}H_{13}ClN_3$ [M + H$^+$], 282.0798; Found 282.0797. HPLC analysis: retention time = 4.292 min; peak area, 100%.

*4.1.16. 2-Chloro-6-propylbenzo[4,5]imidazo[1,2-c]quinazoline **(6n)**: [70]*

Yellow solid (236.6 mg, 80%); mp 196–197 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.66 (s, 1H), 8.0 (dd, J = 8.1, 8.0 Hz, 2H), 7.85–7.83 (m, 1H), 7.70–7.68 (m, 1H), 7.61–7.58 (m, 1H), 7.52–7.48 (m, 1H), 3.42 (t, J = 7.2 Hz, 2H), 2.12 (m, 2H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.85, 146.84, 144.36, 140.55, 133.30, 131.97, 129.12, 128.97, 125.71, 123.50, 120.45, 119.22, 114.37, 37.79, 19.21, 13.85; MS (ESI) m/z: 296.51 (M + H)$^+$; HPLC analysis: retention time = 5.500 min; peak area, 100%.

*4.1.17. 6-Butyl-2-chlorobenzo[4,5]imidazo[1,2-c]quinazoline **(6o)***

White solid (250.9 mg, 81%); mp 186–189 °C; IR (KBr, cm^{-1}) 3408, 1602, 1535, 1466, 1276, 1181, 743; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.69 (d, J = 2.3 Hz, 1H), 8.07–7.96 (m, 2H), 7.86 (d, J = 8.7 Hz, 1H), 7.72–7.69 (m, 1H), 7.65–7.57 (m, 1H), 7.55–7.50 (m, 1H), 3.47 (t, J = 7.8 Hz, 2H), 2.08 (qnt, J = 7.7 Hz, 2H), 1.69 (sxt, J = 7.5 Hz, 2H), 1.09 (t, J = 7.32 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 151.13, 146.87, 144.43, 140.60, 133.32, 132.01, 129.13, 125.74, 123.54, 123.50, 120.50, 119.26, 114.40, 35.75, 27.81, 22.51, 13.96; HRMS (ESI) m/z calcd for $C_{18}H_{17}ClN_3$ 310.1111 [M + H$^+$], Found 310.1105. HPLC analysis: retention time = 6.675 min; peak area, 100%.

*4.1.18. 2-Bromobenzo[4,5]imidazo[1,2-c]quinazoline **(6p)***

White solid (235.5 mg, 79%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.13 (s, 1H), 8.81 (s, 1H), 8.01–7.95 (m, 2H), 7.87–7.83 (m, 2H), 7.62–7.59 (m, 1H), 7.53–7.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 145.02, 143.99, 141.26, 136.38, 134.95, 130.15, 128.12, 126.84, 126.47, 123.75, 122.48, 120.73, 120.54, 110.18; HRMS (ESI) m/z calcd for $C_{14}H_9BrN_3$ [M + H$^+$], 297.9980; Found 297.9990. HPLC analysis: retention time = 4.292 min; peak area, 100%.

*4.1.19. 2-Bromo-6-methylbenzo[4,5]imidazo[1,2-c]quinazoline **(6q)**: [71]*

White solid (252.8 mg, 81%); mp > 220 °C; IR (KBr, cm^{-1}) 3408, 1626, 1536, 308, 1380, 742; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.85 (s, 1H), 8.10–8.04 (m, 2H), 7.84–7.51 (m, 4H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 134.08, 129.08, 126.69, 125.53, 121.31, 120.49,

114.10, 29.70, 24.14; HPLC analysis: retention time = 4.472 min; peak area, 100%.

*4.1.20. 2-Bromo-6-ethylbenzo[4,5]imidazo[1,2-c]quinazoline (**6r**): [71]*

White solid (283.8 mg, 87%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.01 (d, J = 8.0 Hz, 1H), 7.77–7.75 (m, 1H), 7.60–7.52 (m, 3H), 7.28–7.23 (m, 2H), 3.36 (q, J = 2.7 Hz, 2H), 1.30 (t, J = 10.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 151.96, 146.65, 144.40, 140.95, 134.75, 129.34, 128.99, 126.66, 125.74, 123.49, 121.17, 120.46, 119.62, 114.50, 29.39, 10.14; MS (ESI) *m/z*: 326.03 $(M)^+$; HPLC analysis: retention time = 5.675 min; peak area, 100%.

