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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Microwave-assisted synthesis of some new tetrazolo [1,5-*a*]quinoline-based benzimidazoles catalyzed by *p*-TsOH and investigation of their antimicrobial activity

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Abstract Keeping the objective to build up a new structural class of potent antimicrobials, a series of some new 4-Benzimidazol-2-yl tetrazolo[1,5-*a*]quinoline derivatives has been synthesized by reaction of tetrazolo[1,5-*a*]quinoline-4-carbaldehyde and *o*-phenylenediamine in the presence of an organocatalyst *p*-TsOH under the influence of microwave irradiation. The identity of all the compounds has been established by ^{1}H NMR, ^{13}C NMR, FTIR, and elemental analysis. The synthesized compounds were subjected to in vitro antimicrobial screening against a representative panel of pathogenic strains including three Gram-positive bacteria (*Bacillus subtilis*, *Clostridium tetani*, and *Streptococcus pneumoniae*) and three Gram-negative bacteria (*Escherichia coli*, *Salmonella typhi*, and *Vibrio cholerae*) as well as two fungal organisms (*Aspergillus fumigatus* and *Candida albicans*) by employing broth microdilution method. Of the compounds studied, compound **5e** demonstrated significant activity against a Gram-positive bacteria *Bacillus subtilis*.

Keywords Benzimidazole · Tetrazolo[1,5-*a*]quinoline · *p*-TsOH · Microwave irradiation · In vitro antimicrobial screening

Introduction

Benzimidazole incorporating structures are of immense importance pharmacologically due to their significant bioactivities like anti-HIV (Burkholder *et al*., 2001), anticancer (El-Naem *et al*., 2003), local anesthetic (Anisimova *et al*., 2002), antituberculosis (Foks *et al*., 2006), antifungal (Enguehard *et al*., 2000), anti-bacterial (Ramanatham *et al*., 2008), etc. Moreover, the SAR study interestingly evokes that the minor change in the structure of substituent group flanked between two nitrogen atoms of benzimidazole commonly results in the change of its bioactivity (Ge *et al*., 2007; Kazimierczuk *et al*., 2005). Literature survey manifests that the number of benzimidazole derivatives have been synthesized using various aldehydes and *o*-phenylenediamines but there is not a single report where tetrazolo[1,5-*a*]quinoline-4-carbaldehyde is used. As this heterocyclic aldehyde is conjugated with diverse biological activities (Bekhit *et al*., 2004), our research focus is concentrated at an efficient synthesis of new heterocyclic system incorporating above moieties together with an objective to gain more potent heterocycles.

There are two general methods for the synthesis of 2-substituted benzimidazoles. One is the coupling of *o*-phenylenediamines and carboxylic acids (Das and Thakuria, 2008) or their derivatives like imidates (Zarguil *et al*., 2008), orthoesters (Mohammadpoor-Baltork *et al*., 2008), and nitriles (Moskvichev *et al*., 2001), which often requires strong acidic conditions. Second method involves a two-step process that includes the oxidative cyclo-dehydrogenation of Schiff bases, which are often generated from the condensation of *o*-phenylenediamines and aldehydes. Various catalysts such as $FeCl_3{\cdot}6H_2O$ (Shen and Driver, 2008), I_2 (Gogoi and Konwar, 2006), Air (Lin and Yang, 2005), $KHSO_4$ (Ma *et al*., 2006), and $Sc(OTf)_3$ (Itoh *et al*., 2004; Nagata *et al*., 2003) have been employed. Some of these methods suffer from one or more disadvantages such as high reaction temperature, prolonged reaction time, and tedious work-up process. Consequently, the discovery of mild and practicable routes for synthesis of 2-substituted benzimidazoles keeps

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on attracting much attention of researchers. *p*-TsOH has received considerable attention as an inexpensive and easily available catalyst of various organic reactions (Xiangming *et al*., 2007).

