Med Chem Res (2013) 22:3831–3842
DOI 10.1007/s00044-012-0381-7

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Microwave-assisted synthesis of novel 4*H*-chromene derivatives bearing 2-aryloxyquinoline and their antimicrobial activity assessment

Chetan B. Sangani · Nimesh M. Shah · Manish P. Patel · Ranjan G. Patel

Received: 4 January 2012 / Accepted: 27 November 2012 / Published online: 12 December 2012

Abstract A new series of 4*H*-chromene derivatives **6a–x** bearing 2-aryloxyquinoline nucleus have been synthesized under microwave irradiation by reaction of 2-aryloxyquinoline-3-carbaldehyde **3a–l**, malononitrile **4**, and compounds (Cyclohexanedione, Dimidone) **5a–b** in the presence of NaOH as the basic catalyst. All the compounds were screened against three Gram-positive bacteria (*Streptococcus pneumoniae*, *Clostridium tetani*, *Bacillus subtilis*), three Gram-negative bacteria (*Salmonella typhi*, *Vibrio cholerae*, *Escherichia coli*) and two fungi (*Aspergillus fumigatus*, *Candida albicans*) using the broth microdilution MIC (Minimum Inhibitory Concentration) method. Upon study of the antimicrobial screening, it has been observed that a majority of the compounds were found to be active against *C. tetani* and *B. subtilis* as well as against *C. albicans* as compared to the standard drugs.

Keywords 2-Aryloxyquinoline · 4*H*-chromene · One-pot reaction · In vitro antimicrobial activity

Introduction

The alarming increment in pathogenic resistance to existing first-line standard drugs is a serious problem in antimicrobial cure and necessitates continuing research into new classes of antimicrobials (Woodford, 2003). Moreover, the progression of drug-resistant strains has contributed to the inefficiency of the straight antimicrobial therapy. This crops up an enormous interest in antibacterial research and we strongly believe that there is an urgent call for development of new drugs with divergent and unique structure and with a probably unusual mechanism of action from that of existing first-line drugs. Consequently, this spot of research is accorded an immense significance and keeps attracting much attention of an increasing number of medicinal chemists.

The chromene ring system is considered to be one of the most imperative heterocycles in nature as it has the distinction of being the parent ring in countless derivatives of biologic relevance. The current interest in 4*H*-chromene derivatives arises from their potential application as antimicrobial (Kuarm *et al.*, 2011; Rai *et al.*, 2010), anti-HIV (Bhavsar *et al.*, 2011; Park *et al.*, 2008), anti-tubercular (Kamdar *et al.*, 2010), antioxidant (Singh *et al.*, 2010), anticancer (Raju *et al.*, 2011), antitumor (Huang *et al.*, 2009), cytotoxic (Raj *et al.*, 2010; Sabry *et al.*, 2011), antidyslipidemic (Sashidhara *et al.*, 2008), antileishmanial (Nazarian *et al.*, 2010), anti-inflammatory (Gebhardt *et al.*, 2007), anti-helicobacter pylori (Chimenti *et al.*, 2007), and TNF-α inhibitor agents (Cheng *et al.*, 2003).

On the other hand, quinoline derivatives are a possessing high activity profile due to their wide range of useful biologic properties including antibacterial (Kalluraya *et al.*, 2008), antifungal (Rana *et al.*, 2008), antimycobacterial (Mital *et al.*, 2006), antimalarial (Charris *et al.*, 2005; Dave *et al.*, 2009), anti-inflammatory (Bava and Kumar, 2009), and anticancer activities (Shi *et al.*, 2008).

A literature survey manifests that a number of 4*H*-chromene derivatives have been synthesized using various aldehydes (Thumar and Patel, 2011b; Mungra *et al.*, 2011b; Makawana *et al.*, 2011; Kathrotiya and Patel, 2011a), but there is not a single report where 2-aryloxyquinoline-3-carbaldehyde is used.

The molecular manipulation of promising lead compounds is still the chief approach to widen an area of

C. B. Sangani · N. M. Shah · M. P. Patel · R. G. Patel (✉)
Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar, Gujarat 388120, India
e-mail: patelranjanben@yahoo.com

medicine research. It involves an idea to merge the separate pharmacophoric groups of analogous activity into one compound, thus making structural changes in the biologic activity. An attempt has been to undertake the synthesis of chromene derivatives with the assumption that the assimilation of more than one bioactive moiety into a single scaffold may produce novel heterocycles with fascinating antimicrobial activities to combat the infections of microbial pathogens.

In light of the aforementioned facts, and as a prolongation of our investigation on the synthesis of biologically active heterocyclic compounds (Sangani *et al.*, 2011, 2012; Makawana *et al.*, 2011a, b, c, d; Shah *et al.*, 2012; Mungra *et al.*, 2011a, b; Ladani *et al.*, 2010, 2011; Thumar and Patel, 2011a, b, c, d; Kathrotiya and Patel, 2011a), we were provoked to synthesize new aryloxyquinoline-based 4*H*-chromene derivatives and evaluate them as antimicrobial agents.

The conventional procedures are not found to be satisfactory with regard to operational simplicity, effectiveness, and yield. An alternative synthetic approach is microwave irradiation (Mungra *et al.*, 2011a, b; Makawana *et al.*, 2011a). In recent years, microwave irradiation has been demonstrated not only to dramatically accelerate many organic reactions, but also to improve yield and selectivity.

NaOH derives its remarkable ability to catalyze from its strong base characteristic; it is also used as an eco-friendly base. In connection with our earlier work on NaOH catalysis with microwave irradiation (Makawana *et al.*, 2011a), we attempted same strategy to achieve novel 4*H*-chromene derivatives of aryloxyquinoline.

The constitutions of all the products were confirmed using ^{1}H NMR, ^{13}C NMR, FTIR, and elemental analysis. All synthesized compounds were screened for in vitro antimicrobial activity against eight human pathogens, of which three are Gram-positive bacteria (*Streptococcus pneumonia*, *Clostridium tetani*, *Bacillus subtilis*), three are Gram-negative bacteria (*Salmonella typhi*, *Vibrio cholerae*, *Escherichia coli*), and two are fungi (*Aspergillus fumigatus*, *Candida albicans*), using the broth microdilution MIC (Minimum Inhibitory Concentration) method (NCCLS, 2002).

Results and discussion

Chemistry

The key intermediate 2-aryloxyquinoline-3-carbaldehyde **3a–l** was prepared by refluxing 2-chloro-3-formylquinoline **1a–c** and various phenols in the presence of anhydrous potassium carbonate in dry DMF for 3.5 h (Mungra *et al.*, 2011b). The required 2-chloro-3-formylquinoline **1a–c** was prepared by the Vilsmeier–Haack reaction according to the literature procedure (Meth-Cohn and Bramha, 1978).

In the present study, 4*H*-chromene derivatives **6a–x** have been synthesized in moderate to good yield, i.e., 64–89 %, by reaction of 2-aryloxyquinoline-3-carbaldehyde **3a–l**, malononitrile **4** and compounds **5a–b** under microwave irradiation in the presence of NaOH as a basic catalyst (Scheme 1). The substitutions present on the compounds are given in Table 1.