*4.1.21. 2-Bromo-6-propylbenzo[4,5]imidazo[1,2-c]quinazoline (**6s**): [71]*

White solid (241.6 mg, 71%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.86 (s, 1H), 8.03–7.56 (m, 6H), 3.43 (s, 2H), 2.14 (s, 2H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 151.05, 146.51, 144.39, 140.90, 134.77, 129.29, 129.00, 126.66, 125.76, 123.52 121.18, 120.49, 119.61, 114.38, 37.85, 19.22, 13.85; HPLC analysis: retention time = 5.592 min; peak area, 97.32%.

*4.1.22. 2-Bromo-6-butylbenzo[4,5]imidazo[1,2-c]quinazoline (**6t**)*

White solid (283.4 mg, 80%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.86 (s, 1H), 8.04–7.80 (m, 3H), 7.61–7.53 (m, 3H), 3.47 (s, 2H), 2.07 (s, 2H), 1.66 (s, 2H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.0, 147.12, 144.32, 140.92, 134.90, 134.78, 129.27, 129.06, 125.77, 123.53, 121.17, 120.47, 114.39, 35.78, 27.78, 22.51, 13.96; HRMS (ESI) *m/z* calcd for $C_{18}H_{17}BrN_3$ $[M+Na^+]$, 354.0606; Found 354.0614. HPLC analysis: retention time = 7.083 min; peak area, 100%.

*4.1.23. 2-Methylbenzo[4,5]imidazo[1,2-c]quinazoline (**6u**)*

White solid (193.6 mg, 83%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.10 (s, 1H), 8.48 (s, 1H), 8.01–7.96 (m, 2H), 7.88 (d, J = 8.3 Hz, 1H), 7.62–7.56 (m, 2H), 7.51–7.46 (m, 1H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 146.41, 143.97, 140.60, 139.18, 135.41, 133.30, 128.25, 128.20, 126.11, 123.86, 123.19, 120.22, 118.99, 110.10, 21.61; HRMS (ESI) *m/z* calcd for $C_{15}H_{12}N_3$ $[M+H^+]$, 234.1031; Found 234.1040. HPLC analysis: retention time = 4.158 min; peak area, 100%.

*4.1.24. 2,6-Dimethylbenzo[4,5]imidazo[1,2-c]quinazoline (**6v**): [70]*

White solid (192.9 mg, 78%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.41 (bs, 1H), 7.97–7.94 (m, 2H), 7.71–7.69 (m, 1H), 7.51–7.47 (m, 2H), 7.39–7.37 (m, 1H), 3.11 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 147.80, 146.85, 144.35, 140.33, 138.05, 133.29, 129.52, 127.10, 125.56, 123.72, 122.98, 120.17, 117.78, 114.04, 24.06, 21.51; MS (ESI) *m/z*: 248.39 $(M+H)^+$; HPLC analysis: retention time = 4.225 min; peak area, 100%.

*4.1.25. 6-Ethyl-2-methylbenzo[4,5]imidazo[1,2-c]quinazoline (**6w**)*

White solid (201.2 mg, 77%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.48 (s, 1H), 8.04–8.01 (m, 2H), 7.82–7.80 (m, 1H), 7.63–7.54 (m, 2H), 7.47–7.43 (m, 1H), 3.48 (q, J = 6.7 Hz, 2H), 2.58 (s, 3H), 1.63 (t, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.73, 148.02, 144.40, 140.29, 137.87, 133.14, 129.03, 127.34, 125.36, 123.67, 122.91, 120.13, 117.82, 114.41, 29.29, 21.49, 10.31; HRMS (ESI) *m/z* calcd for $C_{17}H_{16}N_3$ $[M+Na^+]$, 262.1344; Found 262.1353. HPLC analysis: retention time = 4.933 min; peak area, 100%.

*4.1.26. 2-Methyl-6-propylbenzo[4,5]imidazo[1,2-c]quinazoline (**6x**): [70]*

Yellow solid (198.3 mg, 72%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.48 (s, 1H), 8.02–7.95 (m, 2H), 7.79 (d, J = 8.3 Hz, 1H), 7.58–7.54 (m, 2H), 7.47–7.43 (m, 1H), 3.40 (t, J = 7.7 Hz, 2H), 2.57 (s, 3H), 2.05 (sxt, J = 5.7 Hz, 2H), 1.23 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.80, 148.10, 144.46, 140.26, 137.88, 133.15, 129.08, 127.33, 125.38, 123.68, 122.94, 120.20, 117.86, 114.28, 37.82, 21.50, 19.39, 13.87; HPLC analysis: retention time = 5.675 min; peak area, 100%.