The conventional procedures are not found to be satisfactory with regard to operational simplicity, effectiveness, and yield. An alternative synthetic approach is microwave irradiation (Jing *et al*., 2006; Rao *et al*., 2004). In recent years, microwave irradiation has been demonstrated not only to dramatically accelerate many organic reactions, but also to improve yields and selectivity. Thus, the drive continues in search of an improved methodology and cleaner chemistry. Encouraged by their potential clinical applications and in continuation of our previous investigations on biologically active heterocycles including tetrazolo[1,5-*a*]quinoline (Ladani *et al*., 2009a, b, 2010; Mungra *et al*., 2009; Nirmal *et al*., 2009; Shah *et al*., 2009; Thakor *et al*., 2008; Thumar and Patel, 2009a, b), we report herein a microwave-assisted synthesis of 4-Benzimidazol-2-yl tetrazolo[1,5-*a*]quinoline catalyzed by an organocatalyst *p*-TsOH as a part of our search to design more biologically potent heterocyclic systems via combination of two therapeutically active moieties tetrazolo[1,5-*a*]quinoline and benzimidazole.

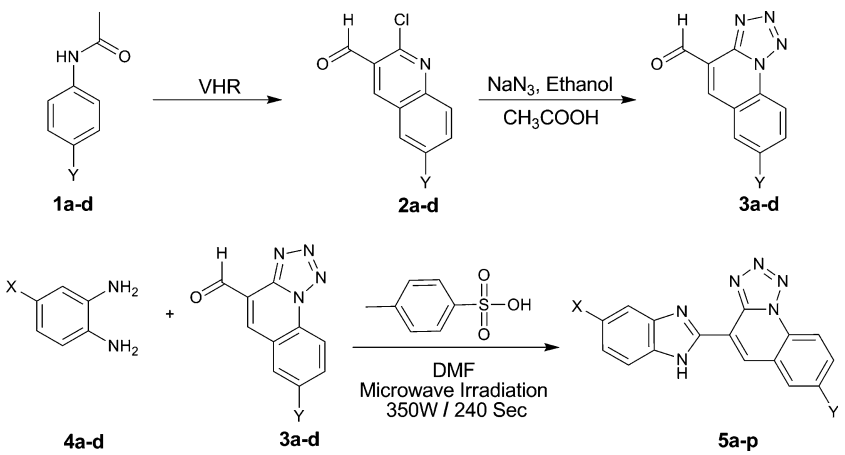
Results and discussion

Chemistry

The key intermediate, tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **3a–d**, was prepared by refluxing 2-chloro-3-formyl quinoline **2a–d**, sodium azide, and acetic acid in ethanol for 3–4 h (Ladani *et al*., 2009a, b). The required 2-chloro-3-formyl quinoline **2a–d** was prepared by Vilsmeier–Haack reaction of acetanilide **1a–d** according to literature procedure (Meth-Cohn and Bramha, 1978).

In the present study, all the 4-Benzimidazol-2-yl tetrazolo[1,5-*a*]quinoline **5a–p** (Scheme 1; Table 1) were obtained in good yields by the *p*-toluenesulphonic acid catalyzed condensation reaction of various tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **3a–d** with *o*-phenylenediamine **4a–d** in DMF under microwave irradiation as depicted in Scheme 1. The formation of compounds **5a–p** may proceed via intramolecular oxidative cyclo-dehydrogenation of Schiff bases (Scheme 2) formed from the condensation of *o*-phenylenediamine **4a–d** and tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **3a–d**. DMF was used as an energy transfer media, and the reaction mixture was irradiated in a microwave oven for 4 min. The reaction conditions were optimized. The course of reaction was followed by TLC, and maximum yield was obtained at (350 W) 50% microwave power level.

