Bioorganic & Medicinal Chemistry Letters 22 (2012) 1643–1648

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Camphorsulfonic acid catalysed facile tandem double Friedlander annulation protocol for the synthesis of phenoxy linked bisquinoline derivatives and discovery of antitubercular agents

Nidhin Paul [a], Muthuchamy Murugavel [a], Shanmugam Muthusubramanian [a,*], Dharmarajan Sriram [b]

[a] Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625021, Tamil Nadu, India
[b] Medicinal Chemistry & Antimycobacterial Research Laboratory, Pharmacy Group, Birla Institute of Technology & Science – Pilani, Hyderabad Campus, Jawahar Nagar, Hyderabad 500 078, Andhra Pradesh, India

ARTICLE INFO

Article history:
Received 29 July 2011
Revised 1 December 2011
Accepted 26 December 2011
Available online 10 January 2012

Keywords:
Double Friedlander annulation
Bisquinoline
(±)-Camphor-10-sulfonic acid (CSA)
Antimycobacterial activity
Mycobacterium tuberculosis

ABSTRACT

A series of phenoxy linked bisquinoline derivatives were synthesised from the Friedlander annulation of 2-(4-acetylphenoxy)-1-aryl-1-ethanones with 2-aminobenzophenone in good yields using (±)-camphor-10-sulfonic acid (CSA) as the catalyst. These compounds were screened for their in vitro activity against *Mycobacterium tuberculosis* H37Rv (MTB) and among the 23 compounds screened, 2-(3-bromophenyl)-6-chloro-3-[4-(6-chloro-4-phenyl-2-quinolyl)phenoxy]-4-phenylquinoline (**3q**) and 2-(4-bromophenyl)-6-chloro-3-[4-(6-chloro-4-phenyl-2-quinolyl)phenoxy]-4-phenylquinoline (**3o**) were found to be the most active compounds with MIC of 1.1 and 2.2 μM against MTB. The cytotoxic effects against mouse fibroblasts (NIH 3T3) in vitro were evaluated for **3o** and **3q**, which displayed no toxic effects against mouse fibroblast cell line NIH 3T3.

The control of tuberculosis (TB) remains one of the most serious challenges of human health. World Health Organization has estimated that nearly a third of the world population is now infected with *Mycobacterium tuberculosis* and 5–10% of the infected individuals will develop active TB disease during their life time.[1] There are also approximately 400,000 new annual cases of TB caused by multi-drug-resistant strains (MDR) that are resistant to isoniazid (INH) and rifampicin (RMP).[2,3] HIV positive patients are more susceptible to MTB with a 50-fold risk increase over HIV negative patients.[4] Recently, the emergence of multi-drug resistant (MDR) strains and the global HIV pandemic have amplified the incidence of TB and have created an urgent need for alternative drug treatments for *M. tuberculosis* infection.[5] At present the most widely used TB treatment regimen DOTS (directly observed therapy short-course) requires taking isoniazid, pyrazinamide and rifampicin for two months followed by an additional four months of treatment with isoniazid and rifampicin alone.[6,7]

Compounds containing a quinoline skeleton have been found applications as pharmaceuticals and agrochemicals, as well as being general synthetic building blocks.[8,9] Quinoline is a ubiquitous sub-structure found in various biologically active natural products[10] and is also found in various drugs such as mefloquine, an antimalarial,[11] talnetant, a potential NK3 receptor antagonist developed by GSK,[12] irinotecan, an anticancer drug[13] and TAK-603, an antirheumatic drug[14] (Fig. 1). The biological activity of quinoline compounds has also been found in the form of antitumor activity,[15] antimicrobial and antioxidant,[16] antiplasmodial activity,[17] HIV-1 Tat–TAR interaction inhibitors[18] and selective PDE4 (phosphodiesterase) inhibitors.[19] Bisquinolines are compounds with two quinoline nuclei bound by a covalent aliphatic or aromatic link and this skeleton occurs in very few natural compounds and pharmacologically active drugs displaying antimalarial activity.[20] The core ring of the natural bisquinoline alkaloid has emerged as a model for synthetic drug design.[21] Bisquinoline alkaloids and their derivatives have been given special attention due to their antimalarial and anticancer activities through the bis-intercalation formation[22,23] with the DNA double helix.[24–26] In addition, the bisquinoline systems display very interesting biological activities such as in vitro antileishmanial, antimicrobial (a panel of pathogenic bacteria and fungi), cytotoxicity, β-hematin inhibitory and methemoglobin (MetHb) formation activities.[27] They also act as antifilarial agent,[28] triple-helix DNA intercalators and antagonists of immunostimulatory CpG-oligodeoxynucleotides.[29] It is pertinent to note that many recently reported monoquinolines were screened against TB.[30] The diarylquinoline drug TMC207 (Fig. 1) is in phase 2 clinical trials and is very promising against MDR-TB.[31] Recently Mital et al. reported that the bisquinolines,

* Corresponding author. Tel./fax: +91 452 2459845.
E-mail address: muthumanian2001@yahoo.com (S. Muthusubramanian).