*4.1.27. 6-Butyl-2-methylbenzo[4,5]imidazo[1,2-c]quinazoline (**6y**)*

Yellow solid (228.6 mg, 79%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.49 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.59–7.55 (m, 2H), 7.49–7.45 (m, 1H), 3.44 (t, J = 7.8 Hz, 2H), 2.58 (s, 3H), 2.05 (qnt, J = 7.7 Hz, 2H), 1.72–1.61 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.05, 144.14, 144.48, 140.29, 137.88, 133.17, 129.10, 127.32, 125.40, 123.69, 122.95, 120.22, 117.87, 114.31, 35.77, 27.98, 22.55, 21.50, 13.98; HRMS (ESI) *m/z* calcd for $C_{19}H_{20}N_3$$[M+H^+]$, 290.1657; Found 290.1666. HPLC analysis: retention time = 5.715 min; peak area, 100%.

*4.1.28. 2-Methoxy-6-methylbenzo[4,5]imidazo[1,2-c]quinazoline (**6z**)*

White solid (171.1 mg, 65%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.09–8.03 (m, 3H), 7.82 (d, J = 8.9 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.50–7.48 (m, 1H), 7.4 (dd, J = 8.9, 2.8 Hz, 1H), 4.02 (s, 3H), 3.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.94, 147.69, 145.39, 144.24, 136.89, 129.51, 128.92, 125.59, 123.00, 122.18, 120.09, 118.85, 114.14, 103.78, 56.01, 23.94; HRMS (ESI) *m/z* calcd for $C_{16}H_{14}N_3O$ $[M+H^+]$, 264.1137; Found 264.1143. HPLC analysis: retention time = 4.333 min; peak area, 100%.

*4.1.29. Naphtho[2′,3′:4,5]imidazo[1,2-c]quinazoline (**6aa**)*

Yellow solid (171.1 mg, 65%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 9.20 (s, 1H), 8.71 (d, J = 8.9 Hz, 1H), 8.43 (s, 1H), 8.38 (s, 1H), 8.12–8.06 (m, 2H), 7.99–7.97 (m, 1H), 7.85–7.81 (m, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.57–7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.26, 136.69, 132.63, 132.35, 130.07, 128.90, 128.66, 128.54, 127.84, 125.20, 125.14, 124.80, 117.07, 106.86; HRMS (ESI) *m/z* calcd for $C_{18}H_{12}N_3$ $[M+H^+]$, 270.1031; Found 270.1034. HPLC analysis: retention time = 4.483 min; peak area, 100%.

*4.1.30. 6-Methylnaphtho[2′,3′:4,5]imidazo[1,2-c]quinazoline (**6ab**)*

White solid (246.5 mg, 87%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.70 (d, J = 7.9 Hz, 1H), 8.42 (d, J = 9.4 Hz, 2H), 8.09–8.04 (m, 2H), 7.89–7.81 (m, 1H), 7.81–7.77 (m, 1H), 7.67–7.62 (m, 1H), 7.55–7.51 (m, 2H), 3.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.34, 143.58, 143.30, 143.07, 132.55, 131.65, 130.22, 129.97, 128.23, 128.03, 127.65, 127.31, 125.29, 124.85, 124.65, 117.86, 116.62, 111.38, 24.28; HRMS (ESI) *m/z* calcd for $C_{19}H_{14}N_3$ $[M+H^+]$, 284.1188; Found 284.1192. HPLC analysis: retention time = 5.492 min; peak area, 97.32%.

*4.1.31. 6-Ethylnaphtho[2′,3′:4,5]imidazo[1,2-c]quinazoline (**6ac**)*

White solid (237.9 mg, 80%); mp 207–209 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.72 (d, J = 8.0 Hz, 1H), 8.44 (d, J = 4.0 Hz, 2H), 8.10–8.09 (m, 2H), 7.94–7.92 (m, 1H), 7.83–7.78 (m, 1H), 7.67–7.63 (m, 1H), 7.57–7.53 (m, 2H), 3.62 (q, J = 6.7 Hz, 2H), 1.72 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.21, 143.70, 143.05, 132.47, 131.58, 130.04, 129.84, 128.30, 127.60, 127.58, 125.26, 124.79, 124.65, 117.94, 116.58, 111.82, 29.48, 10.25; HRMS (ESI) *m/z* calcd for $C_{20}H_{16}N_3$ $[M+H^+]$, 298.1344; Found 298.1343. HPLC analysis: retention time = 5.683 min; peak area, 95.53%.