The identity of the product determined by ^{1}H NMR, ^{13}C NMR, FT-IR spectral data, and molecular weight of some selected compounds were confirmed by mass spectrometry. ^{1}H NMR (DMSO-d_6) spectrum of **5a**, molecule of interest, exhibited singlet peak at δ 11.79 ppm appeared for –NH– proton of benzimidazole ring. Aromatic protons as multiplets appeared at around δ 7.28–9.16 ppm. Moreover, it exhibited the absence of the aldehyde proton. The ^{13}C NMR spectrum is in consonance with the structure assigned. In the ^{13}C NMR spectra, signals around δ 115.48–145.86 ppm are attributed to aromatic carbons of compounds **5a**. The IR spectrum of compound **5a** exhibited characteristic absorption band at 3420 and 3015 cm^{-1} for cyclic –NH– of benzimidazole nucleus and aromatic C–H stretching, respectively. The mass spectra of compounds **5a** and **5j**, molecules of interest, detected the expected molecular ion signals corresponding to respective molecular formula, i.e., mass spectra of compound **5a** (X = H, Y = H) and **5j** (X = CH_3, Y = OCH_3) gave molecular ion peak at *m/z* 287 (M + 1) and *m/z* 331 (M + 1) corresponding to molecular formula $C_{16}H_{10}N_6$ and $C_{18}H_{14}N_6O$, respectively (Scheme 1). The obtained elemental analysis values are in good agreement



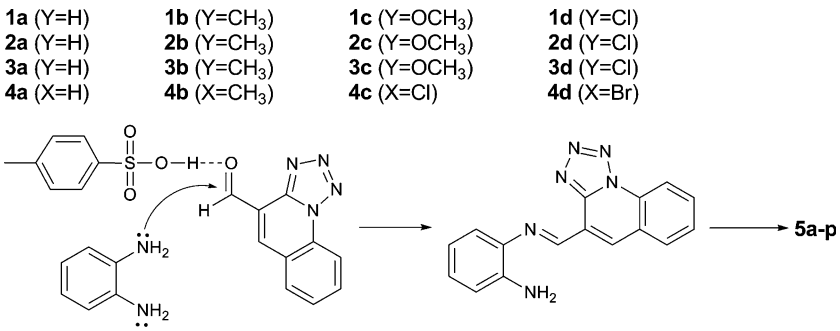
Scheme 1 Representative route for the synthesis of 4-benzimidazol-2-yltetrazolo[1,5-a]quinoline **5a–p**; *VHR* Vilsmeier–Haack reaction

Table 1 Antibacterial and antifungal activity of compounds **5a–p**

Minimum inhibitory concentration (MIC) expressed in μg/ml

Compound	Gram-positive bacteria			Gram-negative bacteria			Fungal species	
	B.S. MTCC 441	C.T. MTCC 449	S.P. MTCC 1936	E.C. MTCC 443	S.T. MTCC 98	V.C. MTCC 3906	A.F. MTCC 3008	C.A. MTCC 227
5a (X = H, Y = H)	200	250	500	500	500	200	>1000	1000
5b (X = CH_3, Y = H)	250	500	500	125	250	500	1000	500
5c (X = Cl, Y = H)	500	500	500	250	100	500	1000	500
5d (X = Br, Y = H)	500	250	250	100	100	250	1000	1000
5e (X = H, Y = CH_3)	100	200	200	100	125	250	1000	1000
5f (X = CH_3, Y = CH_3)	500	500	500	250	1000	500	>1000	1000
5g (X = Cl, Y = CH_3)	500	500	500	250	500	500	>1000	1000
5h (X = Br, Y = CH_3)	500	1000	250	500	500	250	>1000	1000
5i (X = H, Y = OCH_3)	250	500	250	250	250	250	1000	500
5j (X = CH_3, Y = OCH_3)	500	250	500	500	500	500	500	250
5k (X = Cl, Y = OCH_3)	125	500	500	500	500	500	500	250
5l (X = Br, Y = OCH_3)	500	250	1000	500	500	500	1000	1000
5m (X = H, Y = Cl)	250	250	500	1000	250	500	500	125
5n (X = CH_3, Y = Cl)	125	500	250	250	500	250	>1000	1000
5o (X = Cl, Y = Cl)	125	250	250	125	500	500	>1000	1000
5p (X = Br, Y = Cl)	250	500	500	250	250	500	>1000	1000
Ampicillin	250	250	100	100	100	100	–	–
Chloramphenicol	50	50	50	50	50	50	–	–
Ciprofloxacin	50	100	50	25	25	25	–	–
Norfloxacin	100	50	10	10	10	10	–	–
Gentamycin	1	5	0.5	0.05	5	5	–	–
Griseofulvin	–	–	–	–	–	–	100	500
Nystatin	–	–	–	–	–	–	100	100

