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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Microwave-assisted synthesis of pyrido[1,2-*a*]benzimidazole derivatives of *β*-aryloxyquinoline and their antimicrobial and antituberculosis activities

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Abstract A new series containing pyrido[1,2-*a*]benzimidazole derivatives of *β*-aryloxyquinoline has been synthesized via base catalyzed microwave-assisted multicomponent cyclocondensation reaction. This methodology allowed us to achieve the desired products in good yields in very short time with the use of 10 mol% NaOH as a non-hazardous organic base. The chemical structures of compounds **6a**–**x** were elucidated by ^{1}H NMR, ^{13}C NMR, FT-IR, elemental analysis, and mass spectral data. The titled derivatives were tested against a panel of pathogenic strains of bacteria and fungi for antimicrobial activity and against *Mycobacterium tuberculosis* H37Rv for their antitubercular activity. The structural activity relationship study revealed that antimicrobial and antitubercular potency of the title compounds depends not only on the bicyclic heteroaromatic pharmacophore appended through ether linked aryl ring but also on the nature of the peripheral substituents and may also upon their spatial relationship and positional changes.

Keywords Pyrido[1,2-*a*]benzimidazole · Aryloxyquinoline · Microwave-assisted synthesis · Antimicrobial activity · Antitubercular activity

Introduction

Tuberculosis is mainly caused by *Mycobacterium tuberculosis* bacteria (MTB). It is found to be the second leading killer disease from a single infectious agent because around billions of lives were lost during the last two centuries (WHO report, 2010). There is no universally effective vaccine against infection caused by MTB (Russell *et al.*, 2010); therefore, the development of antitubercular drugs becomes thirsty area in the medicinal chemistry research. Moreover, the problems posed by multi-drug-resistant (MDR) microorganisms have reached an alarming level in many countries around the world. Some antimicrobial and antitubercular drugs were failed during the chemotherapy against the infections caused by MDR microorganism (Diekema *et al.*, 2004; WHO report, 2008). These reports encompass the development of new and effective antitubercular and antimicrobial drugs. In pursuit of this goal, we have synthesized pyrido[1,2-*a*]benzimidazole derivatives bearing *β*-aryloxyquinoline nucleus with the hope that amalgamation of these two biopotent moiety into a single scaffold may produce novel heterocyclic scaffold with promising biological activity.

Quinoline derivatives are found to possess wide range of useful biological properties including antitubercular (Mital *et al.*, 2006), antibacterial (Kalluraya *et al.*, 2008), antifungal (Rana *et al.*, 2008), antimalarial (Charris *et al.*, 2005; Dave *et al.*, 2009), anti-inflammatory (Bava and Kumar 2009), and anticancer activities (Shi *et al.*, 2008). Moreover, the presence of aryl ring appended via ether linkage at *β*-position of quinoline moiety is found to be highly active against MTB (H37Rv) and plays a vital role in the development of new antituberculosis drugs (Mungra *et al.*, 2011; Upadhaya *et al.*, 2009).

On the other hand, pyrido[1,2-*a*]benzimidazole derivatives did not receive much attention until the past decades (Panda *et al.*, 2003), but from last few years they attracted organic as well as medicinal chemist due to their diverse syntheses and various biological activities, such as antitubercular (Pieroni *et al.*, 2011), antimicrobial (Rida *et al.*, 2006; Takemura *et al.*, 2004; Rida *et al.*, 1988), anti-HIV-1

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(Rida *et al.*, 2006), anticancer (Rida *et al.*, 2006; El-Hawash *et al.*, 1999), antineoplastic (Badawey *et al.*, 1995a, b; 1999), antiviral (Kotovskaya *et al.*, 2005), and antimalarial (Ndakala *et al.*, 2011).

Previously, pyrido[1,2-*a*]benzimidazoles have been prepared using different synthetic approaches (Bogdanowicz-Szwed and Czarny, 1993; Prostakov *et al.*, 1983; Russell and Van Nievelt, 1995; Sundberg and Ellis, 1982; Yan *et al.*, 2009; Algul *et al.*, 2009; Dawood *et al.*, 2010, 2011; Wu *et al.*, 2011). However, some shortcomings were observed in these methods such as, longer reaction time, use of hazardous organic base, drastic reaction conditions, and poor yield. To overcome these drawbacks, we have adopted the microwave-assisted organic synthesis (MAOS) approach and NaOH as an eco-friendly base which facilitate to construct the title derivatives with more efficacy in shorter reaction time.

In the light of the above-mentioned reports and in continuation of our efforts toward the synthesis of quinoline-based biologically active heterocycles (Shah *et al.*, 2012; Jardosh and Patel, 2011, 2012; Mungra *et al.*, 2011; Makawana *et al.*, 2012; Kathrotiya *et al.*, 2012), an attempt has been through to undertake the microwave-assisted NaOH catalyzed synthesis of pyrido[1,2-*a*]benzimidazole derivatives bearing *β*-aryloxyquinoline nucleus and evaluated their antimicrobial and antitubercular activities.

Results and discussion

Chemistry

The required intermediates 2-chloroquinoline-3-carbaldehydes **1a–c** were prepared by Vilsmeier-Haack reaction of various substituted acetanilide (Meth-Cohn and Bramha, 1978). The synthetic precursors *β*-aryloxyquinoline-3-carbaldehydes **3a–l** were synthesized by nucleophilic displacement of chloro group at C-2 position of **1a–c** with various phenols **2a–d** by refluxing in dimethylformamide using anhydrous potassium carbonate as a base (Scheme 1) (Mungra *et al.*, 2011). Substituted pyrido[1,2-*a*]benzimidazole-2,4-dicarbonitrile derivatives **6a–x** have been synthesized efficiently via microwave-assisted one-pot three-component cyclocondensation of *β*-aryloxyquinoline-3-carbaldehydes **3a–l**, malononitrile **4**, and 2-cyanomethylbenzimidazole **5a,b** in ethanol containing 10 mol% of NaOH at 280 W (Scheme 1).

The reaction was optimized by varying the mole ratio of catalyst (NaOH). A mixture of respective *β*-aryloxyquinoline-3-carbaldehyde, malononitrile, and 2-cyanomethylbenzimidazole was subjected to microwave irradiation (280 W) by varying mole ratio of NaOH 2.5, 5.0, 7.5, 10.0, and 12.5 mol%. It was observed that when the amount of NaOH was increased to 10.0 mol%, the reaction rate was increased within shorter reaction time (4 min). On the other hand, further increase in the amount of NaOH resulted into the sticky mass which required ice-water work-up and gave poor yield. The formation of products was continuously checked by thin layer chromatography (TLC) at regular time interval to optimize reaction time and it was found that reaction was completed within 4 min. The above results showed that the best results were obtained when the reaction was carried out with 10.0 mol% of NaOH under microwave irradiation at 280 W for 4 min.

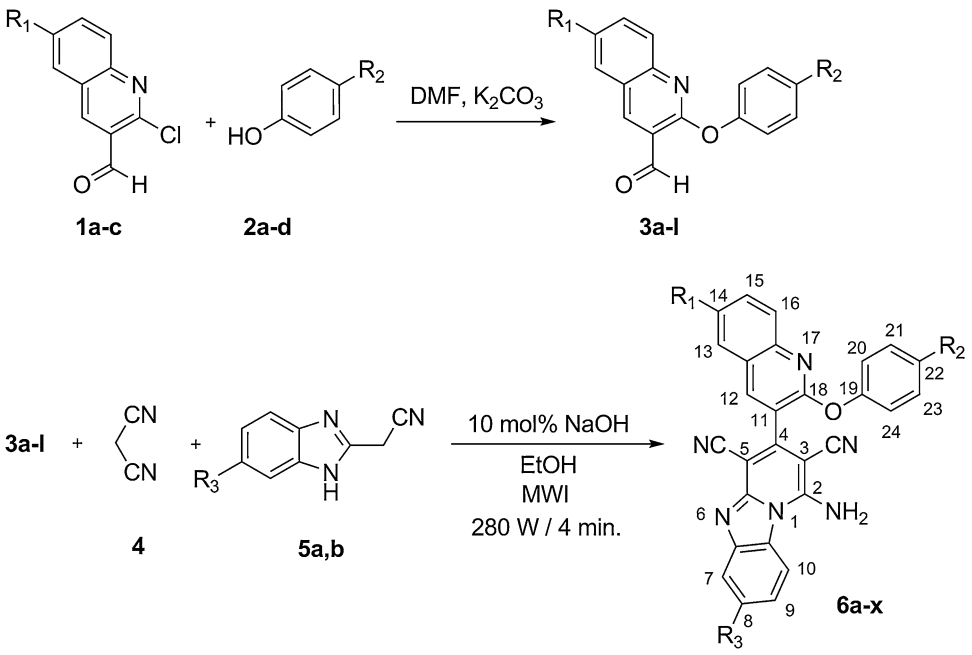
The formation of compounds **6a–x** may proceed via two steps. (i) Initial formation of an intermediate heterylidenenitrile by Knoevenagel condensation of *β*-aryloxyquinoline-3-carbaldehydes **3a–l** with malononitrile **4** and (ii) intermolecular cyclization, driven through the nucleophilic attack of 2-cyanomethylbenzimidazole **5a**,**5b** in basic reaction condition gives **7** which undergoes air oxidation to furnish pyrido[1,2-*a*]benzimidazole as the final product (Scheme 2).

The structures of newly synthesized compounds **6a–x** were confirmed by ^{1}H NMR, ^{13}C NMR, FT-IR, elemental analysis, and mass spectral data. The IR spectrum of title compounds **6a–x** showed absorption bands around 3,500–3,400 and 3,350–3,300 cm^{-1} correspond to asymmetric and symmetric stretching of primary amino group, bands around 2,250–2,190 cm^{-1} for –C≡N stretching of cyano group and 1,250–1,180 cm^{-1} for C–O–C stretching of ether linkage. In ^{1}H NMR spectrum of the compounds **6a–x**, multiplets in the range of δ 6.98–8.83 ppm appeared for aromatic protons. Moreover, a singlet around δ 2.32–2.59 and δ 3.76–3.92 ppm stands for methyl and methoxy protons, respectively. A distinctive broad singlet in the range of δ 8.75–8.97 appeared for the primary amine. In the ^{13}C NMR spectral data of the title compounds **6a–x**, the signal at around δ 77.60–87.95 ppm is assigned to carbon attached with carbonitrile while signals around δ 115.10–158.60 ppm are attributed to all the aromatic carbons. Also, distinctive signals around δ 20.88–21.85 and δ 55.85–56.16 ppm stand for methyl and methoxy of **6a–x** derivatives, respectively. The obtained elemental analysis values are in good agreement with the theoretical data. Furthermore, mass spectral studies of all the title compounds showed molecular ion peak $M^{+\cdot}$ corresponding to their exact mass. All physical, analytical data, as well as spectroscopic characterization data of the synthesized compounds **6a–x** are given in "Experimental" section.