In accordance with the mechanism suggested in the literature (Makawana *et al.*, 2011a), the first step of this process may involve the Knoevenagel condensation of aldehyde and malononitrile to give heterylidenenitrile derivatives followed by Michael addition of **5a–b** to heterylidenenitrile to afford the title compounds **6a–x** (Scheme 2).

The structures of all the newly synthesized compounds were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR, mass and elemental analysis. The IR spectrum of title compounds **6a–x** confirms the presence of amino, cyano, carbonyl, and ether groups due to the appearance of absorption bands at around 3,400–3,460 & 3,290–3,340, 2,180–2,260, 1,650–1,700, and 1,180–1,260 cm^{-1}, respectively. Its ^{1}H NMR spectrum indicated the presence of one singlet in the range δ 4.60–4.80 ppm of –CH proton, and the disappearance of a singlet at δ 10.50 ppm of –CHO clearly confirmed the cyclization of the Knoevenagel intermediate. Moreover, multiplets in the range δ 7.00–8.14 ppm appeared for aromatic protons. In the ^{13}C NMR spectral data of the title compounds **6a–x**, the most characteristic signal around δ 32.25–40.50 ppm indicated the formation of a pyrane ring. The signal at around δ 56.05–57.50 ppm is assigned to carbon attached with carbonitrile, while signals around δ 106.10–165.97 and 196.20–196.60 ppm are attributed to all the aromatic and carbonyl carbons, respectively, of compounds **6a–x**. The obtained elemental analysis values are in good agreement with theoretic data. Further, the molecular weight of selected compounds such as **6h** and **6v** was confirmed by its mass spectral studies. Mass Spectroscopy of the above-mentioned compounds showed a molecular ion peak $[M + 1]^{+}$ corresponding to exact mass. Mass spectra of compound **6h** gave a molecular ion peak at $m/z = 442.69$ $[M + 1]^{+}$ corresponding to molecular formula $C_{26}H_{20}FN_3O_3$ and compound **6v** gave a molecular ion peak at $m/z = 482.27$ $[M + 1]^{+}$ corresponding to molecular formula $C_{28}H_{24}FN_3O_3$. All physical, analytical data as well as spectroscopic characterization data of the synthesized compounds **6a–x** are given in the experimental section. All the compounds were screened for their antibacterial and antifungal activity and the results are expressed in the form of MIC μg/mL.

Scheme 1 General synthetic route for the compounds **6a–x**

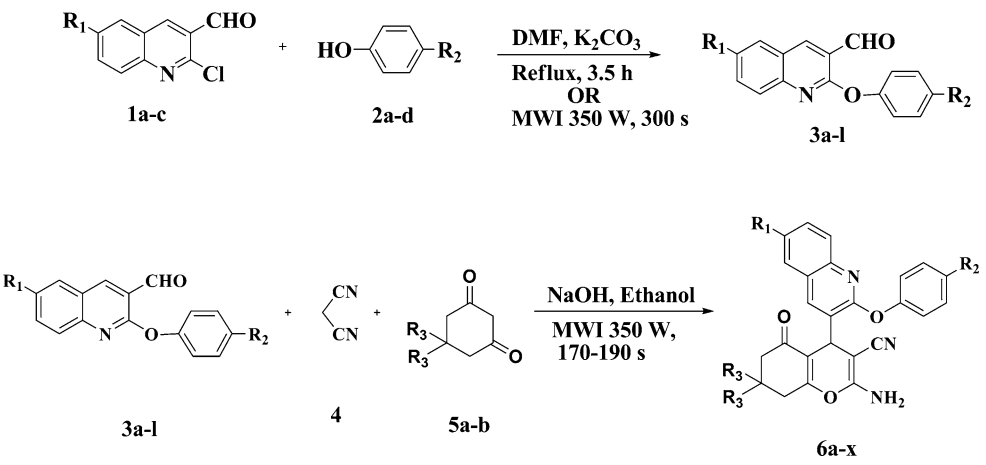
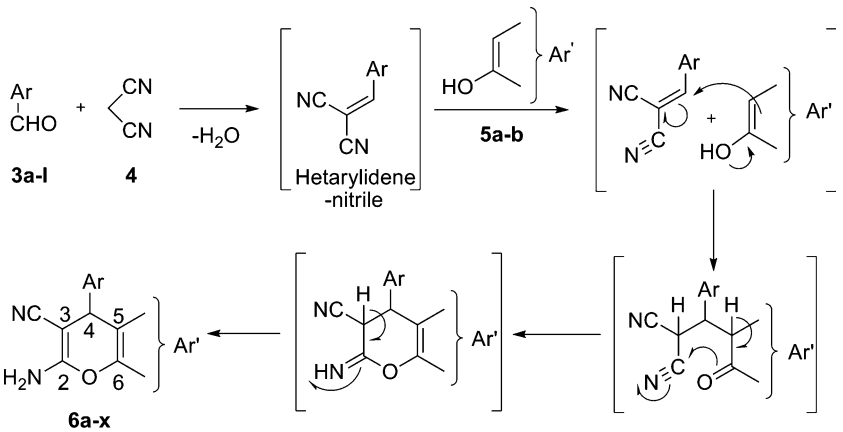


Table 1 Substitution of compounds **6a–x**

Compound	R_1	R_2	R_3	Compound	R_1	R_2	R_3
6a	H	H	H	**6m**	H	H	CH_3
6b	H	CH_3	H	**6n**	H	CH_3	CH_3
6c	H	OCH_3	H	**6o**	H	OCH_3	CH_3
6d	H	F	H	**6p**	H	F	CH_3
6e	CH_3	H	H	**6q**	CH_3	H	CH_3
6f	CH_3	CH_3	H	**6r**	CH_3	CH_3	CH_3
6g	CH_3	OCH_3	H	**6s**	CH_3	OCH_3	CH_3
6h	CH_3	F	H	**6t**	CH_3	F	CH_3
6i	OCH_3	H	H	**6u**	OCH_3	H	CH_3
6j	OCH_3	CH_3	H	**6v**	OCH_3	CH_3	CH_3
6k	OCH_3	OCH_3	H	**6w**	OCH_3	OCH_3	CH_3
6l	OCH_3	F	H	**6x**	OCH_3	F	CH_3

Scheme 2 Plausible mechanistic pathway for 4*H*-chormene derivatives



Antimicrobial activity

All the glass apparatus were sterilized before use. The antimicrobial activity of all the synthesized compounds was carried out by the broth microdilution method. Mueller–Hinton broth was used as the 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] the Institute of Microbial Technology, Chandigarh. Each synthesized compound was diluted obtaining 2,000 μg/mL concentration, as a stock solution. The results are recorded in the form of primary and secondary screening. The compounds **6a–x** were screened for their antibacterial activity against *S. pneumoniae* (MTCC 1936), *C. tetani* (MTCC 449), *B. subtilis* (MTCC 441), *S. typhi* (MTCC 98), *V. cholerae* (MTCC 3906), and *E. coli* (MTCC 443) as well as for antifungal activity against *A. fumigatus* (MTCC 3008) and *C. albicans* (MTCC 227) at concentrations of 1,000, 500, and 250 μg/mL as primary screening. DMSO was used as the vehicle to get the 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, and 50 μg/mL. 10 μL suspensions from each well were 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. In the present study, ampicillin and norfloxacin were used as standard antibacterial drugs, whereas griseofulvin was used as the standard antifungal drug. The protocols are summarized in Table 2.