0960-894X/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2011.12.119

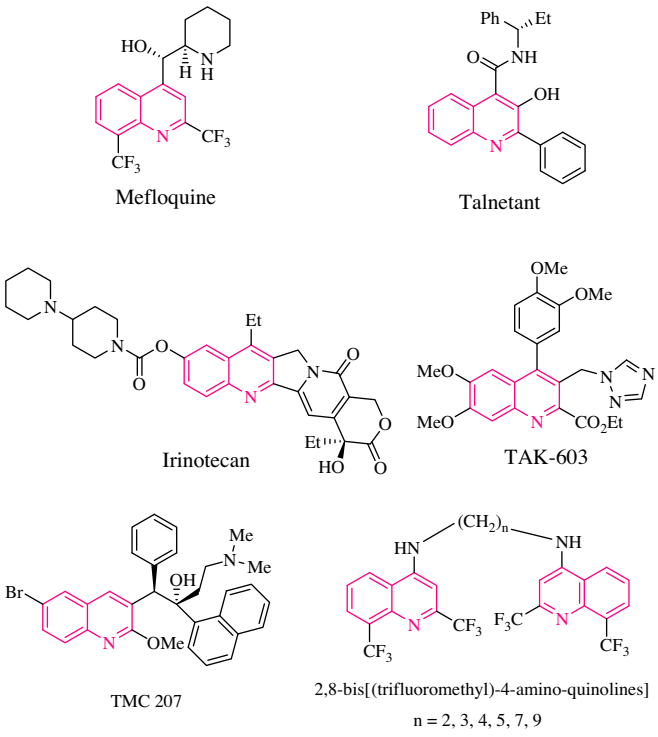


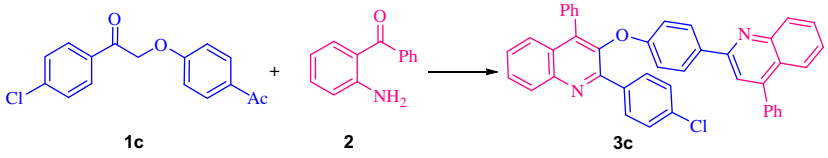
Figure 1. Chemical structures of mono and bisquinoline drugs.

4-amino substituted 2,8-bis(trifluoromethyl)quinoline derivatives (Fig. 1), have been found to have moderate anti-TB activity against *Mycobacterium tuberculosis* (MTB) strain H37Rv.[32]

In this context, as a continuation of our previous work on the discovery of novel heterocyclic compounds and their antimicrobial activities,[33] we decided to focus our attention on the synthesis and preliminary biological evaluation against MTB of mono and bisquinolines. To the best of our knowledge the bisquinolines have not been screened as antitubercular agents, either as a core or incorporated as substituent in other base structures. Herein, we describe the synthesis and the in vitro activity against *M. tuberculosis* strain H37Rv of a novel structural class of bisquinolines.

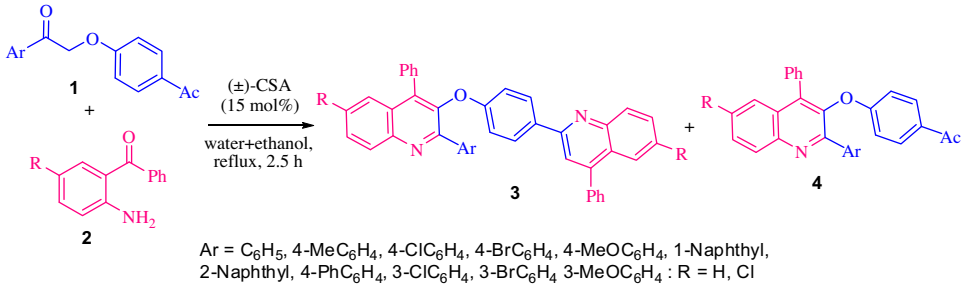
Our initial experiments were focused on the Friedlander reaction of 2-(4-acetylphenoxy)-1-aryl-1-ethanones **1** with 2-aminobenzophenone **2** (1:2) using different catalysts under reflux in water–ethanol (1:1) solvent system, and the results are listed in Table 1 (Scheme 1). It was found that (±)-camphor-10-sulfonic acid (CSA) showed better catalytic activity among other catalysts such as *p*-toluenesulfonic acid, mineral acids, $FeCl_3$, $SbCl_3$, $ZnCl_2$, $SnCl_2{\cdot}6H_2O$, $LaCl_3{\cdot}7H_2O$ and $AlCl_3$. Over the past few years, (±)-camphor-10-sulfonic acid (CSA) is emerging as a powerful non-toxic, inexpensive, eco-friendly, readily available, economical and water soluble Bronsted acid catalyst for various organic transformations.[34] When 15 mol % (±)-camphor-10-sulfonic acid was used, the reaction proceeded smoothly and gave the product **3c** in 85% yield (Table 1). Moreover, we found that the yields were obviously affected by the amount of camphor-10-sulfonic acid loaded. When

Table 1
Catalyst screening for the synthesis of **3c** in water–ethanol medium



Entry	Catalyst	Mol %	Time (h)	Yield of **3c**[a] (%)
1	*p*-TsOH	50	5	67
2	HCl	30	5	54
3	H_2SO_4	30	5	53
4	$AlCl_3$	75	6	28
5	$ZnCl_2$	75	6	34
6	$FeCl_3$	75	6	22
7	$SbCl_3$	35	4	30
8	$SnCl_2{\cdot}6H_2O$	50	4	35
9	$LaCl_3{\cdot}7H_2O$	35	3	24
10	(±)-CSA	**15**	**2.5**	**85**
11	(±)-CSA	5	4	34
12	(±)-CSA	10	3	57
13	(±)-CSA	20	3	84

[a] Isolated yield after purification by column chromatography.The optimized condition is given in bold.



Scheme 1. Synthesis of phenoxy linked bisquinoline derivatives.

5 mol %, 10 mol % and 20 mol % of camphor (±)-CSA were used, the yields were 34%, 57%, and 84%, respectively (Table 1). After optimizing the reaction conditions, different bisquinolines **3a–k** (74–87%) have been obtained using this protocol (Table 2). Only traces of monoquinolines have been noticed in the NMR spectra of crude reaction products. However, when the reaction of **1** with 5-chloro-2-aminobenzophenone was effected under same reaction condition, considerable amount of monoquinolines **4l–q** (6–11%) were isolated, along with the major bisquinolines **3l–q** (76–83%) (Table 2).