*4.1.32. 6-Propylnaphtho[2′,3′:4,5]imidazo[1,2-c]quinazoline (**6ad**)*

Yellow solid (236.6 mg, 76%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.72–8.70 (m, 1H), 8.07–8.05 (m, 2H), 8.02–7.93 (m, 1H), 7.89–7.87 (m, 1H), 7.81–7.76 (m, 1H), 7.68–7.28 (m, 4H), 3.46 (t, J = 8.0 Hz, 2H), 2.19–2.09 (m, 2H), 1.27 (t, J = 6.0 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.64, 148.06, 144.46, 142.20, 131.66, 129.70, 129.42, 129.02, 127.61, 127.58, 126.65, 125.48, 124.11, 123.09, 120.27, 118.17, 114.30, 109.14, 37.87, 19.36, 13.87; Anal. Calcd for $C_{21}H_{17}N_3$ Elemental Analysis: C, 81.00; H, 5.50; N, 13.49. Found: C, 81.02; H, 5.52; N, 13.47. HPLC analysis: retention time = 6.258 min; peak area, 100%.

4.1.33. 6-Butylnaphtho[2′,3′:4,5]imidazo[1,2-c]quinazoline (6ae)

White solid (257.1 mg, 79%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.74–8.71 (m, 1H), 8.46–8.41 (m, 2H), 8.13–8.08 (m, 2H), 7.93–7.92 (m, 1H), 7.83–7.81 (m, 1H), 7.68–7.66 (m, 1H), 7.58–7.55 (m, 2H), 3.59 (t, J = 7.8 Hz, 2H), 2.17–2.13 (m, 2H), 1.77 (q, J = 8.0 Hz, 2H), 1.15 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 151.54, 151.01, 143.76, 143.03, 132.50, 131.61, 130.03, 128.34, 128.04, 127.58, 127.55, 125.29, 124.81, 124.67, 117.96, 116.65, 111.73, 108.49, 35.86, 27.89, 22.60, 14.03; HRMS (ESI) m/z calcd for $C_{22}H_{20}N_3$ [M + H$^+$], 326.1657; Found 326.1662. HPLC analysis: retention time = 7.133 min; peak area, 97.55%.

4.1.34. 9,10-Dichloro-6-methylbenzo[4,5]imidazo[1,2-c]quinazoline (6af): [70]

White solid (90.6 mg, 30%); mp > 220 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.62 (d, J = 7.2 Hz, 1H), 8.13 (s, 1H), 8.09 (s, 1H), 7.90–7.89 (m, 1H), 7.83–7.79 (m, 1H), 7.69–7.66 (m, 1H), 3.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.32, 146.83, 143.71, 142.42, 132.42, 129.96, 128.40, 128.12, 127.60, 126.88, 124.24, 121.10, 117.69, 115.30, 23.90; MS (ESI) m/z: 301.93 (M)$^+$; HPLC analysis: retention time = 5.500 min; peak area, 100%.

4.2. Biological evaluation

4.2.1. Determination of minimum inhibitory concentration

Two-fold serial dilutions of each test compound/drug were prepared and incorporated into agar medium with oleic acid, albumin, dextrose, and catalase growth supplement to get final concentrations of 50, 25, 12.5, 6.25, 3.125, 1.56, and 0.78 μg/mL. Inoculum of *M. tuberculosis* ATCC 27294 was prepared from fresh agar slants with growth supplement adjusted to 1 mg/ mL (wet weight) in Tween 80 (0.05%) saline diluted to 10^{-2} to give a concentration of ~10^7 colony forming unit (cfu)/mL. Five microliters of this bacterial suspension was spotted onto agar tubes containing different concentrations of the drug as discussed above. The tubes were incubated at 37 °C, and final readings (as MIC in μg/mL) were determined after 28 days. The MIC is defined as the minimum concentration of compound required to give complete inhibition of bacterial growth. This method is similar to that recommended by the National Committee for Clinical Laboratory Standards for the determination of MIC in triplicate. Isoniazid (INH), Rifampin (R), Ethambutol (E), Pyrazinamide (Z) and Ciprofloxacin (Cfx) was procured from commercial sources.

4.2.2. In vitro cell viability assay

In-vitro cell viability of the anti-TB compounds with MIC ≤ 6.25 μg/mL was determined against RAW 264.7 cell lines at 50 μg/mL concentration. After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT [(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide)] assay into a formazan product using the non-radioactive cell proliferation assay.

Declaration of Competing Interest

The authors declare no competing financial interest.

Acknowledgements

The authors thank the Department of Pharmaceuticals (DoP), New Delhi for financial assistance. M.D.V. also thanks University Grants Commission (UGC), New Delhi for research fellowship.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2020.103774.

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