The examination of the data (Table 2) reveals that most of the compounds showed excellent activity when compared with standard antibacterial drugs Ampicillin, Ciprofloxacine, Chlormphenicol, and Norfloxacine and antifungal drugs Griseofulvin and Nystatin.

An examination of the antibacterial activity of 4*H*-chromene derivatives **6a–x**, assay indicated that among the Gram-positive bacteria tested, two strains, namely *B. subtilis* and *C. tetani*, showed relative high sensitivity toward the tested compounds. In this view, against Gram-positive bacteria *B. subtilis*, compounds **6c** (R_1=H, R_2=OCH_3, R_3=H), **6f** (R_1=CH_3, R_2=CH_3, R_3=H), **6h** (R_1=CH_3, R_2=F, R_3=H), **6i** (R_1=OCH_3, R_2=H, R_3=H), **6q** (R_1=CH_3, R_2=H, R_3=CH_3), **6r** (R_1=CH_3, R_2=CH_3, R_3=CH_3), and **6x** (R_1=OCH_3, R_2=F, R_3=CH_3) are found more potent than ampicillin, whereas the analogs **6a** (R_1=H, R_2=H, R_3=H), **6d** (R_1=H, R_2=F, R_3=H), **6g** (R_1=CH_3, R_2=OCH_3, R_3=H), **6j** (R_1=OCH_3, R_2=CH_3, R_3=H), **6o** (R_1=H, R_2=OCH_3, R_3=CH_3), **6s** (R_1=CH_3, R_2=OCH_3, R_3=CH_3) (MIC = 250 μg/mL) have shown comparable activity to ampicillin (MIC = 250 μg/mL).

Against *C. tetani* compounds, **6f** (R_1=CH_3, R_2=CH_3, R_3=H), **6k** (R_1=OCH_3, R_2=OCH_3, R_3=H), **6l** (R_1=OCH_3, R_2=F, R_3=H), **6m** (R_1=H, R_2=H, R_3=CH_3), **6o** (R_1=H, R_2=OCH_3, R_3=CH_3), **6q** (R_1=CH_3, R_2=H, R_3=CH_3), **6s** (R_1=CH_3, R_2=OCH_3, R_3=CH_3), **6u** (R_1=OCH_3, R_2=H, R_3=CH_3), **6v** (R_1=OCH_3, R_2=CH_3, R_3=CH_3), and **6x** (R_1=OCH_3, R_2=F, R_3=CH_3) are found to be more potent, whereas the analogs **6a** (R_1=H, R_2=H, R_3=H), **6r** (R_1=CH_3, R_2=CH_3, R_3=CH_3), and **6w** (R_1=OCH_3, R_2=OCH_3, R_3=CH_3) (MIC = 250 μg/mL) have shown comparable activity to ampicillin (MIC = 250 μg/mL). Compounds **6f** (R_1=CH_3, R_2=CH_3, R_3=H), **6k** (R_1=OCH_3, R_2=OCH_3, R_3=H), **6q** (R_1=CH_3, R_2=H, R_3=CH_3), **6u** (R_1=OCH_3, R_2=H, R_3=CH_3), and **6v** (R_1=OCH_3, R_2=CH_3, R_3=CH_3) (MIC = 100 μg/mL) are also found to be equally potent as compared to ciprofloxacin (MIC = 100 μg/mL) against the same organism.

Toward *S. pneumonia*, the compound **6f** (R_1=CH_3, R_2=CH_3, R_3=H) (MIC = 62.5 μg/mL) has shown better activity, whereas **6c** (R_1=H, R_2=OCH_3, R_3=H), **6i** (R_1=OCH_3, R_2=H, R_3=H), **6q** (R_1=CH_3, R_2=H, R_3=CH_3), and **6r** (R_1=CH_3, R_2=CH_3, R_3=CH_3) (MIC = 100 μg/mL) have shown equal activity to ampicillin (MIC = 100 μg/mL).

Compound **6x** (R_1=OCH_3, R_2=F, R_3=CH_3) (MIC = 62.5 μg/mL) is found to be more potent, whereas **6a** (R_1=H, R_2=H, R_3=H), **6d** (R_1=H, R_2=F, R_3=H), **6e** (R_1=CH_3, R_2=H, R_3=H), **6h** (R_1=CH_3, R_2=F, R_3=H), and **6v** (R_1=OCH_3, R_2=CH_3, R_3=CH_3) (MIC = 100 μg/mL) have shown comparable activity to ampicillin (MIC = 100 μg/mL) when employed to inhibit Gram-negative bacteria *E. coli*.

With regard to the activity against *S. typhi*, compounds **6h** (R_1=CH_3, R_2=F, R_3=H), **6q** (R_1=CH_3, R_2=H, R_3=CH_3), **6v** (R_1=OCH_3, R_2=CH_3, R_3=CH_3), and **6x** (R_1=OCH_3, R_2=F, R_3=CH_3) (MIC = 100 μg/mL) show comparable activity to ampicillin (MIC = 100 μg/mL). Toward *V. cholerae*, four compounds **6c** (R_1=H, R_2=OCH_3, R_3=H), **6f** (R_1=CH_3, R_2=CH_3, R_3=H), **6i** (R_1=OCH_3, R_2=H, R_3=H), and **6n** (R_1=H, R_2=CH_3, R_3=CH_3) (MIC = 100 μg/mL) show comparable activity to ampicillin (MIC = 100 μg/mL).

Antifungal screening

Against fungal pathogen *C. albicans*, compounds **6o** (R_1=H, R_2=OCH_3, R_3=OCH_3) (MIC = 100 μg/mL), **6p** (R_1=H, R_2=F, R_3=CH_3) (MIC = 200 μg/mL), **6d** (R_1=H, R_2=F, R_3=H), **6f** (R_1=CH_3, R_2=CH_3, R_3=H), **6h** (R_1=CH_3, R_2=F, R_3=H), **6k** (R_1=OCH_3, R_2=OCH_3, R_3=H), **6m** (R_1=H, R_2=H, R_3=CH_3), **6q** (R_1=CH_3, R_2=H, R_3=CH_3), **6t** (R_1=CH_3, R_2=F, R_3=CH_3), and **6w** (R_1=OCH_3, R_2=OCH_3, R_3=CH_3) (MIC = 250 μg/mL) are found to be more potent, whereas compound **6a** (R_1=H, R_2=H, R_3=H), **6b** (R_1=H, R_2=CH_3, R_3=H), **6e** (R_1=CH_3, R_2=H, R_3=H), **6g** (R_1=CH_3, R_2=OCH_3, R_3=H), **6l** (R_1=OCH_3, R_2=F, R_3=H), **6n** (R_1=H, R_2=CH_3, R_3=CH_3), **6u** (R_1=OCH_3, R_2=H, R_3=CH_3), and **6x** (R_1=OCH_3, R_2=F, R_3=CH_3) (MIC = 500 μg/mL) are found to be equipotent to griseofulvin (MIC =500 μg/mL). The remaining compounds showed poor activity to inhibit the growth of bacterial pathogens and are all less effective than standard drugs. From the antimicrobial study of the title derivatives, it is interesting to note that a minor alteration in the molecular