The structures of the phenoxy linked bisquinolines, **3** were established from ^{1}H, ^{13}C and 2D NMR spectroscopic data as illustrated for a representative example **3n**.[35] In the ^{1}H NMR spectrum of **3n**, the *p*-chloro substituted aryl ring H-2′ proton appears as doublet at 7.96 ppm with $J = 8.4$ Hz, which shows (i) H,H-COSY with the doublet at 7.33 ppm ($J = 8.4$ Hz), [H-3′ protons], (ii) C,H-COSY with the signal at 130.6 ppm assignable to C-2′ and (iii) HMBC with carbon signals at 131.4, 135.4 and 153.7 ppm ascribable to C-1′, C-4′ and C-2 respectively (Fig. 2). Further, H-3′ shows C,H-COSY with the signal at 128.6 ppm and HMBC with carbon signal at 135.4 ppm. The quinoline H-7 proton appears as doublet of doublet at 7.67 ppm with $J = 9.0$ and 1.8 Hz, which shows H,H-COSY with doublet at 8.17 ppm ($J = 9.0$ Hz, H-8), C,H-COSY with the signal at 128.7 ppm and HMBC with C-5 at 131.2 ppm. The doublet of H-8 proton shows HMBC with *ipso* C-4a at 131.9 ppm, C-6 at 133.2 ppm and C-7 at 128.7 ppm. The doublet at 7.59 is ascribable to H-5 and is having C,H-COSY correlation with the signal at 131.2 ppm and HMBC with C-6 at 133.2 ppm and C-8a at 147.0 ppm. The H-2″ proton of phenoxy ring appears as doublet at 6.62 ppm ($J = 8.7$ Hz) and gives: (i) H,H-COSY with the doublet at 7.86 ppm ($J = 8.7$ Hz), [H-3″ protons] (ii) C,H-COSY with the signal at 115.7 ppm and (iii) HMBC with *ipso* C-1″ at 158.8 ppm. The H-3″ proton shows C,H-COSY with carbon signal at 129.3 ppm and HMBC with C-4″ at 132.8 ppm and C-1″ at 158.8 ppm. The second quinoline ring is having a singlet at 7.63 ppm which is gives (i) C,H-COSY with the signal at 119.5 ppm assignable to C-3‴ and (ii) HMBC with carbon signals at 126.2, 137.6 and 156.0 ppm ascribable to C-4a‴, C-4‴ and C-2‴ respectively. H-8‴ proton appears as a doublet at 8.05 ppm with $J = 9.0$ Hz, which shows H,H-COSY with doublet of doublet at 7.61 ppm ($J = 9.0$, 2.1 Hz, H-7‴) and HMBC with C-4a‴ at 126.2 ppm and C-6‴ at 132.1 ppm. The structures of the monoquinolines, **4** were also established from ^{1}H, ^{13}C and 2D NMR spectroscopic data as illustrated for a representative example **4n**. In the spectrum of **4n**,[35] the doublet at 8.17 ppm with coupling constant 9.0 Hz is ascribable to H-8 and is having (i) H,H-COSY with the doublet of doublet at 7.67 ppm ($J = 9.0$, 1.8 Hz), [H-7 proton], (ii) C,H-COSY with the signal at 131.3 ppm assignable to C-8 and (iii) HMBC with carbon signals at 130.3 and 133.4 ppm (Fig. 3) ascribable to C-7 and C-6, respectively. Further the doublet of doublet at 7.67 ppm is giving (i) C, H-COSY with the signal at 130.3 ppm and (ii) HMBC with C-5 at 124.6 ppm and C-8a at 144.7 ppm. The doublet at 7.57 ppm with a coupling constant 1.8 Hz is ascribable to H-5 and is giving C,H-COSY correlation with the carbon signal at 124.6 ppm and HMBC with signals at 133.4, 140.3 and 144.7 ppm ascribable to C-6, C-4 and C-8a respectively. The H-2′ proton of *p*-chloro substituted aryl ring shows doublet at 7.91 ppm with $J = 8.7$ Hz, which has (i) H,H-COSY with the doublet at 7.33 ppm ($J = 8.7$ Hz), [H-3′ protons], (ii) C,H-COSY with the signal at 130.6 ppm assignable to C-2′ and (iii) HMBC with carbon signal at 135.5 ppm ascribable to C-1′. The doublet at 7.33 is giving C,H-COSY correlation with the signal at 128.4 ppm assignable to C-3′ and HMBC with carbon signals at 130.6, 135.2 and 135.5 assignable to C-2′, C-4′ and C-1′, respectively. The acetyl methyl hydrogens exhibit a singlet at 2.44 ppm with the corresponding carbon signal at 26.3 ppm. These hydrogens have HMBC connections with the signal at 131.9 ppm ascribable to C-4″. The doublet at 6.53 ppm with a coupling constant 9.0 Hz is due to H-2″ and is having (i) H,H-COSY with the doublet at 7.64 ppm ($J = 9.0$ Hz), [H-3″ proton], (ii) C,H-COSY correlation with the signal at 115.2 ppm assignable to C-2″ and (iii) HMBC with carbon signals at 131.9 and 161.0 ppm ascribable to C-4″ and C-1″ respectively. The doublet at 7.64 ppm is giving C,H-COSY correlation with carbon at 130.2 ppm and HMBC with C-1″ and carbonyl carbon at 196.5 ppm. The mass spectra for the compounds **3o** and **4o** have