B.S. *Bacillus subtilis*, C.T. *Clostridium tetani*, S.P. *Streptococcus pneumoniae*, E.C. *Escherichia coli*, S.T. *Salmonella typhi*, V.C. *Vibrio cholerae*, A.F. *Aspergillus fumigatus*, C.A. *Candida albicans*



Scheme 2 Plausible mechanistic pathway for the synthesis of 4-benzimidazol-2-yltetrazolo[1,5-a] quinol me **5a–p** involving intramolecular oxidative cyclo-dehydrogenation of Schiff base

with theoretical data. Similarly, all these compounds were characterized on the basis of spectral studies.

Antimicrobial activity

All the glass apparatus used were sterilized before use. Antimicrobial activity of all the synthesized compounds 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. Inoculum size for test strain was adjusted to 10^8 CFU [Colony Forming Unit] per milliliter by comparing the turbidity. The strains used for the activity were procured from [MTCC—Microbial Type Culture Collection]

Institute of Microbial Technology, Chandigarh. Each synthesized compound was diluted obtaining 2000 μg/ml concentration, as a stock solution. The results are recorded in the form of primary and secondary screenings. The compounds **5a–p** 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), *Vibrio cholerae* (MTCC 3906) as well as for antifungal activity against *Aspergillus fumigatus* (MTCC 3008) and *Candida albicans* (MTCC 227) at concentrations of 1000, 500, and 250 μg/ml as primary screening. DMSO was used as vehicle to get desired concentrations of compounds to test upon microbial strains. The compounds found to be active in the primary screening were further screened in a second set of dilution at concentrations of 200, 100, 62.5, 50, 25, 12.5, and 6.25 μg/ml. Ten microliters suspension from each well was further inoculated and growth was noted after 24 and 48 h. The lowest concentration which showed no visible growth (turbidity) after spot subculture was considered as MIC for each compound. The standard drugs used for comparison in the present study were ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, and gentamycin for evaluating antibacterial activity and griseofulvin and nystatin for antifungal activity.

Screening results displayed that compounds **5a–p** exhibited good-to-moderate activity for all the bacterial strains, compared with other standard drugs. An examination of the data (Table 1) reveals that among the compounds **5a–p**, compound **5e** (X = H, Y = CH_3) exhibited excellent activity against *Bacillus subtilis* and *Clostridium tetani* in comparison to standard antibiotic ampicillin. Compounds **5a** (X = H, Y = H), **5k** (X = Cl, Y = OCH_3), **5n** (X = CH_3, Y = Cl), and **5o** (X = Cl, Y = Cl) were found significantly active against *Bacillus subtilis* compared with ampicillin. Remaining compounds showed good-to-moderate activity against other bacteria in comparison to the rest of standard drugs.

None of the compounds was found sufficiently potent to inhibit *Streptococcus pneumoniae*. In case of Gram-negative bacteria *Escherichia coli*, compounds **5d** (X = Br, Y = H) and **5e** (X = H, Y = CH_3) displayed comparable activity to the standard ampicillin, while **5b** (X = CH_3, Y = H) and **5o** (X = Cl, Y = Cl) displayed significant activity. Compounds **5c** (X = Cl, Y = H) and **5d** (X = Br, Y = H) displayed comparable activity, while compound **5e** (X = H, Y = CH_3) showed significant activity against Gram-negative bacteria *Salmonella typhi* as compared to the standard ampicillin. None of the compounds was found sufficiently potent to inhibit *Vibrio cholerae*. The remaining compounds showed moderate activity against other bacteria when compared with the remaining standard drugs.