Table 2 In vitro antimicrobial activity of 4*H*-chromene derivatives **6a–x**

	Gram-positive bacteria			Gram-negative bacteria			Fungal species	
Compd	Bs. MTCC 441	Ct. MTCC 449	Sp. MTCC 1936	Ec. MTCC 443	St. MTCC 98	Vc. MTCC 3906	Af. MTCC 3008	Ca. MTCC 227
Minimum inhibitory concentration (MIC) expressed in μg/ml								
6a	**250**	**250**	250	**100**	250	250	1,000	**500**
6b	1,000	500	500	250	500	200	500	**500**
6c	**200**	1,000	**100**	150	250	**100**	>1,000	1,000
6d	**250**	500	250	100	200	500	>1,000	**250**
6e	500	500	500	100	250	1,000	>1,000	**500**
6f	**100**	**100**	**62.5**	500	500	**100**	500	**250**
6g	**250**	500	500	500	1,000	200	500	**500**
6h	**200**	500	200	100	**100**	500	500	**250**
6i	**100**	500	**100**	150	200	**100**	1,000	1,000
6j	**250**	500	250	250	500	500	1,000	1,000
6k	500	**100**	500	200	1,000	200	500	**250**
6l	500	**200**	250	500	500	200	500	**500**
6m	500	**200**	250	250	500	200	>1,000	**250**
6n	1,000	500	500	200	250	**100**	500	**500**
6o	**250**	**200**	250	250	500	250	250	**100**
6p	500	500	500	500	500	250	250	**200**
6q	**150**	**100**	**100**	200	**100**	250	500	**250**
6r	**100**	**250**	**100**	250	250	200	250	1,000
6s	**250**	**200**	250	500	500	200	250	1,000
6t	500	500	500	500	500	500	250	250
6u	500	**100**	500	200	500	200	1,000	500
6v	500	**100**	500	100	**100**	200	500	1,000
6w	1,000	**250**	1,000	250	250	250	500	250
6x	200	**200**	150	62.5	**100**	250	500	500
A	250	250	100	100	100	100	–	–
B	50	100	50	25	25	25	–	–
C	100	50	10	10	10	10	–	–
D	50	50	50	50	50	50	–	–
E	–	–	–	–	–	–	100	100
F	–	–	–	–	–	–	100	500

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; A: Ampicillin; B: Ciprofloxacin; C: Norfloxacin; D: Chloramphenicol; E: Nystatin; F: Griseofulvin. "–" represents "not tested"

The bold entries indicates that the compounds are either equipotent or more potent than the standard drug used

configuration of the investigated compounds may have a pronounced effect on antimicrobial activity.

Experimental

Chemistry

General procedures

Required acetic anhydride, substituted anilines, acetic acid, malononitrile, phosphorous oxychloride, and sodium hydroxide were obtained from S. D. Fine Chem Ltd., Vadodara, Gujarat, India. Cyclohexanedione and dimedone were obtained from Sigma-Aldrich. Solvents were purified and dried before being used. 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 adjustable output power levels, i.e., 10 levels from 140 to 700 Watts, and with an individual sensor for temperature control (fiber optic is used as an 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 precoated with silica gel, $^{60}F_{254}$, 0.25 mm thickness) (Merck, Darmstadt, Germany) was used for monitoring the progress of all reactions and purity and homogeneity of the synthesized compounds. UV radiation and/or iodine were used as the visualizing agents. Elemental analysis (% C, H, N) was carried out by Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and all compounds are within ±0.4 % of the theory specified. The IR spectra were recorded in KBr on a Perkin-Elmer Spectrum GX FT-IR Spectrophotometer (Perkin-Elmer, USA) and only the characteristic peaks are reported in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using solvent peak as the 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 compounds **6a–x**

2-Aryloxyquinoline-3-carbaldehyde **3a–l** (10 mmol), malononitrile **4** (10 mmol), and Cyclohexanedione/Dimidone **5a–b** (10 mmol) were thoroughly mixed in ethanolic NaOH (5 mmol, 10 mL) and irradiated in a microwave oven at 350 W (50 % of output power) for 170–190 s. After the completion of reaction (checked by TLC), the solution was cooled to room temperature, the solid separated was filtered, washed well with ethanol (10 mL), dried, and recrystallized from chloroform to get the pure solid sample **6a–x**. Physical, analytical, and spectroscopic characterization data of the compounds **6a–x** are given hereafter.

*2-Amino-4-[2-phenoxyquinolin-3-yl]-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6a**)*

Yield 73 %, m.p. 235–236 °C, Anal. Calcd. for $C_{25}H_{19}N_3O_3$ (409.44 g/mol): C 73.34, H 4.68, N 10.26 % Found: C 73.42, H 4.44, N 10.55 %. IR (KBr, cm^{-1}): 3,420 and 3,315 (asym. and sym. stretching of $-NH_2$), 2,215 ($-C\equiv N$ stretching), 1,710 (–C=O str.), 1,190 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83–2.35 (m, 4H, CH_2), 2.59 (m, 2H, CH_2), 4.68 (s, 1H, CH), 7.12–8.02 (m, 12H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.35 (CH_2), 27.03 (CH_2), 34.25 (CH), 36.74 (CH_2), 56.25 (C–CN), 112.48, 120.29, 123.47, 126.40, 126.77, 127.12, 128.24, 128.80, 129.93, 132.00, 135.06, 138.31, 143.35, 153.22, 159.18, 159.68, 164.27 (Ar–C), 196.52 (C=O).

*2-Amino-4-[2-(4-methylphenoxy)quinolin-3-yl]-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6b**)*

Yield 78 %, m.p. 268–269 °C, Anal. Calcd. for $C_{26}H_{21}N_3O_3$ (423.46 g/mol): C 73.74, H 5.00, N 9.92 % Found: C 74.00, H 5.09, N 9.99 %. IR (KBr, cm^{-1}): 3,395 and 3,300 (asym. and sym. stretching of $-NH_2$), 2,195 ($-C\equiv N$ stretching), 1,670 (–C=O str.), 1,205 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90–2.26 (m, 4H, CH_2), 2.43 (s, 3H, CH_3), 4.62 (s, 1H, CH), 2.64 (m, 2H, CH_2), 7.01–8.12 (m, 11H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.27 (CH_2), 20.90 (CH_3), 27.18 (CH_2), 30.50 (CH), 36.90 (CH_2), 56.18 (C–CN), 107.35, 120.19, 123.43, 126.40, 126.64, 127.21, 128.50, 128.83, 129.72, 132.05, 134.94, 138.18, 143.31, 153.17, 159.00, 159.81, 165.85 (Ar–C), 196.38 (C=O).