Table 2
Yield and antimycobacterial activities of mono and bisquinolines

Compound	Ar	R	Yield[a] (%)		MIC (MTB) (μM)	
			3	**4**	**3**	**4**
a	C_6H_5	H	81	Trace[b]	43.4	—
b	4-MeC_6H_4	H	80	Trace[b]	42.3	—
c	4-ClC_6H_4	H	85	Trace[b]	20.5	—
d	4-BrC_6H_4	H	85	Trace[b]	19.1	—
e	4-MeOC_6H_4	H	87	Trace[b]	41.2	—
f	1-Naphthyl	H	76	Trace[b]	39.8	—
g	2-Naphthyl	H	74	Trace[b]	39.9	—
h	4-PhC_6H_4	H	80	Trace[b]	19.1	—
i	3-ClC_6H_4	H	81	Trace[b]	20.5	—
j	3-BrC_6H_4	H	78	Trace[b]	4.7	—
k	3-MeOC_6H_4	H	85	Trace[b]	41.2	—
l	C_6H_5	Cl	77	6	19.4	55.6
m	4-MeC_6H_4	Cl	81	8	37.9	53.8
n	4-ClC_6H_4	Cl	77	11	4.6	51.6
o	4-BrC_6H_4	Cl	80	7	2.2	47.3
p	2-Naphthyl	Cl	76	7	35.9	50.0
q	3-BrC_6H_4	Cl	83	6	1.1	11.8
	Isoniazid					0.4
	Rifampicin					0.1
	Ciprofloxacin					4.7
	Ethambutol					7.6
	Pyrazinamide					50.77

[a] Isolated yield after purification by column chromatography.
[b] Noticed in traces in the crude NMR spectra before purification.

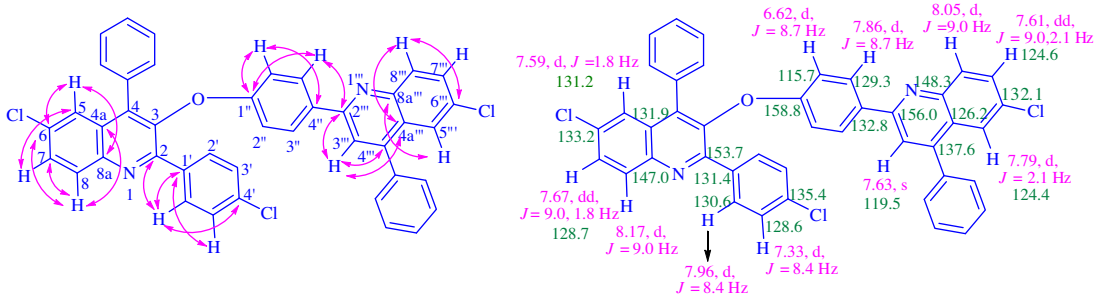


Figure 2. Selected HMBCs and chemical shifts of **3n**.

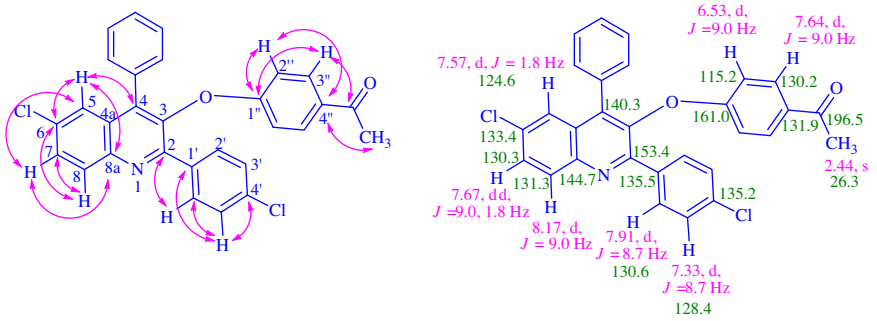
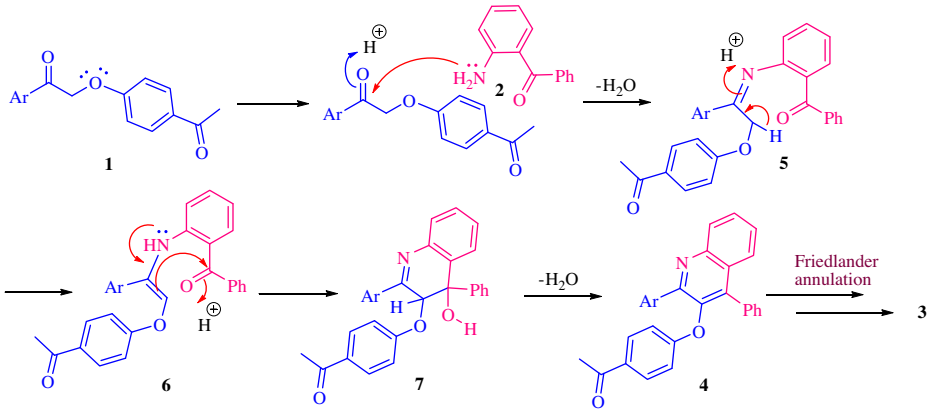
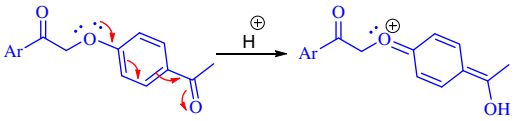


Figure 3. Selected HMBCs and chemical shifts of **4n**.



Scheme 2. Plausible mechanism for the formation of phenoxy linked bisquinolines **3**.



Scheme 3. Electron donation from phenoxy oxygen to acetyl carbonyl.

their [M+1] peaks at 723.0 (calcd. 722.0 [M^+]) and 528.0 (calcd. 527.0 [M^+]), respectively.