Antifungal study revealed that all the compounds have poor activity against *Aspergillus fumigatus*. As compared to the standard, griseofulvin, **5j** (X = CH_3, Y = OCH_3), **5k** (X = Cl, Y = OCH_3), and **5n** (X = CH_3, Y = Cl) exhibited excellent activity against *Candida albicans*. Other compounds showed poor activity against the rest of the fungal species compared with the standard drugs nystatin and griseofulvin.

Experimental

All the reagents were obtained commercially and used with further purification. Solvents used were of analytical grade. All melting points were taken in open capillaries and were 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 IR spectra were recorded on a Shimadzu FTIR 8401 spectrophotometer using KBr discs, 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 400 MHz spectrometer using solvent peak as internal standard. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. Mode of ionization employed was ESI (electrospray ionization). The microwave oven used was specially modified by RAGA's Electromagnetic systems.

Synthesis of the substituted tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **3a–d**

2-Chloro-3-formyl quinoline **2a–d** (5 mmol), sodium azide (10 mmol), acetic acid (1 ml), and ethanol (10 ml) were charged in a 100-ml round bottom flask with mechanical stirrer and condenser. The reaction mixture refluxed for 3–4 h. After the completion of reaction (checked by TLC), the separated tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **3a–d** was filtered and washed with ethanol. The further purification was carried out by leaching in equal volume ratio of chloroform and methanol (10:10 ml) to obtain the pure solid sample.

Synthesis of substituted 4-benzimidazol-2-yl tetrazolo[1,5-*a*]quinoline **5a–p**

Tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **3a–d** (5 mmol) and *o*-phenylenediamine **4a–d** (5 mmol) were thoroughly mixed in DMF (10 ml) and then *p*-TsOH (1 mmol) was

added to it. The mixture was irradiated for 240 s at 350 W of output power. After the completion of reaction (checked by TLC), the solution was cooled to room temperature. The reaction mixture was added dropwise with vigorous stirring into a previously chilled solution of Na_2CO_3 (2 mmol) in H_2O (30 ml). The separated precipitates of 4-Benzimidazol-2-yl tetrazolo[1,5-*a*]quinoline **5a**–**p** were filtered, thoroughly washed well with water, dried, and recrystallized from chloroform. The physicochemical and spectral properties of all the newly synthesized compounds **5a**–**p** are presented below.

4-(1*H*-benzo[*d*]imidazol-2-yl)tetrazolo[1,5-*a*]quinoline (**5a**)

Yield 76%, m.p. 239°C, Anal. Calcd. for $C_{16}H_{10}N_6$ (286.29 gm/mol): C 67.12, H 3.52, N 29.35% Found: C 67.23, H 3.66, N 29.12%. IR (KBr, cm^{-1}): 3420 (cyclic –NH), 3015 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.79 (s, 1H, NH), 7.28–9.16 (m, 9H, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 115.48, 116.69, 123.30, 124.38, 128.95, 129.05, 130.50, 130.85, 132.27, 132.59, 132.65, 145.73, 145.86 (Ar–C), MS: (M + 1) 287.

4-(5-methyl-1*H*-benzo[*d*]imidazol-2-yl)tetrazolo[1,5-*a*]quinoline (**5b**)

Yield 71%, m.p. 216°C, Anal. Calcd. for $C_{17}H_{12}N_6$ (300.32 gm/mol): C 67.99, H 4.03, N 27.98% Found: C 67.86, H 4.13, N 27.86%. IR (KBr, cm^{-1}): 3305 (cyclic –NH), 3000 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.35 (s, 1H, NH), 2.49 (s, 3H, CH_3), 7.14–8.52 (m, 8H, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 21.90 (CH_3), 113.58, 114.58, 115.19, 116.36, 117.09, 121.47, 121.58, 124.64, 126.74, 131.33, 145.71, 145.95, 147.98, 149.69, 158.08, 159.26 (Ar–C).