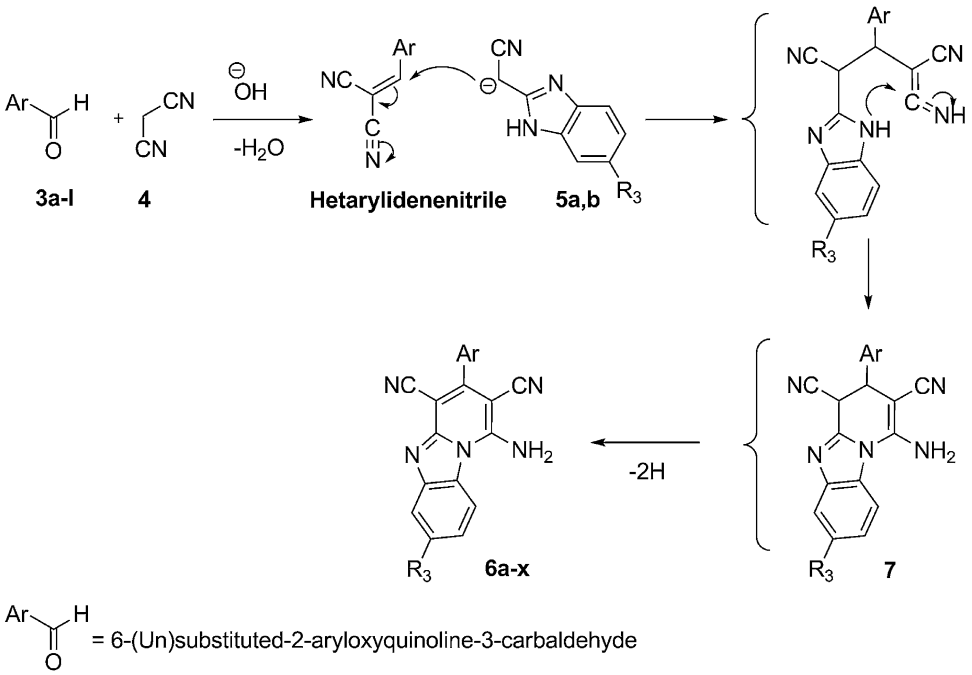
Antimicrobial activity

Antimicrobial activity of the title compounds **6a–x** was carried out by broth microdilution method (NCCLS, 2002). Mueller–Hinton broth was used as nutrient medium to grow and dilute the compound suspension for the test bacteria and Sabouraud Dextrose broth used for fungal nutrition. The strains used for the activity were procured

Scheme 1 Representative route for the synthesis of compounds **3a–l** and **6a–x**



Scheme 2 Plausible mechanistic pathway for the compounds **6a–x**



from [MTCC-Microbial Type Culture Collection] Institute of Microbial Technology, Chandigarh. The compounds **6a–x** were screened for their antibacterial activity against *Bacillus subtilis* (MTCC 441), *Clostridium tetani* (MTCC 449), *Streptococcus pneumoniae* (MTCC 1936), *Escherichia coli* (MTCC 443), *Salmonella typhi* (MTCC 98), and *Vibrio cholerae* (MTCC 3906) as well as for antifungal activity against *Aspergillus fumigatus* (MTCC 3008) and *Candida albicans* (MTCC 227). DMSO was used as diluents to get desired concentration of compounds to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 °C overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the compound concentrations. The MIC was defined as the lowest concentration of the antibiotic or test sample allowing no visible growth. All the tubes not showing visible growth (in the same manner as control tube described above) was

subcultured and incubated overnight at 37 °C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show similar number of colonies indicating bacteriostatic, a reduced number of colonies indicating a partial or slow bactericidal activity, and no growth if the whole inoculum has been killed. The test must include a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized compound was diluted obtaining 2,000 μg/mL concentration as a stock solution. In primary screening, 500, 250, and 200 μg/mL concentrations of the synthesized compounds were taken. The active synthesized compounds found in this primary screening were further tested in a second set of dilution against all microorganisms. The compounds found active in primary screening were similarly diluted to obtain 100, 62.5, 50, and 25 μg/mL concentrations. The highest dilution showing at least 99 % inhibition is taken as MIC. In this study, ampicillin, ciprofloxacin, and norfloxacin were used as standard antibacterial drugs, whereas griseofulvin was used as standard antifungal drug.

The antibacterial screening data (Table 1) revealed that, against Gram-positive bacteria *B. subtilis*, compounds **6a**, **6f**, and **6w** (MIC = 100 μg/mL) were found to be more potent than ampicillin and equipotent to norfloxacin. Compounds **6g**, **6s**, and **6v** (MIC = 125 μg/mL) were found to have significant activity when compared with ampicillin. Compounds **6e**, **6j**, **6l**, **6m**, and **6r** (MIC = 200 μg/mL) were found to possess better activity than ampicillin, while compounds **6b**, **6c**, **6d**, **6h**, **6i**, **6k**, **6n**, **6o**, **6t**, **6u**, and **6x** (MIC = 250 μg/mL) were found equally potent to ampicillin. Against *C. tetani*, compound **6n** (MIC = 62.5 μg/mL) showed fabulous activity when compared with ampicillin and ciprofloxacin, while compounds **6a**, **6i**, **6s**, **6t**, and **6x** (MIC = 100 μg/mL) showed significant activity compare to ampicillin and equivalent to ciprofloxacin. Compounds **6j** and **6r** (MIC = 125 μg/mL) as well as compounds **6d**, **6k**, **6l**, **6o**, **6v**, and **6w** (MIC = 200 μg/mL) were found to be more potent than ampicillin, while compounds **6b**, **6c**, **6e**, **6h**, **6m**, **6p**, **6q**, and **6u** (MIC = 250 μg/mL) were found to be equipotent to ampicillin. Against *S. pneumoniae*, Compound **6a** (MIC = 62.5 μg/mL) was found to have more efficacy, while compounds **6g**, **6p**, **6q**, **6v**, and **6x** were found to have identical activity when compare with ampicillin.

Bold numbers indicates more or equally potent compounds compare to standard drugs

Against Gram-negative bacteria *E coli*, compounds **6e**, **6n**, **6p**, and **6u** (MIC = 62.5 μg/mL) showed remarkable activity, while compounds **6b**, **6f**, **6m**, **6o**, and **6x** (MIC = 100 μg/mL) were found to be equally potent when compared with ampicillin. Against *S. typhi* compounds **6b**, **6e**, **6u**, and **6v** (MIC = 100 μg/mL) showed equal potency with ampicillin. Against *V. cholerae* compounds **6b**, **6f**, and **6t** (MIC = 100 μg/mL) were found to be equipotent to ampicillin.

Exploration of antifungal screening data revealed that, against fungi *C. albicans*, compound **6o** (MIC = 200 μg/mL) was found to exhibit fabulous activity; compounds **6c**, **6e**, **6h**, and **6p** (MIC = 250 μg/mL) showed remarkable activity, while compounds **6d**, **6i**, **6j**, **6m**, **6n**, **6q**, **6r**, **6w**, and **6x** (MIC = 500 μg/mL) were found equally potent when compared with griseofulvin. None of the synthesized compounds was found to be active against *A. fumigatus*.

Antituberculosis activity

The encouraging results from the antimicrobial studies prompted us to go for the preliminary screening of the title compounds **6a–x** for their in vitro antituberculosis activity against *M. tuberculosis* H37Rv by using Lowenstein–Jensen medium (conventional method) as described by Rattan (2000). A primary screen was conducted at primary dilution 6.25 μg/ml against *M. tuberculosis* H37Rv, where 6.25 μg/ml of each test compound were added to liquid Lowenstein–Jensen Medium and then media were sterilized by inspissations method. A culture of *M. tuberculosis* H37Rv growing on Lowenstein–Jensen Medium was harvested in 0.85 % saline in bijou bottles. DMSO was used as vehicle to get desired concentration. These tubes were then incubated at 37 °C for 24 h followed by streaking of *M. tuberculosis* H37Rv (5×10^4 bacilli per tube). These tubes were then incubated at 37 °C. Growth of bacilli was seen after 12, 22, and finally 28 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with *M. tuberculosis* H37Rv. The concentration at which complete inhibition of colonies occurred was taken as active concentration of test compound. The standard strain *M. tuberculosis* H37Rv was tested with known drug isoniazid and rifampicin. The screening results are summarized as % inhibition relative to standard drug isoniazid and rifampicin. Compounds effecting <90 % inhibition in the primary screen were not evaluated further. Compounds demonstrating at least 90 % inhibition in the primary screen were re-tested at lower concentration (MIC) in a Lowenstein–Jensen medium and evaluated their MIC values.

The antimycobacterial activity results of the compounds **6a–x** are shown in Table 2. Of the compounds screened for antituberculosis activity, compounds **6p** (R_1 = H, R_2 = F, R_3 = CH_3), **6t** (R_1 = CH_3, R_2 = F, R_3 = CH_3), **6x** (R_1 = OCH_3, R_2 = F, R_3 = CH_3), and **6h** (R_1 = CH_3, R_2 = F, R_3 = H) found to possess better activity against *M. tuberculosis* H37Rv and exhibited highest % inhibition. The MIC values of these compounds found to be 6.25, 12.5, 12.5, and 25 μg/mL respectively. In this set of