*2-Amino-4-[2-(4-methoxyphenoxy)quinolin-3-yl]-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6c**)*

Yield 80 %, m.p. 191–193 °C, Anal. Calcd. for $C_{26}H_{21}N_3O_4$ (439.46 g/mol): C 71.06, H 4.82, N 9.56 % Found: C 70.92, H 4.67, N 9.35 %. IR (KBr, cm^{-1}): 3,430 and 3,320 (asym. and sym. stretching of $-NH_2$), 2,200 ($-C\equiv N$ stretching), 1,655 (–C=O str.), 1,200 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88–2.32 (m, 4H, CH_2), 2.57 (m, 2H, CH_2), 3.78 (s, 3H, OCH_3), 4.78 (s, 1H, CH), 7.10–8.09 (m, 11H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.62 (CH_2), 27.06 (CH_2), 32.27 (CH), 36.86 (CH_2), 55.88 (OCH_3), 56.29 (C–CN), 106.60, 120.01, 123.62, 126.11, 126.90, 127.03, 128.44, 128.98, 129.77, 132.03, 135.12, 138.17, 143.13, 153.33, 159.21, 159.80, 163.87 (Ar–C), 196.91 (C=O).

*2-Amino-4-(2-(4-fluorophenoxy)quinolin-3-yl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6d**)*

Yield 66 %, m.p. 225–227 °C, Anal. Calcd. for $C_{28}H_{18}FN_3O_3$ (427.43 g/mol): C 70.25, H 4.24, N 9.83 % Found: C 70.42, H 4.59, N 9.61 %. IR (KBr, cm^{-1}): 3,425 and 3,330 (asym. and sym. stretching of $-NH_2$), 2,240 ($-C\equiv N$ stretching), 1,660 (–C=O str.), 1,180 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.85–2.28 (m, 4H, CH_2), 2.58 (m, 2H, CH_2), 4.61 (s, 1H, CH), 7.05–8.10 (m, 11H, >Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.07 (CH_2), 27.00 (CH_2), 30.30 (CH), 36.79 (CH_2), 56.73 (C–CN), 112.88, 120.13, 123.75, 125.96, 126.76, 127.14, 128.28, 128.78, 130.03, 132.21, 135.07, 138.31, 143.28, 153.20, 159.13, 159.83, 164.81 (Ar–C), 196.91 (C=O).

*2-Amino-4-[6-methyl-2-phenoxyquinolin-3-yl]-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6e**)*

Yield 76 %, m.p. 173–175 °C, Anal. Calcd. for $C_{26}H_{21}N_3O_3$ (423.46 g/mol): C 73.74, H 5.00, N 9.92 % Found: C 73.62, H 4.96 N 10.11 %. IR (KBr, cm^{-1}): 3,405 and 3,315 (asym. and sym. stretching of $–NH_2$), 2,180 (–C≡N stretching), 1,680 (–C=O str.), 1,190 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.94–2.29 (m, 4H, CH_2), 2.43 (s, 3H, CH_3), 2.61 (m, 2H, CH_2), 4.77 (s, 1H, CH), 7.12–7.99 (m, 11H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.25 (CH_2), 21.49 (CH_3), 27.14 (CH_2), 31.86 (CH), 36.83 (CH_2), 57.40 (C–CN), 113.07, 120.30, 123.62, 126.53, 126.94, 127.14, 128.23, 128.91, 129.77, 132.11, 135.04, 138.31, 143.28, 153.22, 159.21, 159.81, 165.80 (Ar–C), 196.40 (C=O).

*2-Amino-4-[6-methyl-2-(4-methylphenoxy)quinolin-3-yl]-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6f**)*

Yield 80 %, m.p. 263–265 °C, Anal. Calcd. for $C_{27}H_{23}N_3O_3$ (437.49 g/mol): C 74.12, H 5.30, N 9.60 % Found: C 74.22, H 5.44, N 9.75 %. IR (KBr, cm^{-1}): 3,430 and 3,295 (asym. and sym. stretching of $–NH_2$), 2,245 (–C≡N stretching), 1,700 (–C=O str.), 1,215 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84–2.25 (m, 4H, CH_2), 2.42 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.55 (m, 2H, CH_2), 4.73 (s, 1H, CH), 7.04–8.06 (m, 10H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.42 (CH_2), 20.86 (CH_3), 21.37 (CH_3), 27.19 (CH_2), 34.45 (CH), 36.84 (CH_2), 56.35 (C–CN), 106.10, 119.94, 122.93, 126.46, 126.80, 126.99, 128.54, 128.82, 129.90, 132.00, 134.89, 138.19, 143.17, 153.20, 159.00, 159.81, 164.07 (Ar–C), 196.58 (C=O).

*2-Amino-4-[6-methyl-2-(4-methoxyphenoxy)quinolin-3-yl]-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6g**)*

Yield 84 %, m.p. 167–168 °C, Anal. Calcd. for $C_{27}H_{23}N_3O_4$ (453.49 g/mol): C 71.51, H 5.11, N 9.27 % Found: C 71.39, H 5.00, N 9.42 %. IR (KBr, cm^{-1}): 3,450 and 3,310 (asym. and sym. stretching of $–NH_2$), 2,250 (–C≡N stretching), 1,660 (–C=O str.), 1,250 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.85–2.30 (m, 4H, CH_2), 2.45 (s, 3H, CH_3), 2.60 (m, 2H, CH_2), 3.76 (s, 3H, OCH_3), 4.80 (s, 1H, CH), 7.15–8.10 (m, 10H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.20 (CH_2), 21.43 (CH_3), 27.11 (CH_2), 33.37 (CH), 36.71 (CH_2), 55.87 (OCH_3), 56.19 (C–CN), 110.12, 120.31, 123.54, 126.40, 126.89, 127.01, 128.53, 128.93, 130.01, 132.16, 134.89, 138.30, 143.25, 153.15, 159.00, 159.81, 165.45 (Ar–C), 196.39 (C=O).

*2-Amino-4-[6-methyl-2-(4-fluorophenoxy)quinolin-3-yl]-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6h**)*

Yield 64 %, m.p. 284–285 °C, Anal. Calcd. for $C_{26}H_{20}FN_3O_3$ (441.45 g/mol): C 70.74, H 4.57, N 9.52 % Found: C 70.58, H 4.71, N 9.50 %. IR (KBr, cm^{-1}): 3,435 and 3,320 (asym. and sym. stretching of $–NH_2$), 2,220 (–C≡N stretching), 1,695 (–C=O str.), 1,235 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.92–2.33 (m, 4H, CH_2), 2.44 (s, 3H, CH_3), 2.58 (m, 2H, CH_2), 4.66 (s, 1H, CH), 7.06–8.12 (m, 10H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.31 (CH_2), 21.38 (CH_3), 27.08 (CH_2), 32.27 (CH), 36.84 (CH_2), 56.30 (C–CN), 112.44, 120.27, 123.53, 126.46, 126.81, 127.00, 128.55, 128.83, 129.93, 132.06, 134.97, 138.25, 143.20, 153.16, 159.04, 159.75, 165.86 (Ar–C), 196.50 (C=O). $m/z = 442.69\ [M + 1]^+$

*2-Amino-4-[6-methoxy-2-phenoxyquinolin-3-yl]-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6i**)*

Yield 67 %, m.p. 207–208 °C, Anal. Calcd. for $C_{26}H_{21}N_3O_4$ (439.46 g/mol): C 71.06, H 4.82, N 9.56 % Found: C 71.18, H 5.00, N 9.38 %. IR (KBr, cm^{-1}): 3,435 and 3,310 (asym. and sym. stretching of $–NH_2$), 2,210 (–C≡N stretching), 1,665 (–C=O str.), 1,220 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81–2.31 (m, 4H, CH_2), 2.65 (m, 2H, CH_2), 3.89 (s, 3H, OCH_3), 4.70 (s, 1H, CH), 7.00–8.07 (m, 11H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.57 (CH_2), 27.16 (CH_2), 32.07 (CH), 36.80 (CH_2), 55.93 (OCH_3), 57.27 (C–CN), 112.55, 120.35, 123.71, 126.41, 126.86, 127.14, 128.24, 128.92, 130.02, 132.15, 134.83, 138.20, 143.21, 153.78, 158.98, 159.66, 164.97 (Ar–C), 196.55 (C=O).