4-(5-chloro-1*H*-benzo[*d*]imidazol-2-yl)tetrazolo[1,5-*a*]quinoline (**5c**)

Yield 68%, m.p. 219°C, Anal. Calcd. for $C_{16}H_9N_6Cl$ (320.74 gm/mol): C 59.92, H 2.83, N 26.20% Found: C 59.73, H 2.68, N 26.12%. IR (KBr, cm^{-1}): 3410 (cyclic –NH), 3005 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.71 (s, 1H, NH), 7.38–9.27 (m, 8H, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 114.83, 116.99, 118.67, 123.80, 124.77, 126.07, 127.95, 129.05, 130.53, 130.59, 131.28, 132.51, 132.99, 141.51, 145.47, 146.98 (Ar–C).

4-(5-Bromo-1*H*-benzo[*d*]imidazol-2-yl)tetrazolo[1,5-*a*]quinoline (**5d**)

Yield 74%, m.p. 200°C, Anal. Calcd. for $C_{16}H_9N_6Br$ (365.19 gm/mol): C 52.62, H 2.48, N 23.01% Found: C 52.73, H 2.54, N 23.16%. IR (KBr, cm^{-1}): 3420 (cyclic –NH), 3025 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.84 (s, 1H, NH), 7.45–9.39 (m, 8H, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 113.46, 114.97, 117.77, 122.85, 124.65, 126.72, 127.05, 129.73, 130.43, 130.37, 131.21, 132.69, 132.91, 140.57, 144.40, 145.16 (Ar–C).

4-(1*H*-benzo[*d*]imidazol-2-yl)-7-methyltetrazolo[1,5-*a*]quinoline (**5e**)

Yield 84%, m.p. 234°C, Anal. Calcd. for $C_{17}H_{12}N_6$ (300.32 gm/mol): C 67.99, H 4.03, N 27.98% Found: C 67.80, H 4.14, N 28.10%. IR (KBr, cm^{-1}): 3320 (cyclic –NH), 3005 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.52 (s, 1H, NH), 2.56 (s, 3H, CH_3), 7.14–8.48 (m, 8H, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 23.94 (CH_3), 109.39, 111.56, 114.14, 117.22, 117.97, 120.08, 121.59, 124.73, 125.80, 130.27, 141.81, 146.20, 148.01 (Ar–C).

4-(5-Methyl-1*H*-benzo[*d*]imidazol-2-yl)-7-methyltetrazolo[1,5-*a*]quinoline (**5f**)

Yield 69%, m.p. 242°C, Anal. Calcd. for $C_{18}H_{14}N_6$ (314.34 gm/mol): C 68.78, H 4.49, N 26.74% Found: C 68.68, H 4.40, N 26.66%. IR (KBr, cm^{-1}): 3340 (cyclic –NH), 3005 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.54 (s, 1H, NH), 2.39 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 7.11–8.56 (m, 7H, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 21.90 (CH_3), 22.36 (CH_3), 109.48, 111.57, 114.67, 117.91, 117.93, 121.85, 123.54, 124.36, 125.00, 133.22, 145.97, 145.39, 146.58, 148.12, 158.00, 159.37 (Ar–C).

4-(5-Chloro-1*H*-benzo[*d*]imidazol-2-yl)-7-methyltetrazolo[1,5-*a*]quinoline (**5g**)

Yield 64%, m.p. 212°C, Anal. Calcd. for $C_{17}H_{11}N_6Cl$ (334.76 gm/mol): C 60.99, H 3.31, N 25.10% Found: C 61.12, H 3.43, N 25.33%. IR (KBr, cm^{-1}): 3320 (cyclic –NH), 3025 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.18 (s, 1H, NH), 2.48 (s, 3H, CH_3), 7.29–8.68 (m, 7H, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 22.94 (CH_3), 111.65, 112.68, 114.44, 115.19, 117.00, 122.36, 123.98, 124.36, 125.90, 134.16, 145.90, 145.99, 146.50, 149.98, 157.08, 158.29 (Ar–C).