Table 1 Antimicrobial activity (MIC, μg/mL) of compounds **6a-x**

Compound	Gram-positive bacteria			Gram-negative bacteria			Fungi	
	Bs. MTCC 441	Ct. MTCC 449	Sp. MTCC 1936	Ec. MTCC 443	St. MTCC 98	Vc. MTCC 3906	Af. MTCC 3008	Ca. MTCC 227
6a ($R_1 = H$, $R_2 = H$, $R_3 = H$)	**100**	**100**	**62.5**	250	250	200	500	1,000
6b ($R_1 = H$, $R_2 = CH_3$, $R_3 = H$)	**250**	**250**	125	**100**	**100**	**100**	250	>1,000
6c ($R_1 = H$, $R_2 = OCH_3$, $R_3 = H$)	**250**	**250**	200	125	200	125	500	**250**
6d ($R_1 = H$, $R_2 = F$, $R_3 = H$)	**250**	**200**	125	200	250	250	500	**500**
6e ($R_1 = CH_3$, $R_2 = H$, $R_3 = H$)	**200**	**250**	200	**62.5**	**100**	200	1,000	**250**
6f ($R_1 = CH_3$, $R_2 = CH_3$, $R_3 = H$)	**100**	500	250	**100**	125	**100**	>1,000	1,000
6g ($R_1 = CH_3$, $R_2 = OCH_3$, $R_3 = H$)	**125**	500	**100**	250	200	200	>1,000	1,000
6h ($R_1 = CH_3$, $R_2 = F$, $R_3 = H$)	**250**	**250**	200	200	250	250	500	**250**
6i ($R_1 = OCH_3$, $R_2 = H$, $R_3 = H$)	**250**	**100**	250	250	200	200	1,000	**500**
6j ($R_1 = OCH_3$, $R_2 = CH_3$, $R_3 = H$)	**200**	**125**	500	125	250	250	>1,000	**500**
6k ($R_1 = OCH_3$, $R_2 = OCH_3$, $R_3 = H$)	**250**	**200**	500	125	200	125	250	>1,000
6l ($R_1 = OCH_3$, $R_2 = F$, $R_3 = H$)	**200**	**200**	500	200	500	200	500	>1,000
6m ($R_1 = H$, $R_2 = H$, $R_3 = CH_3$)	**200**	**250**	250	**100**	200	500	500	**500**
6n ($R_1 = H$, $R_2 = CH_3$, $R_3 = CH_3$)	**250**	**62.5**	200	**62.5**	200	200	1,000	**500**
6o ($R_1 = H$, $R_2 = OCH_3$, $R_3 = CH_3$)	**250**	**200**	250	**100**	125	250	1,000	**200**
6p ($R_1 = H$, $R_2 = F$, $R_3 = CH_3$)	500	**250**	**100**	**62.5**	125	500	>1,000	**250**
6q ($R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$)	500	**250**	**100**	250	250	200	>1,000	**500**
6r ($R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$)	**200**	**125**	250	200	250	125	500	**500**
6s ($R_1 = CH_3$, $R_2 = OCH_3$, $R_3 = CH_3$)	**125**	**100**	125	250	250	200	>1,000	1,000
6t ($R_1 = CH_3$, $R_2 = F$, $R_3 = CH_3$)	**250**	**100**	200	200	200	**100**	>1,000	>1,000
6u ($R_1 = OCH_3$, $R_2 = H$, $R_3 = CH_3$)	**250**	**250**	250	**62.5**	**100**	250	500	1,000
6v ($R_1 = OCH_3$, $R_2 = CH_3$, $R_3 = CH_3$)	**125**	**200**	**100**	200	**100**	125	>1,000	1,000
6w ($R_1 = OCH_3$, $R_2 = OCH_3$, $R_3 = CH_3$)	**100**	**200**	200	200	250	125	>1,000	**500**
6x ($R_1 = OCH_3$, $R_2 = F$, $R_3 = CH_3$)	**250**	**100**	**100**	**100**	200	200	1,000	**500**
Ampicillin	250	250	100	100	100	100	–	–
Ciprofloxacin	50	100	50	25	25	25	–	–
Norfloxacin	100	50	10	10	10	10	–	–
Griseofulvin	–	–	–	–	–	–	100	500

Bold numbers indicate more or equally potent compounds compare to standard drugs

– not tested

Bs, *Bacillus subtilis*; *Ct*, *Clostridium tetani*; *Sp*, *Streptococcus pneumoniae*; *Ec*, *Escherichia coli*; *St*, *Salmonella typhi*; *Vc*, *Vibrio cholerae*; *Af*, *Aspergillus fumigatus*; *Ca*, *Candida albicans*; *MTCC*, Microbial Type Culture Collection

heterocyclic compounds, compound **6p** ($R_1 = H$, $R_2 = F$, $R_3 = CH_3$) is appeared as the promising antimicrobial member with significant antitubercular activity.

Structure–Activity Relationship (SAR) study

The exploration of the structure–activity relationship of antimicrobial screening revealed that the unsubstituted compound **6a** shows significant activity against all the Gram-positive bacteria. Against *B. subtilis*, compounds having CH_3 and OCH_3 groups at *para* position of ether linked aryl ring gives better results compare to other members of the series, e.g., compounds **6f**, **6w**, **6g**, **6s**, and **6v**. Compounds with unsubstituted quinoline ring and CH_3 at benzimidazole ring effectively inhibits the growth of *C. tetani* and showed better activity to that of ampicillin and ciprofloxacin, e.g., compounds **6n**, **6r**, **6s**, **6t**, **6v**, **6w**, and **6x**. Compounds having H/CH_3 at quinoline ring and CH_3 at benzimidazole ring enhance the antibacterial effectiveness against *S. pneumoniae*. Against *E. coli*, compounds with CH_3 group at quinoline and benzimidazole ring found to have more potential than the other compounds, e.g., **6e**, **6n**, **6p**, and **6u**. Compounds containing CH_3 group at quinoline, aryloxy, and benzimidazole rings found to have more potential to inhibit the growth of *S. typhi*, e.g., compounds **6b**, **6e**, **6u**, and **6v**. In case of *V. cholerae*, compounds having CH_3 group at quinoline and aryloxy rings found to be equipotent to ampicillin, e.g., compounds **6b**, **6f**, and **6t**. Compounds with unsubstituted quinoline ring and H/F at aryloxy ring showed more potency compare to griseofulvin, e.g., compounds **6c**, **6e**, **6h**, **6o**, and **6p**.

Table 2 Antimycobacterial activity of the compounds **6a–x**

Compound	Primary screen (6.25 μg/mL) % Inhibition	Actual MIC μg/mL
6a	80	–
6b	52	–
6c	24	–
6d	75	–
6e	19	–
6f	32	–
6g	62	–
6h	**94**	25
6i	46	–
6j	58	–
6k	79	–
6l	86	–
6m	49	–
6n	12	–
6o	64	–
6p	**99**	6.25
6q	71	–
6r	58	–
6s	25	–
6t	**97**	12.5
6u	78	–
6v	10	–
6w	70	–
6x	**96**	12.5
Isoniazid	99	0.2
Rifampicin	98	40

Bold numbers indicate >90 % inhibition

On the other hand, the evaluation of the structure–activity relationship of antitubercular activity exposed that compounds having F group at ether linked aryl ring appended to quinoline and CH_3 group at benzimidazole unit found to exhibit more potency against *M. tuberculosis* H37Rv, e.g., compounds **6h**, **6p**, **6t**, and **6x** except compound.

The above-mentioned results shows that electronic influence of both the OCH_3 (electron-donating) group and F (electron-withdrawing) group affects the antimicrobial activity in some extent, while only F group influences the antitubercular activity of the tested compounds. On the other hand, effect of lipophilic CH_3 group becomes more dominant compare to hydrophilic OCH_3 group to enhance the antimicrobial and antitubercular effectiveness of the tested compounds.

Experimental

All reactions were performed with commercially available reagents and they were used without further purification. Organic solvents were purified by standard methods (Furniss, 2004) and stored over molecular sieves. The microwave-assisted reactions are conducted in a "RAGA's Modified Electromagnetic Microwave System" whereby microwaves are generated by magnetron at a frequency of 2,450 MHz having an adjustable output power levels, i.e., 10 levels from 140 to 700 W and with an individual sensor for temperature control (fiber optic is used as a individual sensor for temperature control) with attachment of reflux condenser with constant stirring (thus avoiding the risk of high-pressure development). All melting points were taken in open capillaries and are uncorrected. Thin-layer chromatography (TLC, on aluminum plates coated with silica gel 60 F_{254}, 0.25 mm thickness, Merck) was used for monitoring the progress of all reactions, purity, and homogeneity of the synthesized compounds. Elemental analysis (% C, H, N) was carried out by Perkin-Elmer 2400 series-II elemental analyzer and all compounds are within ±0.4 % of theory specified. The FT-IR spectra were recorded using potassium bromide disc on a Shimadzu FT-IR 8401 spectrophotometer and only the characteristic peaks are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 400F (MHz) spectrometer using TMS as an internal standard at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer.

General procedure for the synthesis of pyrido-[1,2-*a*]benzimidazole derivatives **6a–x**

In a 50-mL round-bottomed flask, *β*-aryloxyquinoline-3-carbaldehyde **3a–l** (3 mmol), malononitrile **4** (3 mmol), 2-cyanomethyl-benzimidazole **5a,b** (3 mmol), and NaOH (10 mol%) in ethanol (15 mL) were thoroughly mixed and subjected to microwave irradiation at 280 W (40 % of output power) for 4 min. After the completion of reaction (evidenced by TLC—Hexane::Ethyl acetate::4:6), the mixture was allowed to stir at room temperature for 10–15 min, the solid mass separated was filtered, washed well with ethanol (10 mL), dried and purified by leaching in equal volume ratio of chloroform and methanol (40 mL) to obtain pure solid sample. Analytical, physical, and spectroscopic characterization data of synthesized compounds **6a–x** are mentioned below.

*1-Amino-3-(2-phenoxyquinolin-3-yl)pyrido [1,2-a]benzimidazole-2,4-dicarbonitrile (**6a**)*

Yield 87 %; m.p. 240–241 °C; IR (KBr, cm^{-1}): 3,455 and 3,315 (asym. and sym. str. of $–NH_2$), 2,215 ($–C\equiv N$ str.), 1,215 (C–O–C ether str.); ^1H NMR (400 MHz, DMSO-d_6): δ 7.00 (d, 2H, $J = 8.4$ Hz, H-20,24), 7.12 (m, 3H,

H-21,22,23), 7.41 (t, 1H, $J_1 = 7.6$, $J_2 = 8.0$, H-9), 7.52 (m, 2H, H-8,14), 7.68 (d, 1H, $J = 8.0$ Hz, H-13), 7.75 (t, 1H, $J_1 = 7.2$, $J_2 = 8.0$, H-15), 7.87 (d, 1H, $J = 8.0$ Hz, H-10), 8.08 (d, 1H, $J = 8.0$ Hz, H-7), 8.59 (d, 1H, $J = 8.4$ Hz, H-16), 8.67 (s, 1H, H-12), 8.80 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 77.68 (C–CN), 87.79 (C–CN), 115.15, 115.91, 119.11, 120.03, 123.37, 124.09, 125.19, 127.02, 127.22, 127.65, 128.54, 132.72, 134.02, 135.60, 141.13, 144.88, 145.61, 146.76, 147.01, 148.71, 152.19, 154.48, 156.91, 158.58, (Ar–C); Anal. Calcd. for $C_{28}H_{16}N_6O$ (452.47 g/mol): C 74.33, H 3.56, N 18.57 % Found: C 74.15, H 3.49, N 18.53 %; MS (*m*/*z*): 452.2 (M^+).