*2-Amino-4-[6-methoxy-2-(4-methylphenoxy)quinolin-3-yl]-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6j**)*

Yield 80 %, m.p. 290–291 °C, Anal. Calcd. for $C_{27}H_{23}N_3O_4$ (453.49 g/mol): C 71.51, H 5.11, N 9.27 % Found: C 71.62, H 5.14, N 9.46 %. IR (KBr, cm^{-1}): 3,415 and 3,290 (asym. and sym. stretching of $–NH_2$), 2,210 (–C≡N stretching), 1,675 (–C=O str.), 1,185 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90–2.27 (m, 4H, CH_2), 2.44 (s, 3H, CH_3), 2.59 (m, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.60 (s, 1H, CH), 7.14–8.10 (m, 10H, Ar–H + NH_2). ^{13}C NMR

(100 MHz, DMSO-d_6) δ: 20.26 (CH_2), 20.88 (CH_3), 27.20 (CH_2), 33.71 (CH), 36.81 (CH_2), 55.95 (OCH_3), 56.05 (C–CN), 106.65, 120.38, 123.03, 126.12, 126.57, 127.12, 128.16, 128.76, 129.64, 132.13, 134.82, 138.13, 143.15, 153.00, 159.04, 159.80, 163.58 (Ar–C), 196.20 (C=O).

*2-Amino-4-[6-methoxy-2-(4-methoxyphenoxy)quinolin-3-yl]-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6k**)*

Yield 88 %, m.p. 184–185 °C, Anal. Calcd. for $C_{27}H_{23}N_3O_5$ (469.49 g/mol): C 69.07, H 4.94, N 8.95 % Found: C 69.14, H 5.07, N 8.88 %. IR (KBr, cm^{-1}): 3,405 and 3,300 (asym. and sym. stretching of $–NH_2$), 2,200 (–C≡N stretching), 1,670 (–C=O str.), 1,170 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87–2.34 (m, 4H, CH_2), 2.56 (m, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.63 (s, 1H, CH), 7.15–8.13 (m, 10H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.01 (CH_2), 27.07 (CH_2), 34.44 (CH), 36.85 (CH_2), 55.86 (OCH_3), 55.90 (OCH_3), 56.39 (C–CN), 111.96, 119.77, 123.42, 125.38, 126.73, 127.21, 128.63, 129.12, 130.01, 132.15, 135.02, 138.17, 143.25, 153.22, 159.00, 159.81, 162.11 (Ar–C), 196.37 (C=O).

*2-Amino-4-[6-methoxy-2-(4-fluorophenoxy)quinolin-3-yl]-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6l**)*

Yield 70 %, m.p. 276–278 °C, Anal. Calcd. for $C_{26}H_{20}FN_3O_4$ (457.45 g/mol): C 68.26, H 4.41, N 9.19 % Found: C 68.32, H 4.63, N 9.49 %. IR (KBr, cm^{-1}): 3,400 and 3,335 (asym. and sym. stretching of $–NH_2$), 2,190 (–C≡N stretching), 1,700 (–C=O str.), 1,210 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.92–2.33 (m, 4H, CH_2), 2.63 (m, 2H, CH_2), 3.82 (s, 3H, OCH_3), 4.65 (s, 1H, CH), 7.01–8.07 (m, 10H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.24 (CH_2), 27.12 (CH_2), 31.20 (CH), 36.76 (CH_2), 55.89 (OCH_3), 56.30 (C–CN), 112.11, 121.01, 123.24, 125.93, 127.15, 127.76, 128.02, 128.80, 129.88, 132.17, 136.02, 138.31, 143.81, 153.34, 159.00, 159.84, 165.88 (Ar–C), 196.50 (C=O).

*2-Amino-4-[2-phenoxyquinolin-3-yl]-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6m**)*

Yield 75 %, m.p. 245–246 °C, Anal. Calcd. for $C_{27}H_{23}N_3O_3$ (437.49 g/mol): C 74.12, H 5.30, N 9.60 % Found: C 74.31, H 5.43, N 9.29 %. IR (KBr, cm^{-1}): 3,420 and 3,300 (asym. and sym. stretching of $–NH_2$), 2,225 (–C≡N stretching), 1,685 (–C=O str.), 1,205 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.05 (s, 3H, CH_3), 1.06 (s, 3H, CH_3) 2.16 (dd, 2H, CH_2), 2.55 (s, 2H, CH_2), 4.80 (s, 1H, CH), 7.17–8.10 (m, 12H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.65 (CH_3), 28.78 (CH_3), 32.26 (C), 39.61 (CH), 40.23 (CH_2), 50.49 (CH_2), 57.16 (C–CN), 111.40, 113.34, 120.12, 121.50, 121.82, 127.03, 128.30, 130.41, 133.64, 137.98, 139.00, 140.38, 152.06, 156.63, 158.51, 160.01, 163.83 (Ar–C), 196.32 (C=O).

*2-Amino-4-[2-(4-methylphenoxy)quinolin-3-yl]-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6n**)*

Yield 65 %, m.p. 271–272 °C, Anal. Calcd. for $C_{28}H_{25}N_3O_3$ (451.52 g/mol): C 74.48, H 5.58, N 9.31 % Found: C 74.52, H 5.64, N 9.47 %. IR (KBr, cm^{-1}): 3,450 and 3,310 (asym. and sym. stretching of $–NH_2$), 2,205 (–C≡N stretching), 1,650 (–C=O str.), 1,200 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.03 (s, 3H, CH_3), 1.04 (s, 3H, CH_3) 2.11 (dd, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.54 (s, 2H, CH_2), 4.78 (s, 1H, CH), 7.03–8.08 (m, 11H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.47 (CH_3), 27.20 (CH_3), 29.05 (CH_3), 32.17 (C), 38.45 (CH), 40.35 (CH_2), 50.46 (CH_2), 56.41 (C–CN), 111.40, 113.76, 120.41, 121.47, 122.04, 127.11, 128.31, 130.45, 133.58, 137.87, 139.14, 140.48, 152.14, 156.83, 158.51, 159.87, 163.89 (Ar–C), 196.40 (C=O).