4-(5-Bromo-1*H*-benzo[*d*]imidazol-2-yl)-7-methyltetrazolo[1,5-*a*]quinoline (**5h**)

Yield 73%, m.p. 238°C, Anal. Calcd. for $C_{17}H_{11}N_6Br$ (379.21 gm/mol): C 53.84, H 2.92, N 22.16% Found: C 53.77, H 2.80, N 22.13%. IR (KBr, cm^{-1}): 3340 (cyclic –NH), 3005 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.96 (s, 1H, NH), 2.41 (s, 3H, CH_3), 7.34–8.53 (m, 7H,

Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 22.94 (CH_3), 110.01, 112.78, 114.08, 115.63, 117.40, 120.36, 122.91, 124.82, 125.00, 133.30, 143.85, 145.15, 146.18, 149.90, 158.16, 159.36 (Ar–C).

4-(1*H*-Benzo[*d*]imidazol-2-yl)-7-methoxytetrazolo[1,5-*a*]quinoline (**5i**)

Yield 79%, m.p. 213°C, Anal. Calcd. for $C_{17}H_{12}N_6O$ (316.32 gm/mol): C 64.55, H 3.82, N 26.57% Found: C 64.68, H 3.94, N 26.40%. IR (KBr, cm^{-1}): 3325 (cyclic –NH), 3015 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.12 (s, 1H, NH), 3.84 (s, 3H, OCH_3), 7.24–8.39 (m, 8H, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 57.08 (OCH_3), 110.10, 112.50, 114.21, 116.20, 117.17, 121.02, 121.65, 123.73, 125.23, 131.98, 140.12, 145.24, 147.56 (Ar–C).

4-(5-Methyl-1*H*-benzo[*d*]imidazol-2-yl)-7-methoxytetrazolo[1,5-*a*]quinoline (**5j**)

Yield 64%, m.p. 204°C, Anal. Calcd. for $C_{18}H_{14}N_6O$ (330.34 gm/mol): C 65.44, H 4.27, N 25.44% Found: C 65.12, H 4.36, N 25.56%. IR (KBr, cm^{-1}): 3300 (cyclic –NH), 3010 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.61 (s, 1H, NH), 2.43 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 7.04–8.99 (m, 7H, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 21.90 (CH_3), 56.34 (OCH_3), 110.36, 111.50, 115.65, 117.86, 117.99, 121.00, 121.51, 124.84, 125.78, 131.27, 145.01, 145.29, 146.58, 147.89, 158.99, 159.10 (Ar–C), MS: (M + 1) 331.

4-(5-Chloro-1*H*-benzo[*d*]imidazol-2-yl)-7-methoxytetrazolo[1,5-*a*]quinoline (**5k**)

Yield 66%, m.p. 222°C, Anal. Calcd. for $C_{17}H_{11}N_6OCl$ (350.76 gm/mol): C 58.21, H 3.16, N 23.96% Found: C 58.12, H 3.22, N 23.86%. IR (KBr, cm^{-1}): 3340 (cyclic –NH), 3015 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.69 (s, 1H, NH), 3.79 (s, 3H, OCH_3), 7.16–8.46 (m, 7H, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 56.34 (OCH_3), 109.12, 111.65, 115.94, 117.00, 117.94, 121.84, 122.52, 124.26, 126.71, 130.15, 145.98, 147.29, 148.50, 149.09, 157.35, 156.17 (Ar–C).

4-(5-Bromo-1*H*-benzo[*d*]imidazol-2-yl)-7-methoxytetrazolo[1,5-*a*]quinoline (**5l**)

Yield 69%, m.p. 243°C, Anal. Calcd. for $C_{17}H_{11}N_6OBr$ (395.21gm/mol): C 51.66, H 2.81, N 21.26% Found: C 51.49, H 2.92, N 21.20%. IR (KBr, cm^{-1}): 3335 (cyclic –NH), 3005 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.52 (s, 1H, NH), 3.84 (s, 3H, OCH_3), 7.20–8.41 (m, 7H, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 56.49 (OCH_3), 110.84, 113.67, 115.90, 117.52, 117.90, 121.00, 122.57, 123.23, 126.35, 133.48, 145.08, 146.24, 148.41, 149.82, 156.35, 158.23 (Ar–C).