*1-Amino-3-[2-(4-methylphenoxy)quinolin-3-yl]pyrido [1,2-a]benzimidazole-2,4-dicarbonitrile (**6b**)*

Yield 82 %; m.p. 233–235 °C; IR (KBr, cm^{-1}): 3,430 and 3,330 (asym. and sym. str. of $–NH_2$), 2,205 (–C≡N str.), 1,195 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.34, (s, 3H, CH_3, C-22), 7.18 (d, 2H, $J = 8.4$ Hz, H-23,21), 7.26 (d, 2H, $J = 8.0$ Hz, H-20,24), 7.44 (t, 1H, $J_1 = 7.6$, $J_2 = 8.0$, H-9), 7.58 (m, 2H, H-8,14), 7.70 (d, 1H, $J = 8.0$ Hz, H-13), 7.77 (t, 1H, $J_1 = 7.2$, $J_2 = 8.0$, H-15), 7.90 (d, 1H, $J = 8.0$ Hz, H-10), 8.11 (d, 1H, $J = 8.0$ Hz, H-7), 8.63 (d, 1H, $J = 8.4$ Hz, H-16), 8.72 (s, 1H, H-12), 8.85 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.92 (CH_3), 78.10 (C–CN), 87.84 (C–CN), 115.49, 115.98, 116.39, 119.53, 120.18, 122.18, 122.68, 125.20, 126.19, 127.10, 127.40, 128.85, 128.96, 130.48, 132.06, 134.87, 141.81, 145.03, 146.56, 147.40, 148.79, 151.15, 152.49, 158.24 (Ar–C); Anal. Calcd. for $C_{29}H_{18}N_6O$ (466.49 g/mol): C 74.67, H 3.89, N 18.02 % Found: C 74.42, H 4.04, N 17.95 %; MS (*m*/*z*): 466.1 (M^+).

*1-Amino-3-[2-(4-methoxyphenoxy)quinolin-3-yl]pyrido[1,2-a]benzimidazole-2,4-dicarbonitrile (**6c**)*

Yield 79 %; m.p. 277–279 °C; IR (KBr, cm^{-1}): 3,400 and 3,320 (asym. and sym. str. of $–NH_2$), 2,200 (–C ≡ N str.), 1,200 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.77 (s, 3H, OCH_3, C-22), 7.09 (d, 2H, $J = 8.4$ Hz, H-23,21), 7.20 (d, 2H, $J = 8.0$ Hz, H-20,24), 7.41 (t, 1H, $J_1 = 7.6$, $J_2 = 8.0$, H-9), 7.54 (m, 2H, H-8,14), 7.69 (d, 1H, $J = 8.0$ Hz, H-13), 7.75 (t, 1H, $J_1 = 7.2$, $J_2 = 8.0$, H-15), 7.88 (d, 1H, $J = 8.0$ Hz, H-10), 8.09 (d, 1H, $J = 8.0$ Hz, H-7), 8.57 (d, 1H, $J = 8.4$ Hz, H-16), 8.62 (s, 1H, H-12), 8.77 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.87 (OCH_3), 78.03 (C–CN), 87.77 (C–CN), 115.04, 115.94, 116.55, 119.42, 120.21, 122.20, 122.71, 125.22, 126.21, 127.11, 127.25, 129.05, 129.01, 130.52, 132.11, 134.88, 141.92, 144.92, 146.55, 147.43, 148.80, 151.15, 152.51, 158.00 (Ar–C); Anal. Calcd. for $C_{29}H_{18}N_6O_2$ (482.49 g/mol): C 72.19, H 3.76, N 17.42 % Found: C 72.32, H 4.00, N 17.55 %; MS (*m*/*z*): 482.7 (M^+).

*1-Amino-3-[2-(4-fluorophenoxy)quinolin-3-yl]pyrido [1,2-a]benzimidazole-2,4-dicarbonitrile (**6d**)*

Yield 75 %; m.p. 254–255 °C; IR (KBr, cm^{-1}): 3,425 and 3,340 (asym. and sym. str. of $–NH_2$), 2,210 (–C≡N str.), 1,225 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.22 (d, 2H, $J = 8.4$ Hz, H-23,21), 7.30 (d, 2H, $J = 8.4$ Hz, H-20,24), 7.49 (t, 1H, $J_1 = 7.6$, $J_2 = 8.0$, H-9), 7.61 (m, 2H, H-8,14), 7.74 (d, 1H, $J = 8.0$ Hz, H-13), 7.79 (t, 1H, $J_1 = 7.2$, $J_2 = 8.0$, H-15), 7.93 (d, 1H, $J = 8.0$ Hz, H-10), 8.15 (d, 1H, $J = 8.0$ Hz, H-7), 8.66 (d, 1H, $J = 8.4$ Hz, H-16), 8.75 (s, 1H, H-12), 8.88 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 77.95 (C–CN), 87.93 (C–CN), 115.28, 116.03, 116.41, 119.62, 120.17, 122.20, 122.94, 125.30, 126.22, 127.13, 127.44, 128.77, 129.05, 130.49, 132.06, 134.84, 141.76, 145.01, 146.60, 147.45, 148.80, 151.37, 152.50, 157.95 (Ar–C); Anal. Calcd. for $C_{28}H_{15}FN_6O$ (470.46 g/mol): C 71.48, H 3.21, N 17.86 % Found: C 71.44, H 3.37, N 17.94 %; MS (*m*/*z*): 470.7 (M^+).

*1-Amino-3-[2-(4-phenoxy)-6-methylquinolin-3-yl]pyrido[1,2-a]benzimidazole-2,4-dicarbonitrile (**6e**)*

Yield 89 % m.p. 261–263 °C; IR (KBr, cm^{-1}): 3,450 and 3,335 (asym. and sym. str. of $–NH_2$), 2,205 (–C≡N str.), 1,205 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3, C-14), 7.15 (d, 2H, $J = 8.4$ Hz, H-20,24), 7.26 (m, 3H, H-21,22,23), 7.56 (t, 1H, $J_1 = 7.6$, $J_2 = 7.6$, H-9), 7.72 (m, 3H, H-13,8,15), 7.89 (d, 1H, $J = 8.0$ Hz, H-16), 7.98 (d, 1H, $J = 8.0$ Hz, H-10), 8.64 (s, 1H, H-12), 8.79 (d, 1H, $J = 8.0$, H-7), 8.97 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.33 (CH_3), 78.25 (C–CN), 87.84 (C–CN), 115.60, 115.83, 116.32, 119.21, 119.94, 122.53, 123.40, 125.14, 126.98, 127.89, 129.12, 134.04, 135.58, 141.18, 145.02, 145.18, 146.80, 147.60, 148.89, 152.60, 154.78, 157.03, 157.84, 158.08 (Ar–C); Anal. Calcd. for $C_{29}H_{18}N_6O_2$ (466.49 g/mol): C 74.67, H 3.89, N 18.02 % Found: C 74.59, H 4.01, N 17.89 %; MS (*m*/*z*): 466.4 (M^+).

*1-Amino-3-[2-(4-methylphenoxy)-6-methylquinolin-3-yl]pyrido[1,2-a]benzimidazole-2,4-dicarbonitrile (**6f**)*

Yield 83 %; m.p. 243–245 °C; IR (KBr, cm^{-1}): 3,470 and 3,315 (asym. and sym. str. of $–NH_2$), 2,195 (–C≡N str.), 1,220 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.32, (s, 3H, CH_3, C-22), 2.53, (s, 3H, CH_3, C-14), 7.02

(d, 2H, $J = 8.4$ Hz, H-23,21), 7.24 (d, 2H, $J = 8.4$ Hz, H-20,24), 7.48 (t, 1H, $J_1 = 7.6$, $J_2 = 7.6$, H-9), 7.61 (m, 3H, H-13,8,15), 7.86 (d, 1H, $J = 8.0$ Hz, H-16), 7.93 (d, 1H, $J = 8.0$ Hz, H-10), 8.61 (s, 1H, H-12), 8.72 (d, 1H, $J = 8.0$, H-7), 8.87 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.93 ($\underline{C}H_3$), 21.30 ($\underline{C}H_3$), 78.20 ($\underline{C}$–CN), 87.93 ($\underline{C}$–CN), 115.11, 115.66, 116.31, 119.99, 120.06, 122.73, 123.41, 125.14, 127.20, 127.82, 129.11, 133.84, 135.61, 141.38, 144.87, 145.17, 146.71, 147.60, 149.00, 152.61, 154.75, 157.01, 158.00, 158.60 (Ar–$\underline{C}$); Anal. Calcd. for $C_{30}H_{20}N_6O$ (480.52 g/mol): C 74.99, H 4.20, N 17.49 % Found: C 75.09, H 4.12, N 17.31 %; MS (*m*/*z*): 480.3 (M^+).

*1-Amino-3-[2-(4-methoxyphenoxy)-6-methylquinolin-3-yl]pyrido[1,2-a]benzimidazole-2,4-dicarbonitrile (**6g**)*

Yield 81 %; m.p. 273–275 °C; IR (KBr, cm^{-1}): 3,475 and 3,325 (asym. and sym. str. of –NH_2), 2,225 (–C≡N str.), 1,240 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.52 (s, 3H, CH_3, C-14), 3.78 (s, 3H, OCH_3, C-22), 7.00 (d, 2H, $J = 8.4$ Hz, H-23,21), 7.21 (d, 2H, $J = 8.4$ Hz, H-20,24), 7.45 (t, 1H, $J_1 = 7.6$, $J_2 = 7.6$, H-9), 7.62 (m, 3H, H-13,8,15), 7.87 (d, 1H, $J = 8.0$ Hz, H-16), 7.90 (d, 1H, $J = 8.0$ Hz, H-10), 8.58 (s, 1H, H-12), 8.64 (d, 1H, $J = 8.0$, H-7), 8.82 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.33 ($\underline{C}H_3$), 55.89 ($O\underline{C}H_3$), 78.15 ($\underline{C}$–CN), 87.89 ($\underline{C}$–CN), 115.08, 115.65, 116.01, 119.58, 120.04, 122.72, 123.32, 125.13, 127.18, 127.75, 129.05, 133.99, 135.60, 141.08, 144.94, 145.09, 146.79, 147.54, 148.99, 152.58, 154.72, 156.97, 157.95, 158.48 (Ar–$\underline{C}$); Anal. Calcd. for $C_{30}H_{20}N_6O_2$ (496.52 g/mol): C 72.57, H 4.06, N 16.93 % Found: C 72.59, H 4.12, N 17.01 %; MS (*m*/*z*): 496.6 (M^+).