A possible reaction mechanism for the tandem double Friedlander reaction was proposed in Scheme 2. The condensation of 2-aminobenzophenone **2** and ketones **1** promoted by (±)-camphor-10-sulfonic acid (CSA) afforded the imine **5**, which tautomerises to furnish the enamine **6**, whose subsequent cyclization affords the monoquinoline derivatives **4**. This monoquinoline **4** undergoes another Friedlander reaction with 2-aminobenzophenone **2** to provide the bisquinolines **3**. It is to be noted that this stepwise reaction pathway proposed is further supported by the isolation of monoquinolines **4** as minor product. The Friedlander annulation takes place primarily on the phenoxy end carbonyl and not on the acetyl end, probably due to the fact that the electron donation from the phenoxy oxygen makes the acetyl carbonyl less electrophilic compared to the former (Scheme 3).

The compounds were screened for their in vitro antimycobacterial activity against MTB in Middlebrook 7H11 agar medium supplemented with OADC by agar dilution method for the determination of MIC in triplicates.[36] The MTB clinical isolate was resistant to isoniazid, rifampicin, ethambutol and ciprofloxacin. The minimum inhibitory concentration (MIC) of the synthesized compounds along with the standard drugs for comparison is reported in Table 1. All the twenty three compounds screened in the present study against MTB had MICs ranging from 1.1–55.6 μM and four compounds inhibited MTB with MIC less than 10 μM. In both series **3** and **4**, all the compounds showed moderate to good activity except **3a**, **3b**, **3e**, **3f**, **3g**, **3k**, **3m**, **4l**, **4m**, **4n**, **4o** and **4p**. Four compounds (**3j**, **3n**, **3o** and **3q**) showed good activity with MICs less than 10 μM. These four compounds with MICs ranging from 1.1–4.7 μM are more potent than the standard drug ethambutol[37] (MIC: 7.6 μM). When compared to ciprofloxacin[38] (MIC: 4.7 μM), three compounds **3n**, **3o** and **3q** were found to be more potent against MTB. In both series compounds **3c**, **3d**, **3h**, **3i**, **3l** and **4q** showed moderate activity with MIC ranging from 11.8 to 20.5. 2-(3-Bromophenyl)-6-chloro-3-[4-(6-chloro-4-phenyl-2-quinolyl)-phenoxy]-4-phenylquinoline (**3q**) was found to be the most active compound in vitro with MIC of 1.1 μM against MTB and was 4.27 times more potent than ciprofloxacin. 2-(4-Bromophenyl)-6-chloro-3-[4-(6-chloro-4-phenyl-2-quinolyl)phenoxy]-4-phenylquinoline (**3o**) was also found to be more active with MIC of 2.2 μM

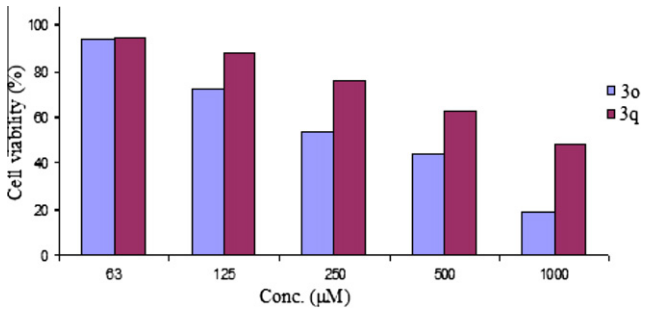


Figure 4. Comparison of cytotoxicity on NIH 3T3 cells after 48 h of incubation with compounds **3o** and **3q** using MTT assay.

against MTB and was 2.14 and 3.45 times more potent than ciprofloxacin and ethambutol, respectively.

With respect to the structure-MTB studies, introduction of substituents, particularly halogens, in the 6 and 6‴-positions of bisquinolines is found to have enhanced the activity. In general, the bisquinoline compounds showed better activity than the respective monoquinoline compounds.

The cytotoxicity of the compounds **3o** and **3q** were studied in vitro using NIH 3T3 mouse embryonic fibroblasts cell line (NIH 3T3) by MTT assay.[39] MTT is a yellow colored water soluble tetrazolium salt. A mitochondrial enzyme in living cells, succinate-dehydrogenase, cleaves the tetrazolium ring, converting the MTT to an insoluble purple formazan product that was read spectrophotometrically at 570 nm on the basis of linear absorbance to the number of living cells in culture. The MTT assay was validated using various concentrations of DMSO. A dose response graph given in Figure 4 reveals that the percentage cell viability was decreased with increasing the concentration of both **3o** and **3q**. However, the half maximal inhibitory concentration (IC_{50}) value determined by GraphPad Prism software was found to be 333 μM for **3o** and 887 μM for **3q**. This indicates that the synthesized compounds **3o** and **3q** are not toxic to the normal fibroblasts (NIH 3T3).

In conclusion, we have synthesised phenoxy linked bisquinolines using (±)-camphor-10-sulfonic acid (CSA) as a metal free catalyst under reflux condition via the tandem double Friedlander annulation reaction. The simple experimental procedure, good yield and utilization of an inexpensive and water soluble catalyst are the advantages. These mono and bisquinolines displayed good in vitro antimycobacterial activity against MTB. Both **3o** and **3q** did not produce any cytotoxicity on NIH 3T3 cells. This lack of cytotoxic potential for compounds **3o** and **3q** makes them as potential candidates in the treatment of MTB.

Acknowledgements

The authors thank DST for funds under IRHPA program towards high resolution NMR spectrometer and Dr. N. Adhirajan, KMCH College of Pharmacy, Coimbatore, India for cytotoxicity studies. Financial support from UGC, New Delhi to one of the authors, NP, is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.12.119.