*2-Amino-4-[2-(4-methoxyphenoxy)quinolin-3-yl]-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6o**)*

Yield 74 %, m.p. 180–181 °C, Anal. Calcd. for $C_{28}H_{25}N_3O_4$ (467.52 g/mol): C 71.93, H 5.39, N 8.99 % Found: C 72.02, H 5.58, N 9.21 %. IR (KBr, cm^{-1}): 3,390 and 3,310 (asym. and sym. stretching of $–NH_2$), 2,200 (–C≡N stretching), 1,705 (–C=O str.), 1,210 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.99 (s, 3H, CH_3), 1.05 (s, 3H, CH_3) 2.14 (dd, 2H, CH_2), 2.57 (s, 2H, CH_2), 3.76 (s, 3H, OCH_3), 4.63 (s, 1H, CH), 7.11–7.97 (m, 11H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.42 (CH_3), 28.75 (CH_3), 32.16 (C), 40.33 (CH_2), 42.25 (CH), 50.53 (CH_2), 55.88 (OCH_3), 56.32 (C–CN), 108.78, 111.44, 120.41, 121.14, 121.82, 127.13, 128.31, 130.45, 133.86, 137.72, 139.16, 140.64, 152.11, 156.52, 158.32, 159.83, 162.78 (Ar–C), 196.42 (C=O).

*2-Amino-4-[2-(4-fluorophenoxy)quinolin-3-yl]-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6p**)*

Yield 70 %, m.p. 253–254 °C, Anal. Calcd. for $C_{27}H_{22}FN_3O_3$ (455.48 g/mol): C 71.20, H 4.87, N 9.23 % Found: C 71.37,

H 4.96, N 9.44 %. IR (KBr, cm^{-1}): 3,450 and 3,305 (asym. and sym. stretching of $–NH_2$), 2,235 (–C≡N stretching), 1,685 (–C=O str.), 1,180 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.04 (s, 3H, CH_3), 1.07 (s, 3H, CH_3) 2.15 (dd, 2H, CH_2), 2.49 (s, 2H, CH_2), 4.67 (s, 1H, CH), 7.05–8.05 (m, 11H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.36 (CH_3), 28.80 (CH_3), 32.32 (C), 40.39 (CH_2), 40.49 (CH), 50.45 (CH_2), 56.18 (C–CN), 106.75, 110.95, 120.24, 121.44, 121.98, 126.94, 128.54, 130.31, 133.98, 138.02, 139.15, 140.78, 152.17, 156.86, 158.50, 160.01, 163.97 (Ar–C), 196.49 (C=O).

*2-Amino-4-[6-methyl-2-phenoxyquinolin-3-yl]-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6q**)*

Yield 87 %, m.p. 212–213 °C, Anal. Calcd. for $C_{28}H_{25}N_3O_3$ (451.52 g/mol): C 74.48, H 5.58, N 9.31 % Found: C 74.52, H 5.70, N 9.33 %. IR (KBr, cm^{-1}): 3,430 and 3,325 (asym. and sym. stretching of $–NH_2$), 2,185 (–C≡N stretching), 1,655 (–C=O str.), 1,225 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.04 (s, 3H, CH_3), 1.05 (s, 3H, CH_3) 2.12 (dd, 2H, CH_2), 2.47 (s, 3H, CH_3), 2.58 (s, 2H, CH_2), 4.69 (s, 1H, CH), 7.00–8.07 (m, 11H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.42 (CH_3), 27.23 (CH_3), 28.73 (CH_3), 32.27 (C), 40.30 (CH_2), 41.50 (CH), 50.51 (CH_2), 57.17 (C–CN), 106.25, 111.49, 120.45, 121.63, 121.95, 126.94, 128.30, 130.34, 133.84, 137.83, 139.11, 140.52, 152.23, 156.87, 158.54, 159.68, 164.49 (Ar–C), 196.45 (C=O).

*2-Amino-4-[6-methyl-2-(4-methylphenoxy)quinolin-3-yl]-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6r**)*

Yield 82 %, m.p. 274–275 °C, Anal. Calcd. for $C_{29}H_{27}N_3O_3$ (465.54 g/mol): C 74.82, H 5.85, N 9.03 % Found: C 75.01, H 5.74, N 8.91 %. IR (KBr, cm^{-1}): 3,410 and 3,325 (asym. and sym. stretching of $–NH_2$), 2,220 (–C≡N stretching), 1,665 (–C=O str.), 1,195 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.97 (s, 3H, CH_3), 1.07 (s, 3H, CH_3) 2.16 (dd, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 2.56 (s, 2H, CH_2), 4.66 (s, 1H, CH), 7.02–7.95 (m, 10H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.96 (CH_3), 21.38 (CH_3), 27.28 (CH_3), 28.75 (CH_3), 32.35 (C), 40.15 (CH), 40.29 (CH_2), 50.59 (CH_2), 56.30 (C–CN), 106.69, 111.46, 119.88, 121.39, 121.64, 127.00, 128.31, 130.31, 133.82, 138.02, 139.15, 140.46, 152.11, 156.81, 158.51, 159.84, 163.83 (Ar–C), 196.50 (C=O).

*2-Amino-4-[6-methyl-2-(4-methoxyphenoxy)quinolin-3-yl]-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6s**)*

Yield 75 %, m.p. 280–281 °C, Anal. Calcd. for $C_{29}H_{27}N_3O_4$ (481.54 g/mol): C 72.33, H 5.65, N 8.73 % Found: C 72.10, H 5.90, N 8.82 %. IR (KBr, cm^{-1}): 3,410 and 3,320 (asym. and sym. stretching of $–NH_2$), 2,200 (–C≡N stretching), 1,675 (–C=O str.), 1,200 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.01 (s, 3H, CH_3), 1.04 (s, 3H, CH_3) 2.15 (dd, 2H, CH_2), 2.44 (s, 3H, CH_3), 2.55 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 4.72 (s, 1H, CH), 7.18–8.12 (m, 10H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.39 (CH_3), 27.31 (CH_3), 28.30 (CH_3), 32.22 (C), 39.48 (CH), 40.36 (CH_2), 50.50 (CH_2), 55.87 (OCH_3), 57.10 (C–CN), 106.97, 111.36, 120.28, 121.23, 121.89, 127.16, 128.54, 130.32, 133.89, 138.05, 139.17, 140.65, 152.15, 156.87, 158.51, 159.89, 164.91 (Ar–C), 196.25 (C=O).

*2-Amino-4-[6-methyl-2-(4-fluorophenoxy)quinolin-3-yl]-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6t**)*

Yield 67 %, m.p. 240–241 °C, Anal. Calcd. for $C_{28}H_{24}FN_3O_3$ (469.51 g/mol): C 71.63, H 5.15, N 8.95 % Found: C 71.46, H 5.26, N 9.13 %. IR (KBr, cm^{-1}): 3,415 and 3,295 (asym. and sym. stretching of $–NH_2$), 2,210 (–C≡N stretching), 1,690 (–C=O str.), 1,175 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.96 (s, 3H, CH_3), 1.03 (s, 3H, CH_3) 2.10 (dd, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.60 (s, 2H, CH_2), 4.73 (s, 1H, CH), 7.05–8.11 (m, 10H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.45 (CH_3), 27.44 (CH_3), 29.00 (CH_3), 32.19 (C), 40.25 (CH_2), 42.17 (CH), 50.41 (CH_2), 57.50 (C–CN), 112.40, 112.43, 119.75, 121.23, 121.69, 127.14, 128.31, 130.42, 133.84, 138.11, 139.13, 140.60, 152.11, 156.81, 158.12, 160.04, 162.50 (Ar–C), 196.60 (C=O).