*1-Amino-3-[2-(4-fluorophenoxy)-6-methylquinolin-3-yl]pyrido[1,2-a]benzimidazole-2,4-dicarbonitrile (**6h**)*

Yield 78 %; m.p. 265–267 °C; IR (KBr, cm^{-1}): 3,450 and 3,320 (asym. and sym. str. of –NH_2), 2,210 (–C≡N str.), 1,250 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H, CH_3, C-22), 7.02 (d, 2H, $J = 8.4$ Hz, H-23,21), 7.27 (d, 2H, $J = 8.4$ Hz, H-20,24), 7.50 (t, 1H, $J_1 = 7.6$, $J_2 = 7.6$, H-9), 7.65 (m, 3H, H-13,8,15), 7.88 (d, 1H, $J = 8.0$ Hz, H-16), 7.91 (d, 1H, $J = 8.0$ Hz, H-10), 8.61 (s, 1H, H-12), 8.72 (d, 1H, $J = 8.0$, H-7), 8.90 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.34 ($\underline{C}H_3$), 78.06 ($\underline{C}$–CN), 87.90 ($\underline{C}$–CN), 115.24, 115.73, 116.06, 119.60, 120.01, 122.62, 123.30, 125.16, 127.19, 127.82, 128.95, 134.01, 135.59, 141.07, 144.88, 145.14, 146.80, 147.55, 148.92, 152.44, 154.80, 157.02, 157.91, 158.38 (Ar–$\underline{C}$); Anal. Calcd. for $C_{29}H_{17}FN_6O$ (484.48 g/mol): C 71.89, H 3.54, N 17.35 % Found: C 72.14, H 3.70, N 17.19 %; MS (*m*/*z*): 484.2 (M^+).

*1-Amino-3-[2-(4-phenoxy)-6-methoxyquinolin-3-yl]pyrido[1,2-a]benzimidazole-2,4-dicarbonitrile (**6i**)*

Yield 85 %; m.p. 237–238 °C; IR (KBr, cm^{-1}): 3,420 and 3,345 (asym. and sym. str. of –NH_2), 2,190 (–C≡N str.), 1,190 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.80 (s, 3H, OCH_3, C-14), 7.20 (d, 2H, $J = 8.4$ Hz, H-20,24), 7.32 (m, 3H, H-21,22,23), 7.61 (t, 1H, $J_1 = 7.6$, $J_2 = 7.6$, H-9), 7.77 (m, 3H, H-13,8,15), 7.86 (d, 1H, $J = 8.0$ Hz, H-16), 7.98 (d, 1H, $J = 8.0$ Hz, H-10), 8.62 (s, 1H, H-12), 8.81 (d, 1H, $J = 8.0$, H-7), 8.92 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 56.03 ($O\underline{C}H_3$), 78.08 ($\underline{C}$–CN), 87.75 ($\underline{C}$–CN), 115.31, 115.71, 116.05, 119.42, 120.10, 122.70, 123.29, 125.32, 127.23, 127.74, 128.91, 133.98, 135.60, 141.33, 144.90, 145.13, 146.69, 147.63, 149.03, 152.43, 154.71, 156.93, 157.94, 158.25 (Ar–$\underline{C}$); Anal. Calcd. for $C_{29}H_{18}N_6O_2$ (482.49 g/mol): C 72.19, H 3.76, N 17.42 % Found: C 72.23, H 3.65, N 17.58 %; MS (*m*/*z*): 482.6 (M^+).

*1-Amino-3-[2-(4-methylphenoxy)-6-methoxyquinolin-3-yl]pyrido[1,2-a]benzimidazole-2,4-dicarbonitrile (**6j**)*

Yield 80 %; m.p. 269–270 °C; IR (KBr, cm^{-1}): 3,400 and 3,310 (asym. and sym. str. of –NH_2), 2,205 (–C≡N str.), 1,225 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3, C-22), 3.92 (s, 3H, OCH_3, C-14), 7.14 (d, 2H, $J = 8.4$ Hz, H-23,21), 7.27 (d, 2H, $J = 8.4$ Hz, H-20,24), 7.51 (t, 1H, $J_1 = 7.6$, $J_2 = 7.6$, H-9), 7.67 (m, 3H, H-13,8,15), 7.85 (d, 1H, $J = 8.0$ Hz, H-16), 7.94 (d, 1H, $J = 8.0$ Hz, H-10), 8.57 (s, 1H, H-12), 8.62 (d, 1H, $J = 8.0$, H-7), 8.78 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.88 ($\underline{C}H_3$), 56.12, ($O\underline{C}H_3$), 77.65 ($\underline{C}$–CN), 87.89 ($\underline{C}$–CN), 115.20, 115.60, 115.99, 119.48, 119.95, 122.70, 123.30, 125.10, 126.98, 127.80, 129.02, 133.88, 135.61, 140.99, 144.95, 145.07, 146.80, 147.60, 149.02, 152.60, 154.69, 157.01, 157.90, 157.90 (Ar–$\underline{C}$); Anal. Calcd. for $C_{30}H_{20}N_6O_2$ (496.52 g/mol): C 72.57, H 4.06, N 16.93 % Found: C 72.39, H 3.92, N 17.11 %; MS (*m*/*z*): 496.2 (M^+).

*1-Amino-3-[2-(4-methoxyphenoxy)-6-methoxyquinolin-3-yl]pyrido[1,2-a]benzimidazole-2,4-dicarbonitrile (**6k**)*

Yield 77 %; m.p. 270–272 °C; IR (KBr, cm^{-1}): 3,440 and 3,350 (asym. and sym. str. of –NH_2), 2,200 (–C≡N str.), 1,200 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.78 (s, 3H, OCH_3, C-22), 3.85 (s, 3H, OCH_3, C-14), 6.98 (d, 2H, $J = 8.4$ Hz, H-23,21), 7.14 (d, 2H, $J = 8.4$ Hz, H-20,24), 7.42 (t, 1H, $J_1 = 7.6$, $J_2 = 7.6$, H-9), 7.58 (m, 3H, H-13,8,15), 7.86 (d, 1H, $J = 8.0$ Hz, H-16), 7.96 (d, 1H, $J = 8.0$ Hz, H-10), 8.59 (s, 1H, H-12), 8.65 (d, 1H, $J = 8.0$, H-7), 8.84 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.85 ($O\underline{C}H_3$), 55.95 ($O\underline{C}H_3$), 78.08 ($\underline{C}$–CN), 87.88

(C–CN), 115.40, 115.70, 116.13, 119.32, 120.14, 122.80, 123.20, 125.10, 127.19, 127.80, 129.17, 133.89, 135.61, 141.03, 145.02, 145.21, 146.89, 147.55, 149.03, 152.61, 154.74, 157.02, 157.90, 157.99 (Ar–C); Anal. Calcd. for $C_{30}H_{20}N_6O_3$ (512.52 g/mol): C 70.30, H 3.93, N 16.40 % Found: C 70.45, H 4.17, N 16.52 %; MS (*m/z*): 512.5 (M^+).

*1-Amino-3-[2-(4-fluorophenoxy)-6-methoxyquinolin-3-yl]pyrido[1,2-a]benzimidazole-2,4-dicarbonitrile (**6l**)*

Yield 76 %; m.p. 260–261 °C; IR (KBr, cm^{-1}): 3,435 and 3,300 (asym. and sym. str. of $-NH_2$), 2,180 (–C≡N str.), 1,220 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.82 (s, 3H, OCH_3, C-14), 7.12 (d, 2H, $J = 8.4$ Hz, H-23,21), 7.25 (d, 2H, $J = 8.4$ Hz, H-20,24), 7.53 (t, 1H, $J_1 = 7.6$, $J_2 = 7.6$, H-9), 7.68 (m, 3H, H-13,8,15), 7.87 (d, 1H, $J = 8.0$ Hz, H-16), 7.95 (d, 1H, $J = 8.0$ Hz, H-10), 8.57 (s, 1H, H-12), 8.64 (d, 1H, $J = 8.0$, H-7), 8.80 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.00 (OCH_3), 77.60 (C–CN), 87.80 (C–CN), 115.55, 115.78, 116.19, 119.56, 120.05, 122.74, 123.40, 125.17, 127.27, 127.64, 129.11, 133.88, 135.77, 141.12, 144.89, 145.19, 146.81, 147.60, 149.01, 152.61, 154.73, 156.95, 157.99, 158.07 (Ar–C); Anal. Calcd. for $C_{29}H_{17}FN_6O_2$ (500.48 g/mol): C 69.59, H 3.42, N 16.79 % Found: C 69.67, H 3.28, N 17.03 %; MS (*m/z*): 500.1 ($M^{+\cdot}$).

*1-Amino-3-[2-(4-phenoxy)quinolin-3-yl]-8-methylpyrido[1,2-a]benzimidazole-2,4-dicarbonitrile (**6m**)*

Yield 88 %; m.p. 233–235 °C; IR (KBr, cm^{-1}): 3,420 and 3,340 (asym. and sym. str. of $-NH_2$), 2,220 (–C≡N str.), 1,230 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.57 (s, 3H, CH_3, C-8), 7.18 (d, 2H, $J = 8.4$ Hz, H-20,24), 7.25 (m, 3H, H-21,22,23), 7.51 (d, 1H, $J = 8.0$ Hz, H-9), 7.64 (m, 2H, H-14,13), 7.75 (t, 1H, $J_1 = 7.2$, $J_2 = 8.0$, H-15), 7.82 (d, 1H, $J = 8.0$ Hz, H-10), 7.94 (s, 1H, H-7), 8.51 (d, 1H, $J = 8.4$ Hz, H-16), 8.62 (s, 1H, H-12), 8.75 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.78 (CH_3), 78.21 (C–CN), 87.94 (C–CN), 115.22, 115.83, 116.38, 119.54, 120.15, 122.09, 122.70, 125.22, 126.20, 127.11, 127.52, 128.90, 129.01, 130.52, 132.11, 134.90, 141.85, 145.13, 146.60, 147.42, 148.80, 151.14, 152.50, 158.50 (Ar–C); Anal. Calcd. for $C_{29}H_{18}N_6O$ (466.49 g/mol): C 74.67, H 3.89, N 18.02 % Found: C 74.45, H 4.06, N 17.84 %; MS (*m/z*): 466.5 ($M^{+\cdot}$).