References and notes

1. (a) Duncan, K. *Chem. Ind.* **1997**, 861; (b) Daffe, M.; Draper, P. *Adv. Microb. Physiol.* **1998**, *39*, 131.
2. Cole, S. T.; Alzari, P. M. *Biochem. Soc. Trans.* **2007**, *35*, 1321.
3. Young, D. B.; Perkins, M. D.; Duncan, K.; Barry, C. E. *Clin. Invest.* **2008**, *118*, 1255.
4. (a) De cock, K. M.; Chaission, R. E. *Int. J. Tuberc. Lung Dis.* **1999**, *3*, 457; (b) Upadhayaya, R. S.; Kulkarni, G. M.; Vasireddy, N. R.; Vandavasi, J. K.; Dixit, S. S.; Sharma, V.; Chattopadhyaya, J. *Bioorg. Med. Chem.* **2009**, *17*, 4681.
5. (a) Nivin, B.; Nicolas, P.; Gayer, M.; Frieden, T. R.; Fujiwara, P. I. *Clin. Infect. Dis.* **1998**, *26*, 303; (b) Weltman, A. C.; Rose, D. N. *Arch. Intern. Med.* **1994**, *154*, 2161; (c) Pablos-Mendez, A.; Raviglione, M. C.; Laszlo, A.; Binkin, N.; Rieder, H. L.; Bustreo, F.; Cohn, D. L.; Lambregts-van Weezenbeck, C. S. B.; Kim, S. J.; Chaulet, P.; Nunn, P. N. *Eng. J. Med.* **1998**, *338*, 1641; (d) Sivakumar, P. M.; Babu, S. K. G.; Mukesh, D. *Chem. Pharm. Bull.* **2007**, *55*, 44; (e) Brown, A. K.; Papaemmanouil, A.; Bhowruth, V.; Bhatt, A.; Dover, L. G.; Besra, G. S. *Microbiology* **2007**, *153*, 3314; (f) Mao, J.; Eoh, H.; He, R.; Wang, Y.; Wan, B. G.; Franzblau, S. G.; Crick, D. C.; Kozikowski, A. P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5320.
6. Bass, J. B.; Farer, L. S.; Hopewell, P. C.; O'Brien, R.; Jacobs, R. F.; Ruben, F.; Snider, D. E.; Thornton, G. *Am. J. Respir. Crit. Care Med.* **1994**, *149*, 1359.
7. Davies, P. D. O.; Yew, W. W. *Expert Opin. Investig. Drugs* **2003**, *12*, 1297.
8. Larsen, R. D.; Corley, E. G.; King, A. O.; Carroll, J. D.; Davis, P.; Verhoeven, T. R.; Reider, P. J.; Labelle, M.; Gauthier, J. Y.; Xiang, Y. B.; Zamboni, R. J. *J. Org. Chem.* **1996**, *61*, 3398.
9. (a) Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. *J. Med. Chem.* **2001**, *44*, 2374; (b) Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Ghia, M. *Eur. J. Med. Chem.* **2000**, *35*, 1021.
10. (a) Kouznetsov, V. V.; Vargas Mendez, L. Y.; Melendez Gomez, C. M. *Curr. Org. Chem.* **2005**, *9*, 141; (b) Eswaran, S.; Adhikari, A. V.; Chowdhury, I. H.; Pal, N. K.; Thomas, K. D. *Eur. J. Med. Chem.* **2010**, *45*, 3374; (c) Zora, M.; Velioglu, O. *J. Organomet. Chem.* **2008**, *693*, 2159; (d) Eswaran, S.; Adhikari, A. V.; Shetty, N. S. *Eur. J. Med. Chem.* **2009**, *44*, 4637; (e) David, E.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron* **2007**, *63*, 8999; (f) Chen, Y. L.; Zhao, Y. L.; Lu, C. M.; Tzeng, C. C.; Wang, J. P. *Bioorg. Med. Chem.* **2006**, *14*, 4373.
11. Wiesner, J.; Ortmann, R.; Jomaa, H.; Schlitzer, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5274.
12. Elliott, J. M.; Carling, R. W.; Chambers, M.; Chicchi, G. G.; Hutson, P. H.; Jones, A. B.; MacLeod, A.; Marwood, R.; Meneses-Lorente, G.; Mezzogori, E.; Murray, F.; Rigby, M.; Royo, I.; Russell, M. G. N.; Sohal, B.; Tsao, K. L.; Williams, B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5748.
13. Fuchs, C.; Mitchell, E. P.; Hoff, P. M. *Cancer Treat. Rev.* **2006**, *32*, 491.
14. (a) Mizuno, M.; Inagaki, A.; Yamashita, M.; Soma, N.; Maeda, Y.; Nakatani, H. *Tetrahedron* **2006**, *62*, 4065; (b) Mizuno, M.; Yamashita, M.; Sawai, Y.; Nakamoto, K.; Goto, M. *Tetrahedron* **2006**, *62*, 8707.
15. Mikata, Y.; Yokoyama, M.; Ogura, S.-I.; Okura, I.; Kawasaki, M.; Maeda, M.; Yano, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1243.
16. Praveen, C.; DheenKumar, P.; Muralidharan, D.; Perumal, P. T. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7292.
17. Lombard, M. C.; N'Da, D. D.; Breytenbach, J. C.; Smith, P. J.; Lategan, C. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6975.
18. Chen, S.; Chen, R.; He, M.; Pang, R.; Tan, Z.; Yang, M. *Bioorg. Med. Chem.* **2009**, *17*, 1948.
19. Woodrow, M. D.; Ballantine, S. P.; Barker, M. D.; Clarke, B. J.; Dawson, J.; Dean, T. W.; Delves, C. J.; Evans, B.; Gough, S. L.; Guntrip, S. B.; Holman, S.; Holmes, D. S.; Kranz, M.; Lindvaal, M. K.; Lucas, F. S.; Neu, M.; Ranshaw, L. E.; Solanke, Y. E.; Somers, D. O.; Ward, P.; Wiseman, J. O. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5261.