*2-Amino-4-[6-methoxy-2-phenoxyquinolin-3-yl]-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6u**)*

Yield 73 %, m.p. 220–221 °C, Anal. Calcd. for $C_{28}H_{25}N_3O_4$ (467.52 g/mol): C 71.93, H 5.39, N 8.99 % Found: C 71.87, H 5.57, N 9.13 %. IR (KBr, cm^{-1}): 3,400 and 3,340 (asym. and sym. stretching of $–NH_2$), 2,205 (–C≡N stretching), 1,680 (–C=O str.), 1,215 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.05 (s, 3H, CH_3), 1.08 (s, 3H, CH_3) 2.19 (dd, 2H, CH_2), 2.53 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 4.67 (s, 1H, CH), 7.06–8.03 (m, 11H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.38 (CH_3),

28.47 (CH_3), 32.23 (C), 38.67 (CH), 40.38 (CH_2), 50.55 (CH_2), 55.94 (OCH_3), 57.21 (C–CN), 109.08, 111.37, 120.31, 121.61, 121.84, 126.24, 128.32, 130.33, 133.84, 137.83, 139.17, 140.55, 151.57, 156.80, 158.51, 160.13, 165.03 (Ar–C), 196.47 (C=O).

*2-Amino-4-[6-methoxy-2-(4-methylphenoxy)quinolin-3-yl]-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6v**)*

Yield 89 %, m.p. 199–201 °C, Anal. Calcd. for $C_{28}H_{27}N_3O_4$ (481.54 g/mol): C 72.33, H 5.65, N 8.73 % Found: C 72.40, H 5.73, N 8.86 %. IR (KBr, cm^{-1}): 3,430 and 3,320 (asym. and sym. stretching of $–NH_2$), 2,200 (–C≡N stretching), 1,680 (–C=O str.), 1,250 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.98 (s, 3H, CH_3), 1.04 (s, 3H, CH_3) 2.13 (dd, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.55 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.62 (s, 1H, CH), 7.01–8.10 (m, 10H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.89 (CH_3), 27.43 (CH_3), 28.77 (CH_3), 32.26 (C), 40.31 (CH_2), 40.47 (CH), 50.54 (CH_2), 55.91 (OCH_3), 56.18 (C–CN), 106.67, 111.36, 120.30, 121.52, 121.71, 127.07, 128.28, 130.25, 133.71, 137.94, 139.02, 140.41, 152.09, 156.72, 158.47, 159.92, 163.88 (Ar–C), 196.38 (C=O). $m/z = 482.27\ [M + 1]^+$

*2-Amino-4-[6-methoxy-2-(4-methoxyphenoxy)quinolin-3-yl]-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6w**)*

Yield 87 %, m.p. 249–250 °C, Anal. Calcd. for $C_{29}H_{27}N_3O_5$ (497.54 g/mol): C 70.01, H 5.47, N 8.45 % Found: C 69.92, H 5.64, N 8.70 %. IR (KBr, cm^{-1}): 3,415 and 3,300 (asym. and sym. stretching of $–NH_2$), 2,190 (–C≡N stretching), 1,695 (–C=O str.), 1,230 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.03 (s, 3H, CH_3), 1.09 (s, 3H, CH_3) 2.20 (dd, 2H, CH_2), 2.52 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.71 (s, 1H, CH), 7.08–8.08 (m, 10H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.38 (CH_3), 28.71 (CH_3), 32.30 (C), 39.30 (CH), 40.38 (CH_2), 50.42 (CH_2), 55.86 (OCH_3), 55.86 (OCH_3), 56.31 (C–CN), 112.37, 111.41, 120.42, 121.65, 122.04, 127.23, 128.33, 130.37, 133.44, 138.02, 139.34, 140.52, 152.23, 156.54, 158.51, 159.74, 165.70 (Ar–C), 196.49 (C=O).

*2-Amino-4-[6-methoxy-2-(4-fluorophenoxy)quinolin-3-yl]-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (**6x**)*

Yield 70 %, m.p. 258–259 °C, Anal. Calcd. for $C_{28}H_{24}FN_3O_4$ (485.51 g/mol): C 69.27, H 4.98, N 8.65 % Found: C 69.36, H 4.86, N 8.73 %. IR (KBr, cm^{-1}): 3,425 and 3,320 (asym. and sym. stretching of $–NH_2$), 2,230 (–C≡N stretching), 1,670 (–C=O str.), 1,225 (C–O–C ether stretching). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.00 (s, 3H, CH_3), 1.04 (s, 3H, CH_3) 2.14 (dd, 2H, CH_2), 2.51 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.75 (s, 1H, CH), 7.09–8.14 (m, 10H, Ar–H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.66 (CH_3), 28.69 (CH_3), 32.25 (C), 40.27 (CH_2), 39.49 (CH), 50.47 (CH_2), 55.92 (OCH_3), 56.49 (C–CN), 106.08, 111.28, 119.98, 121.38, 121.84, 127.12, 128.33, 130.09, 133.44, 137.95, 139.04, 140.33, 152.11, 156.83, 158.51, 160.00, 165.88 (Ar–C), 196.41 (C=O).

Conclusion

A series of some new 4*H*-chromene derivatives containing 2-aryloxyquinoline moiety **6a–x** have been synthesized through a facile one-pot multicomponent reaction by the microwave irradiation method. This synthetic strategy allows the construction of relatively complicated nitrogen- and oxygen-containing heterocyclic system as well as the introduction of various heteroaromatic substitutions into 4-positions of pyrane. It can be concluded from antimicrobial screening (Table 2), against a panel of human pathogens, that many of the synthesized above derivatives are found to be highly active, compared to standard drugs, against *B. subtilis* and *C. tetani* bacterial pathogens.

The interesting point to be noted is that compounds **6f** (R_1=CH_3, R_2=CH_3, R_3=H), **6q** (R_1=CH_3, R_2=H, R_3=CH_3), and **6r** (R_1=CH_3, R_2=CH_3, R_3=CH_3) having CH_3 substituent on all of the three positions $\mathbf{R_1}$, $\mathbf{R_2}$, and $\mathbf{R_3}$ or at any two position are more or equally potent to ampicilin against the three Gram-positive bacteria. Also, the compounds **6o** (R_1=H, R_2=OCH_3, R_3=CH_3) and **6s** (R_1=CH_3, R_2=OCH_3, R_3=CH_3) having OCH_3 substituent at $\mathbf{R_2}$ and CH_3 substituent at $\mathbf{R_3}$ are found active against Gram-positive bacteria.

Examination of the antifungal activity of the compounds reveals that most of the compounds of the present series are potent against *C. albicans*, but having poor activity against *A. fumigatus*. It is worth mentioning that a minor change in molecular configuration of these compounds profoundly influences the activity. 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.

Acknowledgments We are thankful to the Department of Chemistry, Sardar Patel University, for providing research facilities. We are also thankful to the Vaibhav Analytical Laboratory, Ahmedabad, for the FT-IR; the Sophisticated Instrumentation Centre for Applied Research and Training (SICART), Vallabh Vidyanagar, for elemental analysis; Oxygen Healthcare Research Pvt. Ltd., Ahmadabad, for providing mass spectrometry facilities; and Microcare Laboratory,

Surat, for antimicrobial screening of the compounds reported herein. One of the authors is grateful to UGC, New Delhi, for a Research Fellowship in Sciences for Meritorious Students.

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