*1-Amino-3-[2-(4-methylphenoxy)quinolin-3-yl]-8-methylpyrido[1,2-a]benzimidazole-2,4-dicarbonitrile (**6n**)*

Yield 84 %; m.p. 257–259 °C; IR (KBr, cm^{-1}): 3,455 and 3,320 (asym. and sym. str. of $-NH_2$), 2,215 (–C≡N str.), 1,180 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3, C-22), 2.58 (s, 3H, CH_3, C-8), 7.00 (d, 2H, $J = 8.4$ Hz, H-23,21), 7.19 (d, 1H, $J = 8.8$ Hz, H-20), 7.26 (d, 1H, $J = 8.8$ Hz, H-24), 7.41 (d, 1H, $J = 8.0$ Hz, H-9), 7.57 (m, 2H, H-14,13), 7.74 (t, 1H, $J_1 = 7.2$, $J_2 = 8.0$, H-15), 7.82 (d, 1H, $J = 8.0$ Hz, H-10), 7.91 (s, 1H, H-7), 8.53 (d, 1H, $J = 8.4$ Hz, H-16), 8.68 (s, 1H, H-12), 8.84 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.92 (CH_3), 21.81 (CH_3), 77.84 (C–CN), 87.80 (C–CN), 115.00, 115.88, 116.40, 119.43, 120.34, 122.30, 122.70, 125.19, 125.99, 127.11, 127.44, 128.80, 129.01, 130.40, 132.07, 134.90, 141.80, 144.98, 146.60, 147.32, 148.80, 151.16, 152.51, 157.92 (Ar–C); Anal. Calcd. for $C_{30}H_{20}N_6O$ (480.52 g/mol): C 74.99, H 4.20, N 17.49 % Found: C 75.12, H 3.94, N 17.29 %; MS (*m/z*): 480.8 ($M^{+\cdot}$).

*1-Amino-3-[2-(4-methoxyphenoxy)quinolin-3-yl]-8-methylpyrido[1,2-a]benzimidazole-2,4-dicarbonitrile (**6o**)*

Yield 81 %; m.p. 269–271 °C; IR (KBr, cm^{-1}): 3,400 and 3,330 (asym. and sym. str. of $-NH_2$), 2,200 (–C≡N str.), 1,245 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.56 (s, 3H, CH_3, C-8), 3.76 (s, 3H, OCH_3, C-22), 7.15 (d, 2H, $J = 8.4$ Hz, H-23,21), 7.23 (d, 1H, $J = 8.8$ Hz, H-20), 7.33 (d, 1H, $J = 8.8$ Hz, H-24), 7.45 (d, 1H, $J = 8.0$ Hz, H-9), 7.56 (m, 2H, H-14,13), 7.75 (t, 1H, $J_1 = 7.2$, $J_2 = 8.0$, H-15), 7.84 (d, 1H, $J = 8.0$ Hz, H-10), 7.95 (s, 1H, H-7), 8.61 (d, 1H, $J = 8.4$ Hz, H-16), 8.75 (s, 1H, H-12), 8.94 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.75 (CH_3), 55.90, (OCH_3), 78.12 (C–CN), 87.77 (C–CN), 115.43, 115.94, 116.42, 119.50, 120.23, 122.17, 122.70, 125.21, 126.16, 126.91, 127.42, 128.90, 129.02, 130.59, 132.03, 134.88, 141.84, 145.00, 146.60, 147.38, 148.81, 151.19, 152.66, 158.39 (Ar–C); Anal. Calcd. for $C_{30}H_{20}N_6O_2$ (496.52 g/mol): C 72.57, H 4.06, N 16.93 % Found: C 72.61, H 4.19, N 17.13 %; MS (*m/z*): 496.7 ($M^{+\cdot}$).

*1-Amino-3-[2-(4-fluorophenoxy)quinolin-3-yl]-8-methylpyrido[1,2-a]benzimidazole-2,4-dicarbonitrile (**6p**)*

Yield 80 %; m.p. 237–239 °C; IR (KBr, cm^{-1}): 3,445 and 3,310 (asym. and sym. str. of $-NH_2$), 2,185 (–C≡N str.), 1,200 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.57 (s, 3H, CH_3, C-8), 7.09 (d, 2H, $J = 8.4$ Hz, H-23,21), 7.25 (d, 1H, $J = 8.8$ Hz, H-20), 7.38 (d, 1H, $J = 8.8$ Hz, H-24), 7.47 (d, 1H, $J = 8.0$ Hz, H-9), 7.55 (m, 2H, H-14,13), 7.76 (t, 1H, $J_1 = 7.2$, $J_2 = 8.0$, H-15), 7.87 (d, 1H, $J = 8.0$ Hz,

H-10), 7.96 (s, 1H, H-7), 8.51 (d, 1H, $J = 8.4$ Hz, H-16), 8.66 (s, 1H, H-12), 8.81 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.84 ($\underline{C}H_3$), 78.10 ($\underline{C}$–CN), 87.95 ($\underline{C}$–CN), 115.03, 116.00, 116.33, 119.50, 120.01, 122.22, 122.80, 125.21, 126.20, 127.11, 127.45, 128.90, 129.00, 130.50, 132.06, 134.88, 141.79, 145.04, 146.43, 147.39, 148.80, 151.16, 152.90, 158.48 (Ar–$\underline{C}$); Anal. Calcd. for $C_{29}H_{17}FN_6O$ (484.48 g/mol): C 71.89, H 3.54, N 17.35 % Found: C 71.75, H 4.71, N 17.42 %; MS (*m/z*): 484.4 ($M^{+\cdot}$).

1-Amino-3-[2-(4-phenoxy)-6-methylquinolin-3-yl]-8-methylpyrido[1,2-a]benzimidazole-2,4-dicarbonitrile ***(6q)***

Yield 87 %; m.p. 246–248 °C; IR (KBr, cm^{-1}): 3,410 and 3,325 (asym. and sym. str. of –NH_2), 2,195 (–C≡N str.), 1,235 (C–O–C ether str.); ^1H NMR (400 MHz, DMSO-d_6): δ 2.53 (s, 3H, CH_3, C-8), 2.56 (s, 3H, CH_3, C-14), 7.16 (d, 2H, $J = 8.4$ Hz, H-20,24), 7.28 (m, 3H, H-21,22,23), 7.46 (d, 1H, $J = 8.0$ Hz, H-9), 7.63 (s, 1H, H-13), 7.73 (d, 1H, $J = 8.4$ Hz, H-15), 7.79 (d, 1H, $J = 8.0$ Hz, H-10), 7.89 (s, 1H, H-7), 8.51 (d, 1H, $J = 8.0$ Hz, H-16), 8.68 (s, 1H, H-12), 8.87 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.32 ($\underline{C}H_3$), 21.78 ($\underline{C}H_3$), 55.87 (O$\underline{C}H_3$), 78.13 ($\underline{C}$–CN), 87.84 ($\underline{C}$–CN), 115.50, 115.95, 118.89, 120.04, 123.30, 124.10, 125.09, 127.00, 127.24, 127.70, 128.50, 132.65, 134.06, 135.44, 141.33, 145.01, 145.63, 146.70, 147.08, 148.70, 152.66, 154.52, 157.35, 158.09, (Ar–$\underline{C}$); Anal. Calcd. for $C_{30}H_{20}N_6O$ (480.52 g/mol): C 74.99, H 4.20, N 17.49 % Found: C 74.83, H 4.33, N 17.52 %; MS (*m/z*): 480.5 ($M^{+\cdot}$).

1-Amino-3-[2-(4-methylphenoxy)-6-methylquinolin-3-yl]-8-methylpyrido[1,2-a]benzimidazole-2,4-dicarbonitrile ***(6r)***

Yield 83 %; m.p. 244–245 °C; IR (KBr, cm^{-1}): 3,480 and 3,310 (asym. and sym. str. of –NH_2), 2,190 (–C≡N str.), 1,210 (C–O–C ether str.); ^1H NMR (400 MHz, DMSO-d_6): δ ^1H NMR (400 MHz, DMSO-d_6): δ 2.33 (s, 3H, CH_3, C-22), 2.52 (s, 3H, CH_3, C-8), 2.59 (s, 3H, CH_3, C-14), 7.08 (d, 2H, $J = 8.4$ Hz, H-23,21), 7.26 (d, 1H, $J = 8.8$ Hz, H-20), 7.34 (d, 1H, $J = 8.8$ Hz, H-24), 7.49 (d, 1H, $J = 8.0$ Hz, H-9), 7.65 (s, 1H, H-13), 7.70 (d, 1H, $J = 8.4$ Hz, H-15), 7.78 (d, 1H, $J = 8.0$ Hz, H-10), 7.87 (s, 1H, H-7), 8.54 (d, 1H, $J = 8.0$ Hz, H-16), 8.68 (s, 1H, H-12), 8.83 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.94 ($\underline{C}H_3$), 21.31 ($\underline{C}H_3$), 21.85 ($\underline{C}H_3$), 78.25 ($\underline{C}$–CN), 87.89 ($\underline{C}$–CN), 115.37, 116.02, 118.99, 120.08, 123.30, 124.20, 125.17, 126.90, 127.21, 127.80, 128.60, 132.70, 133.95, 135.60, 141.13, 144.77, 145.51, 146.80, 147.03, 148.65, 152.20, 154.50, 156.90, 157.96, (Ar–$\underline{C}$); Anal. Calcd. for $C_{31}H_{22}N_6O$ (494.55 g/mol): C 75.29, H 4.48, N 16.99 % Found: C 75.38, H 4.30, N 17.17 %; MS (*m/z*): 494.6 ($M^{+\cdot}$).

1-Amino-3-[2-(4-methoxyphenoxy)-6-methylquinolin-3-yl]-8-methylpyrido[1,2-a]benzimidazole-2,4-dicarbonitrile ***(6s)***

Yield 78 %; m.p. 251–253 °C; IR (KBr, cm^{-1}): 3,470 and 3,320 (asym. and sym. str. of –NH_2), 2,220 (–C≡N str.), 1,245 (C–O–C ether str.); ^1H NMR (400 MHz, DMSO-d_6): δ 2.53 (s, 3H, CH_3, C-8), 2.56 (s, 3H, CH_3, C-14), 3.78 (s, 3H, OCH_3, C-22), 7.01 (d, 2H, $J = 8.4$ Hz, H-23,21), 7.21 (d, 1H, $J = 8.8$ Hz, H-20), 7.27 (d, 1H, $J = 8.8$ Hz, H-24), 7.43 (d, 1H, $J = 8.0$ Hz, H-9), 7.61 (s, 1H, H-13), 7.70 (d, 1H, $J = 8.4$ Hz, H-15), 7.77 (d, 1H, $J = 8.0$ Hz, H-10), 7.86 (s, 1H, H-7), 8.49 (d, 1H, $J = 8.0$ Hz, H-16), 8.58 (s, 1H, H-12), 8.77 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.31 ($\underline{C}H_3$), 21.78 ($\underline{C}H_3$), 55.87 (O$\underline{C}H_3$), 77.68 ($\underline{C}$–CN), 87.79 ($\underline{C}$–CN), 115.04, 116.01, 119.09, 120.01, 123.33, 124.15, 125.13, 126.95, 127.13, 127.72, 128.53, 132.66, 133.96, 135.59, 141.10, 144.91, 145.50, 146.75, 147.00, 148.69, 152.21, 154.48, 156.95, 157.95, (Ar–C); Anal. Calcd. for $C_{31}H_{22}N_6O_2$ (510.55 g/mol): C 72.93, H 4.34, N 16.46 % Found: C 73.04, H 4.32, N 16.51 %; MS (*m/z*): 510.2 (M^{+}).