20. (a) Raynes, K. *Int. J. Parasitol.* **1999**, *29*, 67; (b) Guillon, J.; Moreau, S.; Mouray, E.; Sinou, V.; Forfar, I.; Fabre, S. B.; Desplat, V.; Millet, P.; Parzy, D.; Jarry, C.; Grellier, P. *Bioorg. Med. Chem.* **2008**, *16*, 9133.
21. Jachak, S. M.; Saklani, A. *Curr. Sci.* **2007**, *92*, 1251.
22. Vennerstrom, J. L.; Ellis, W. Y.; Ager, A. L.; Anderaen, S. L.; Gerena, L.; Milhous, W. K. *J. Med. Chem.* **1992**, *35*, 2129.
23. Alfredson, T. V.; Maki, A. H.; Waring, M. *J. Biochem.* **1991**, *30*, 9665.
24. Raynes, K.; Galatis, D.; Cowman, A. F.; Tilley, L.; Deady, L. W. *J. Med. Chem.* **1995**, *38*, 204.
25. Palit, P.; Paira, P.; Hazra, A.; Banerjee, S.; Gupta, A. D.; Dastidar, S. G.; Mondal, N. B. *Eur. J. Med. Chem.* **2009**, *44*, 845.
26. Larghi, E. L.; Bohn, M. L.; Kaufman, T. S. *Tetrahedron* **2009**, *65*, 4257.
27. Kaur, K.; Jain, M.; Khan, S. I.; Jacob, M. R.; Tekwani, B. L.; Singh, S.; Pal Singh, P.; Jaina, R. *Bioorg. Med. Chem.* **2011**, *19*, 197.
28. Tewari, S.; Chauhan, P. M. S.; Bhaduri, A. P.; Fatima, N.; Chatterjee, R. K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1409.
29. Strekowski, L.; Say, M.; Zegrocka, O.; Tanious, F. A.; David Wilson, W.; Manzel, L.; Macfarlane, D. E. *Bioorg. Med. Chem.* **2003**, *11*, 1079.
30. (a) Murugesan, D.; Palaniappan, S.; Perumal, Y.; Arnab, C.; Valakunja, N.; Sriram, D. *Bioorg. Med. Chem.* **2008**, *16*, 3408; (b) Annamaria, L.; Jialin, M.; Baojie, W.; Yuehong, W.; Scott, G. F.; Alan, P. K. *J. Med. Chem.* **2009**, *52*, 2109; (c) Sarva, J.; Yasuyoshi, I.; Baojie, W.; Scott, G. F.; Alan, P. K. *Chem. Med. Chem.* **2006**, *1*, 593; (d) Amit, N.; Vikramdeep, M.; Alpeshkumar, M.; Rahul, E. J. *Bioorg. Med. Chem.* **2007**, *15*, 626; (e) Dinakaran, M.; Senthilkumar, P.; Yogeeswari, P.; China, A.; Nagaraja, V.; Dharmarajan, S. *Int. J. Antimicrob. Agents* **2008**, *31*, 337; (f) Jain, R.; Vaitilingam, B.; Nayyar, A.; Palde, P. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1051.
31. Rustomjee, R.; Diacon, A. H.; Allen, J.; Venter, A.; Reddy, C.; Patientia, R. F.; Mthiyane, T. C. P.; De Marez, T.; Van Heeswijk, R.; Kerstens, R.; Koul, A.; De Beule, K.; Donald, P. R.; McNeeley, A. F. *Antimicrob. Agents Chemother.* **2008**, *52*, 2831.
32. Mital, A.; Singh Negi, V.; Ramachandran, U. *ARKIVOC* **2006**, *10*, 220.
33. (a) Manikannan, R.; Muthusubramanian, S.; Yogeeswari, P.; Sriram, D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3352; (b) Manikannan, R.; Venkatesan, R.; Muthusubramanian, S.; Yogeeswari, P.; Sriram, D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6920; (c) Ponpandian, T.; Muthusubramanian, S. *Tetrahedron Lett.* **2011**, *52*, 1520; (d) Saravanan, S.; Azath, I. A.; Muthusubramanian, S. *J. Org. Chem.* **2008**, *73*, 2323; (e) Paul, N.; Muthusubramanian, S. *Tetrahedron Lett.* **2011**, *52*, 3743; (f) Ravindran, G.; Paul, N.; Muthusubramanian, S.; Perumal, S. *J. Sulfur Chem.* **2008**, *29*, 575; (g) Nagaraj, M.; Boominathan, M.; Muthusubramanian, S.; Bhuvanesh, N. *Org. Biomol. Chem.* **2011**, *9*, 4642; (h) Boominathan, M.; Nagaraj, M.; Muthusubramanian, S.; Krishnakumar, R. V. *Tetrahedron* **2011**, *67*, 6057; (i) Paul, N.; Muthusubramanian, S.; Bhuvanesh, N. *New J. Chem.* **2011**, *35*, 2607; Paul, N.; Kaladevi, S.; Muthusubramanian, S. *Helv. Chim. Acta* **2011**. doi:10.1002/hlca.201100263; (k) Chitra, S.; Paul, N.; Muthusubramanian, S.; Manisankar, P.; Yogeeswari, P.; Sriram, D. *Eur. J. Med. Chem.* **2011**, *46*, 4897; (l) Chitra, S.; Paul, N.; Muthusubramanian, S.; Manisankar, P.; Yogeeswari, P.; Sriram, D. *Eur. J. Med. Chem.* **2011**, *46*, 5465; (m) Chitra, S.; Paul, N.; Muthusubramanian, S.; Manisankar, P. *Green Chem.* **2011**, *13*, 2777.
34. (a) Wu, Y.-S.; Cai, J.; Hu, Z.-Y.; Lin, G. H. *Tetrahedron Lett.* **2004**, *45*, 8949; (b) Cheng, H.-G.; Chen, C. B.; Tan, F.; Chang, N.-J.; Chen, J.-R.; Xiao, W.-J. *Eur. J. Org. Chem.* **2010**, 4976; (c) Kazuhiro, K.; Yuu, S.; Hisatoshi, K. J. *Heterocycles* **2009**, *78*, 2033; (d) Kazuhiro, K.; Yuta, O.; Hisatoshi, K. *Synthesis* **2009**, *9*, 1494.