4-(1*H*-Benzo[*d*]imidazol-2-yl)-7-chlorotetrazolo[1,5-*a*]quinoline (**5m**)

Yield 66%, m.p. 242°C, Anal. Calcd. for $C_{16}H_9N_6Cl$ (320.74 gm/mol): C 59.92, H 2.83, N 26.20% Found: C 59.99, H 2.74, N 26.16%. IR (KBr, cm^{-1}): 3335 (cyclic –NH), 3005 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.84 (s, 1H, NH), 7.22–8.56 (m, 8H, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 110.45, 111.92, 113.24, 115.27, 117.28, 120.98, 121.66, 123.70, 125.25, 132.47, 142.56, 146.72, 149.92 (Ar–C).

4-(5-Methyl-1*H*-benzo[*d*]imidazol-2-yl)-7-chlorotetrazolo[1,5-*a*]quinoline (**5n**)

Yield 72%, m.p. 205°C, Anal. Calcd. for $C_{17}H_{11}N_6Cl$ (334.76 gm/mol): C 60.99, H 3.31, N 25.10% Found: C 60.82, H 3.46, N 25.30%. IR (KBr, cm^{-1}): 3315 (cyclic –NH), 3020 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.25 (s, 1H, NH), 2.41 (s, 3H, CH_3), 7.34–8.65 (m, 7H, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 22.63 (CH_3), 109.27, 111.78, 114.04, 115.23, 117.70, 122.33, 123.98, 124.84, 125.94, 133.10, 143.97, 145.09, 146.43, 149.00, 154.74, 157.38 (Ar–C).

4-(5-Chloro-1*H*-benzo[*d*]imidazol-2-yl)-7-chlorotetrazolo[1,5-*a*]quinoline (**5o**)

Yield 64%, m.p. 229°C, Anal. Calcd. for $C_{16}H_8N_6Cl_2$ (355.18 gm/mol): C 54.11, H 2.27, N 23.66% Found: C 54.00, H 2.21, N 23.48%. IR (KBr, cm^{-1}): 3305 (cyclic –NH), 3010 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.36 (s, 1H, NH), 7.48–8.82 (m, 7H, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 110.95, 111.45, 113.14, 115.00, 119.78, 122.30, 123.98, 125.65, 125.90, 132.18, 142.94, 144.16, 146.38, 149.95, 153.12, 156.30 (Ar–C).

4-(5-Bromo-1*H*-benzo[*d*]imidazol-2-yl)-7-chlorotetrazolo[1,5-*a*]quinoline (**5p**)

Yield 73%, m.p. 236°C, Anal. Calcd. for $C_{16}H_8N_6ClBr$ (399.63 gm/mol): C 48.09, H 2.02, N 21.03% Found: C 48.22, H 1.98, N 21.16%. IR (KBr, cm^{-1}): 3315 (cyclic –NH), 3015 (ArC–H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.48 (s, 1H, NH), 7.40–8.89 (m, 7H, Ar–H). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 111.15, 111.95, 112.20, 115.47, 119.71, 123.34, 123.90, 125.12, 125.96, 131.63, 141.35, 144.00, 145.30, 148.03, 152.39, 157.43 (Ar–C).

Conclusion

Rapid, simple, and efficient method has been developed for the synthesis of some new tetrazolo[1,5-*a*]quinoline-based benzimidazole derivatives under the microwave irradiation conditions in the presence of an organocatalyst *p*-TsOH. This synthetic strategy allows the construction of relatively complicated nitrogen containing heterocyclic system as well as the introduction of various heteroaromatic substitutions in between two nitrogen atoms of benzimidazole scaffold. It can be concluded from Table 1 that compound **5e** having a methyl group at 7-position of tetrazolo[1,5-*a*]quinoline nucleus and unsubstituted fused phenyl ring of benzimidazole is highly active against *Bacillus subtilis* and *Clostridium tetani*. It is worth mentioning that minor changes in molecular configuration of these compounds profoundly influence the bioactivity. Further work to intensify the potency of this series by changing molecular configuration of cyclic –NH– of benzimidazole nucleus is in progress at our laboratory. The present study throws light on the identification of this new structural class as antimicrobials which can be of interest for further detailed preclinical investigations.

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