1-Amino-3-[2-(4-fluorophenoxy)-6-methylquinolin-3-yl]-8-methylpyrido[1,2-a]benzimidazole-2,4-dicarbonitrile ***(6t)***

Yield 75 %; m.p. 275–277 °C; IR (KBr, cm^{-1}): 3,465 and 3,345 (asym. and sym. str. of –NH_2), 2,225 (–C≡N str.), 1,230 (C–O–C ether str.); ^1H NMR (400 MHz, DMSO-d_6): δ ^1H NMR (400 MHz, DMSO-d_6): δ 2.50 (s, 3H, CH_3, C-8), 2.58 (s, 3H, CH_3, C-14), 6.99 (d, 2H, $J = 8.4$ Hz, H-23,21), 7.18 (d, 1H, $J = 8.8$ Hz, H-20), 7.25 (d, 1H, $J = 8.8$ Hz, H-24), 7.40 (d, 1H, $J = 8.0$ Hz, H-9), 7.57 (s, 1H, H-13), 7.69 (d, 1H, $J = 8.4$ Hz, H-15), 7.75 (d, 1H, $J = 8.0$ Hz, H-10), 7.85 (s, 1H, H-7), 8.47 (d, 1H, $J = 8.0$ Hz, H-16), 8.65 (s, 1H, H-12), 8.79 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.33 ($\underline{C}H_3$), 21.80 ($\underline{C}H_3$), 77.64 ($\underline{C}$–CN), 87.89 ($\underline{C}$–CN), 115.08, 116.04, 119.06, 120.02, 123.23, 124.12, 124.93, 127.05, 127.09, 127.92, 128.83, 132.46, 134.07, 135.79, 141.17, 144.81, 145.56, 146.77, 147.07, 148.59, 152.29, 154.38, 157.11, 158.60, (Ar–$\underline{C}$); Anal. Calcd. for $C_{30}H_{19}FN_6O$ (498.51 g/mol): C 72.28, H 3.84, N 16.86 % Found: C 72.44, H 3.72, N 17.01 %; MS (*m/z*): 498.1 ($M^{+\cdot}$).

1-Amino-3-[2-(4-phenoxy)-6-methoxyquinolin-3-yl]-8-methylpyrido[1,2-a]benzimidazole-2,4-dicarbonitrile ***(6u)***

Yield 86 %; m.p. 275–276 °C, IR (KBr, cm^{-1}): 3,410 and 3,340 (asym. and sym. str. of –NH_2), 2,210 (–C≡N str.),

1,185 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.56 (s, 3H, CH_3, C-8), 3.90 (s, 3H, OCH_3, C-14), 7.12 (d, 2H, J = 8.4 Hz, H-20,24), 7.21 (m, 3H, H-21,22,23), 7.40 (d, 1H, J = 8.0 Hz, H-9), 7.58 (s, 1H, H-13), 7.68 (d, 1H, J = 8.4 Hz, H-15), 7.75 (d, 1H, J = 8.0 Hz, H-10), 7.84 (s, 1H, H-7), 8.53 (d, 1H, J = 8.0 Hz, H-16), 8.67 (s, 1H, H-12), 8.82 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.80 ($\underline{C}H_3$), 56.10 ($O\underline{C}H_3$), 77.73 ($\underline{C}$–CN), 87.80 ($\underline{C}$–CN), 115.07, 116.05, 119.19, 120.21, 123.53, 124.25, 125.17, 127.05, 127.34, 127.82, 128.63, 132.72, 134.11, 135.75, 141.33, 144.97, 145.60, 146.75, 147.09, 148.59, 152.11, 154.58, 156.87, 157.18, (Ar–$\underline{C}$); Anal. Calcd. for $C_{30}H_{20}N_6O_2$ (496.52 g/mol): C 72.57, H 4.06, N 16.93 % Found: C 72.51, H 4.26, N 16.84 %; MS (*m/z*): 496.3 ($M^{+\cdot}$).

1-Amino-3-[2-(4-methylphenoxy)-6-methoxyquinolin-3-yl]-8-methylpyrido[1,2-a]benzimidazole-2,4-dicarbonitrile ***(6v)***

Yield 82 %; m.p. 250–252 °C; IR (KBr, cm^{-1}): 3,440 and 3,325 (asym. and sym. str. of –NH_2), 2,200 (–C≡N str.), 1,200 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3, C-22), 2.56 (s, 3H, CH_3, C-8), 3.92 (s, 3H, OCH_3, C-14), 7.11 (d, 2H, J = 8.4 Hz, H-23,21), 7.28 (d, 1H, J = 8.8 Hz, H-20), 7.32 (d, 1H, J = 8.8 Hz, H-24), 7.48 (d, 1H, J = 8.0 Hz, H-9), 7.62 (s, 1H, H-13), 7.72 (d, 1H, J = 8.4 Hz, H-15), 7.79 (d, 1H, J = 8.0 Hz, H-10), 7.88 (s, 1H, H-7), 8.54 (d, 1H, J = 8.0 Hz, H-16), 8.73 (s, 1H, H-12), 8.92 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.91 ($\underline{C}H_3$), 21.85 ($\underline{C}H_3$), 56.16 ($O\underline{C}H_3$), 78.15 ($\underline{C}$–CN), 87.84 ($\underline{C}$–CN), 115.49, 116.03, 118.99, 120.18, 123.16, 124.20, 125.16, 126.90, 127.05, 127.68, 128.50, 132.70, 133.94, 135.60, 141.11, 144.77, 145.54, 146.80, 147.01, 148.70, 152.20, 154.50, 156.90, 158.24, (Ar–C); Anal. Calcd. for $C_{31}H_{22}N_6O_2$ (510.55 g/mol): C 72.93, H 4.34, N 16.46 % Found: C 73.08, H 4.29, N 16.54 %; MS (*m/z*): 510.2 ($M^{+\cdot}$).

1-Amino-3-[2-(4-methoxyphenoxy)-6-methoxyquinolin-3-yl]-8-methylpyrido[1,2-a]benzimidazole-2,4-dicarbonitrile ***(6w)***

Yield 80 %; m.p. 279–280 °C; IR (KBr, cm^{-1}): 3,405 and 3,320 (asym. and sym. str. of –NH_2), 2,200 (–C≡N str.), 1,235 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.57 (s, 3H, CH_3, C-8), 3.78 (s, 3H, OCH_3, C-22), 3.83 (s, 3H, OCH_3, C-14), 7.01 (d, 2H, J = 8.4 Hz, H-23,21), 7.22 (d, 1H, J = 8.8 Hz, H-20), 7.28 (d, 1H, J = 8.8 Hz, H-24), 7.42 (d, 1H, J = 8.0 Hz, H-9), 7.60 (s, 1H, H-13), 7.69 (d, 1H, J = 8.4 Hz, H-15), 7.78 (d, 1H, J = 8.0 Hz, H-10), 7.92 (s, 1H, H-7), 8.64 (d, 1H, J = 8.0 Hz, H-16), 8.71 (s, 1H, H-12), 8.85 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.83 ($\underline{C}H_3$), 55.89 ($O\underline{C}H_3$), 55.98 ($O\underline{C}H_3$), 78.00 ($\underline{C}$–CN), 87.92 ($\underline{C}$–CN), 115.08, 115.90, 119.16, 120.05, 123.24, 124.17, 125.18, 127.12, 127.22, 127.68, 128.86, 132.73, 133.78, 135.60, 141.17, 144.99, 145.54, 146.70, 147.06, 148.70, 152.20, 154.50, 157.24, 158.55, (Ar–$\underline{C}$); Anal. Calcd. for $C_{31}H_{22}N_6O_3$ (526.54 g/mol): C 70.71, H 4.21, N 15.96 % Found: C 70.55, H 4.33, N 16.03 %; MS (*m/z*): 526.6 ($M^{+\cdot}$).

1-Amino-3-[2-(4-fluorophenoxy)-6-methoxyquinolin-3-yl]-8-methylpyrido[1,2-a]benzimidazole-2,4-dicarbonitrile ***(6x)***

Yield 77 %; m.p. 255–256 °C; IR (KBr, cm^{-1}): 3,460 and 3,330 (asym. and sym. str. of –NH_2), 2,210 (–C≡N str.), 1,240 (C–O–C ether str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55 (s, 3H, CH_3, C-8), 3.82 (s, 3H, OCH_3, C-14), 7.04 (d, 2H, J = 8.4 Hz, H-23,21), 7.23 (d, 1H, J = 8.8 Hz, H-20), 7.29 (d, 1H, J = 8.8 Hz, H-24), 7.42 (d, 1H, J = 8.0 Hz, H-9), 7.60 (s, 1H, H-13), 7.71 (d, 1H, J = 8.4 Hz, H-15), 7.79 (d, 1H, J = 8.0 Hz, H-10), 7.87 (s, 1H, H-7), 8.51 (d, 1H, J = 8.0 Hz, H-16), 8.65 (s, 1H, H-12), 8.95 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.77 ($\underline{C}H_3$), 56.05 ($O\underline{C}H_3$), 78.15 ($\underline{C}$–CN), 87.83 ($\underline{C}$–CN), 115.23, 116.09, 119.11, 119.98, 123.24, 124.26, 125.32, 126.98, 127.34, 127.68, 128.60, 132.59, 133.90, 135.61, 141.23, 144.77, 144.99, 146.81, 147.05, 148.72, 152.20, 155.97, 157.44, 158.04, (Ar–$\underline{C}$); Anal. Calcd. for $C_{30}H_{19}FN_6O_2$ (514.51 g/mol): C 70.03, H 3.72, N 16.33 % Found: C 69.95, H 3.63, N 16.50 %; MS (*m/z*): 514.3 ($M^{+\cdot}$).

Conclusion

A series of some new pyrido[1,2-*a*]benzimidazole derivatives **6a–x** containing *β*-aryloxyquinoline moiety has been synthesized via microwave-assisted one-pot multicomponent reaction in the presence of non-hazardous base (NaOH). This synthetic strategy allows the construction of relatively complicated pyridine frameworks equipped with a benzimidazole unit and introduction of substituted *β*-aryloxyquinolines at the fourth positions of pyridine with fascinating yield in short time. From the appraisal of the antimicrobial activity data, it can be concluded that compounds **6a**, **6e**, **6n**, **6p**, and **6u** having excellent antibacterial property, while compounds **6o** and **6p** showed better antifungal property. Evaluation of antitubercular activity shows that compounds **6t** and **6x** found to have better antitubercular activity and compound **6p** is appeared as the promising antimicrobial member with significant antitubercular activity. From the SAR study, it is commendable to mention that the antimicrobial and antitubercular activities of the title compounds depends not only on the

bicyclic heteroaromatic pharmacophore appended through ether linked aryl ring but also on the nature of the peripheral substituents and may also upon their spatial relationship and positional changes. This study highlights the identification of new molecules as good antimicrobial and antitubercular agents which can be of interest for further detailed pre-clinical investigations.