35. 6-Chloro-2-(4-chlorophenyl)-3-[4-(6-chloro-4-phenyl-2-quinolyl)phenoxy]-4-phenylquinoline (**3n**): Isolated as colorless solid; mp 250–251 °C; IR (KBr): 3052 (C–H), 1593 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 6.62 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.33 (d, 2H, *J* = 8.4 Hz), 7.38–7.40 (m, 4H, Ar-H), 7.45–7.53 (m, 6H, Ar-H), 7.59 (d, 1H, *J* = 1.8 Hz, Ar-H), 7.61 (dd, 1H, *J* = 9.0, 2.1 Hz, Ar-H), 7.63 (s, 1H, Ar-H), 7.67 (dd, 1H, *J* = 9.0, 1.8 Hz, Ar-H), 7.79 (d, 1H, *J* = 2.1 Hz, Ar-H), 7.86 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.96 (d, 2H, *J* = 8.4 Hz, Ar-H), 8.05 (d, 1H, *J* = 9.0 Hz, Ar-H), 8.17 (d, 1H, *J* = 9.0 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 115.7, 119.5, 124.4, 124.6, 126.2, 128.4 (2C), 128.5, 128.6, 128.7, 128.8, 129.3 (2C), 129.7, 130.1, 130.4, 130.6, 131.4, 131.9, 132.1, 132.9, 133.2, 135.4 (2C), 135.5, 137.6, 140.5, 143.5, 144.6, 147.0, 148.3, 153.7, 156.0, 158.8. Anal. Calcd for $C_{42}H_{25}Cl_3N_2O$: C, 74.18; H, 3.71; N, 4.12%. Found C, 74.15; H, 3.68; N, 4.17%. 1-(4-[6-Chloro-2-(4-chlorophenyl)-4-phenyl-3-quinolyl]oxyphenyl)-1-ethanone (**4n**): Isolated as colorless solid; mp 220–221 °C; IR (KBr): 3068 (C–H), 1677 (C=O), 1594 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.44 (s, 3H, CH_3), 6.53 (d, 2H, *J* = 9.0 Hz, Ar-H), 7.26–7.29 (m, 3H, Ar-H), 7.33 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.37–7.39 (m, 2H, Ar-H), 7.57 (d, 1H, *J* = 1.8 Hz, Ar-H), 7.64 (d, 2H, *J* = 9.0 Hz, Ar-H), 7.67 (dd, 1H, *J* = 9.0, 1.8 Hz, Ar-H), 7.91 (d, 2H, *J* = 8.7 Hz, Ar-H), 8.17 (d, 1H, *J* = 9.0 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 26.3, 115.2, 124.6, 128.4, 128.6 (2C), 128.7, 129.6, 130.2, 130.3, 130.6 (2C), 131.3, 131.9, 133.4, 135.2, 135.5, 140.3, 143.2, 144.7, 153.4, 161.0, 196.5. Anal. Calcd for $C_{29}H_{19}Cl_2NO_2$: C, 71.91; H, 3.95; N, 2.89%. Found C, 71.88; H, 3.90; N, 2.94%.

36. National Committee for Clinical Laboratory Standards, Antimycobacterial susceptibility testing for *Mycobacterium tuberculosis*, Proposed Standard M24-T, National Committee for Clinical Laboratory Standards, Villanova, PA, 1995.
37. (a) Reynolds, R. C.; Bansal, N.; Rose, J.; Friedrich, J.; Suling, W. J.; Maddry, J. A. *Carbohydr. Res.* **1999**, *317*, 164; (b) Lees, A. W.; Tyrrell, W. F.; Smith, J.; Allan, G. W. *Br. J. Dis. Chest* **1970**, *64*, 85; (c) Kahana, L. M. *Biomed. Pharmacother.* **1990**, *44*, 21; (d) Marshall Clarke, G. B.; Cuthbert, J.; Cuthbert, R. J.; Lees, A. W. *Br. J. Dis. Chest* **1972**, *66*, 272; (e) Dickinson, J. M.; Ellard, G. A.; Mitchison, D. A. *Tubercle* **1968**, *49*, 351; (f) Yendapally, R.; Lee, R. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1607; (g) *Tuberculosis* **2008**, *88*, 102.; (h) Dover, L. G.; Coxon, G. D. *J. Med. Chem.* **2011**, *54*, 6157.
38. (a) Uttley, A. H. C.; Collins, C. H. *Tubercle* **1988**, *69*, 193; (b) Chadwick, M.; Nicholson, G.; Gaya, H. *Am. J. Med.* **1989**, *87*, S35; (c) Sriram, D.; Yogeeswari, P.; Basha, J. S.; Radha, D. R.; Nagaraja, V. *Bioorg. Med. Chem* **2005**, *13*, 5774; (d) Jonchevska, M.; Talevski, S.; Bakalova, E.; Kungulovska, O. *Tuber. Lung Dis.* **1995**, *76*, 85; (e) Cobanlt, B.; Zamani, A. *Tuber. Lung Dis.* **1994**, *75*, 13; (f) Donald, P. R.; Diacon, A. H. *Tuberculosis* **2008**, *88*, S75.
39. (a) Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55; (b) Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A.; Campbell, H.; Mayo, J.; Boyd, M. *J. Natl. Cancer Inst.* **1991**, *83*, 757.