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References

Algul O, Meric A, Polat S, Yuksek ND, Serin MS (2009) Comparative studies on conventional and microwave-assisted synthesis of a series of 2,4-di and 2,3,4-trisubstituted benzimidazo[1,2-*a*]pyrimidines and their antimicrobial activities. Cent Eur J Chem 7:337–342

Badawey ESAM, Kappe C (1995a) Benzimidazole condensed ring system. IX. Potential antineoplastics. New synthesis of some pyrido[1,2-*a*]benzimidazoles and related derivatives. Eur J Med Chem 30:327–332

Badawey ESAM, Kappe C (1995b) Synthesis of some new imidazo-[1,2-*a*]pyrimidine-5(1*H*)-ones as potential antineoplastic agents. J Heterocycl Chem 32:1003–1006

Badawey ESAM, Kappe T (1999) Benzimidazole condensed ring systems. XI. Synthesis of some substituted cycloalkyl pyrido[1,2-*a*]benzimidazoles with anticipated antineoplastic activity. Eur J Med Chem 34:663–667

Bava S, Kumar S (2009) Synthesis of schiff's bases of 8-methyltetrazolo[1,5-*a*]quinoline as potential anti-inflammatory and antimicrobial agents. Indian J Chem 48B:142–145

Bogdanowicz-Szwed K, Czarny A (1993) Synthesis of polyazaheterocycles by Michael addition of CH acids to α, β-unsaturated nitriles. Synthesis of pyrido[1,2-a]benzimidazole and pyrimido[5′,4′:5,6]pyrido[1,2-a]benzimidazole derivatives. J Prakt Chem 335:279–282

Charris JE, Dominguez JN, Gamboa N, Rodrigues JR, Angel JE (2005) Synthesis and antimalarial activity of E-2-quinolinylbenzocycloalcanones. Eur J Med Chem 40:875–881

Dave SS, Ghatole AM, Rahatgaonkar AM, Chorghade MS, Chuhan PMS, Srivastava K (2009) Experimental and computational evaluation of new quinolyl chalcones as potent antiplasmodium agents. Indian J Chem 48B:1780–1793

Dawood KM, Elwan NM, Farahat AA, Abdel-Wahab BF (2010) 1*H*-Benzimidazole-2-acetonitriles as synthon in fused benzimidazole synthesis. J Heterocyclic Chem 47:243–267

Diekema DJ, Bootsmiller BJ, Vaughn TE, Woolson RF, Yankey JW, Ernst EJ (2004) Antimicrobial resistance trends and outbreak frequency in united states hospitals. Clin Infect Dis 38:78–85

El-Hawash SAM, Badawey ESAM, Kappe T (1999) Benzimidazole condensed ring systems. XII. Synthesis and anticancer evaluation of certain pyrido[1,2-*a*]benzimidazole derivatives. Pharmazie 54:341–346

Furniss BS, Hannaford AJ, Smith PWG, Tatchell AR (2004) Vogel's Textbook of Practical Organic Chemistry, 5th edn. Longman, Harlow

Jardosh HH, Patel MP (2011) Lanthanum triflate triggered synthesis of tetrahydroquinazolinone derivatives of *N*-allyl quinolone and their biological assessment. J Serb Chem Soc. doi: 10.2298/JSC120121039J

Jardosh HH, Patel MP (2012) Microwave-assisted CAN-catalyzed solvent-free synthesis of *N*-allyl quinolone-based pyrano[4,3-*b*]chromene and benzopyrano[3,2-*c*]chromene derivatives and their antimicrobial activity. Med Chem Res doi:10.1007/s00044-012-0085-z

Dawood KM, Elwan NM, Abdel-Wahab BF (2011) Recent advances on the synthesis of azoles, azines and azepines fused to benzimidazole. Arkivoc i:111–195

Kalluraya B, Nayak J, Adhikari A, Sujith KV, Sucheta N, Shetty MW (2008) Synthesis and characterization of some novel quinolinothiazines of biological interest. Phosphorus, Sulfur Silicon Relat Elem 183:1870–1883

Kathrotiya HG, Patel NA, Patel RG, Patel MP (2012) An efficient synthesis of 3′-quinolinyl substituted imidazole-5-one derivatives catalyzed by zeolite and their antimicrobial activity. Chin Chem Lett 23:273–276

Kotovskaya SK, Baskakova ZM, Charushin VN, Chupakhin ON, Belanov EF, Bormotov NI, Balakhnin SM, Serova OA (2005) Synthesis and antiviral activity of fluorinated pyrido[1,2-*a*]benzimidazoles. Pharm Chem J 39:12–16

Makawana JA, Patel MP, Patel RG (2012) Synthesis and in vitro antimicrobial evaluation of penta-substituted pyridine derivatives bearing the quinoline nucleus. Med Chem Res 21:616–623

Meth-Cohn O, Bramha NA (1978) A versatile new synthesis of quinolines, thienopyridine and related fused pyridines. Tetrahedron Lett 23:2045–2048

Mital A, Negi V, Ramachandran U (2006) Synthesis and antimycobacterial activities of certain trifluoromethyl-aminoquinoline derivatives. Arkivoc X:220–227

Mungra DC, Patel MP, Rajani DP, Patel RG (2011) Synthesis and identification of *β*-aryloxyquinolines and their pyrano[3,2-*c*]chromene derivatives as a new class of antimicrobial and antituberculosis agents. Eur J Med Chem 46:4192–4200

National Committee for Clinical Laboratory Standards (NCCLS) (2002) Performance standards for antimicrobial susceptibility testing: twelfth informational supplement. ISBN 1-56238-454-6, M100-S12 (M7)

Ndakala AJ, Gessner RK, Gitari PW, October N, White KL, Hudson A, Fakorede F, Shackleford DM, Kaiser M, Yeates C, Charman SA, Chibale K (2011) Antimalarial pyrido[1,2-*a*]benzimidazoles. J Med Chem 54:4581–4589

Panda K, Suresh JR, Ila H, Junjappa H (2003) Heteroaromatic annulation of 2-methyl/2-cyanomethylbenzimidazole dianions with-oxoketene dithioacetals: a highly regioselective synthetic protocol for 1,2-and 2,3-substituted/annulated pyrido[1,2-*a*]benzimidazoles. J Org Chem 68:3498–3506

Pieroni M, Tipparaju SK, Lun S, Song Y, Sturm AW, Bishai WR, Kozikowski AP (2011) Pyrido[1,2-*a*]benzimidazole-Based agents active against tuberculosis (TB), multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB. Chem Med Chem 6:334–342

Prostakov NS, Varlamov AV, Shendrik IV, Anisimov BN, Krapivko AP, Lavani-Edogiaverie S, Fomichev AA (1983) New method for the synthesis of pyrido[1,2-*a*]benzimidazole. Chem Heterocycl Compd 19:1102–1104

Rana PB, Mistry BD, Desai KR (2008) Green chemistry: conventional and microwave induced synthesis of various thiazolidinone derivatives from 3-{[(1E)-(2′-chloro-7′-methoxyquinoline-3′-yl)methylene]

amino}-4 (substitutedphenyldiazenyl)phenol and their antimicrobial screening. Arkivoc xv:262-279

Rattan A (2000) Antimicrobials in Laboratory Medicine. Churchill B I. Livingstone, New Delhi, p 85

Rida SM, Soliman FSG, Badawey ESAM, El-Ghazzawi E, Kader O, Kappe T (1988) Benzimidazole condensed ring systems. 1. Syntheses and biological investigations of some substituted pyrido[1,2-*a*]benzimidazoles. J Heterocycl Chem 25: 1087–1093

Rida SM, EI-Hawash SAM, Fahmy HTY, Hazzaa AA, EI-Meligy MMM (2006) Synthesis of novel benzofuran and related benzimidazole derivatives for evaluation of in vitro anti-HIV-1, anticancer and antimicrobial activities. Arch Pharm Res 29:826–833

Russell RK, Van Nievelt CE (1995) The synthesis of cycloalkylpyrido[1,2-*a*]benzimidazole carbonitrile analogs. J Heterocyclic Chem 32:299–306

Russell DG, Barry CE, Flynn JL (2010) Tuberculosis: what we don't know can, and does, hurt us. Science 328:852–856

Shah NM, Patel MP, Patel RG (2012) New *N*-arylamino biquinoline derivatives: Synthesis, antimicrobial, antituberculosis and antimalarial evaluation. Eur J Med Chem, doi:10.1016/j.ejmech.2012.05.004

Shi A, Nguyen TA, Battina SK, Rana S, Takemoto DJ, Chiang PK, Hua DH (2008) Synthesis and anti-breast cancer activities of substituted quinolines. Bioorg Med Chem Lett 18:3364–3368

Sundberg RJ, Ellis JE (1982) Synthesis of pyrido[1,2-*a*]benzimidazoles by cyclizative condensation of 2-halopyridines and 1,2-benzenediamines. Scope and mechanism of the reaction. J Heterocyclic Chem 19:585–588

Takemura M, Takashi H, Kawakami K, Takeshita H, Kimura Y, Watanabe J, Sugimoto Y, Kitamura A, Nakajima R, Kanai K, Fujisawa T. (2004) Imidazo[1,2-*a*]pyridine derivative. Eur. Pat. Appl.1479681

Upadhaya RS, Kulkarni GM, Vasireddy NR, Vandavasi JK, Dixit SS, Sharma V, Chattopadhyaya J (2009) Design, synthesis and biological evaluation of novel triazole, urea and thiourea derivatives of quinoline against *Mycobacterium tuberculosis*. Bioorg Med Chem 17:4681–4692

World Health Organization. (2008) Global TB control: surveillance, planning, financing: WHO report. Geneva, Switzerland: WHO Press

World Health Organization. (2010) Global tuberculosis control: WHO report 2010; WHO Press: Geneva, Switzerland

Wu Z, Huang Q, Zhou X, Yu L, Li Z, Wu D (2011) Synthesis of Pyrido[1,2-a]benzimidazoles through a copper-catalyzed cascade C-N coupling process. Eur J Org Chem 2011:5242–5245

Yan CG, Wang QF, Song XK, Sun J (2009) One-step synthesis of pyrido[1,2-*a*]benzimidazole derivatives by a novel multicomponent reaction of chloroacetonitrile, malononitrile, aromatic aldehyde, and pyridine. J Org Chem 74:710–718