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Bioorganic & Medicinal Chemistry Letters 15 (2005) 4526–4530
Bioorganic & Medicinal Chemistry Letters

An efficient synthesis of aryloxyphenyl cyclopropyl methanones: a new class of anti-mycobacterial agents☆

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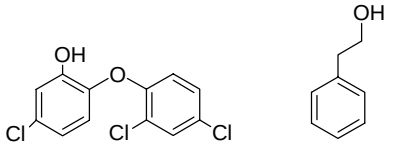
Received 25 May 2005; revised 28 June 2005; accepted 4 July 2005
Available online 8 August 2005

Abstract—An efficient, high yield and one-pot synthesis of phenyl cyclopropyl methanones by reaction of different aryl alcohols with 4′-fluoro-4-chloro-butyrophenone in THF/DMF in the presence of NaH/TBAB is reported. Most of the methanones were further reduced to respective alcohols or methylenes. All the compounds were evaluated for their anti-tubercular activities against *M. tuberculosis* H37Rv in vitro displaying MICs ranging from 25 to 3.125 μg/mL. The most active compounds showed activity against MDR strains and two of them (**14** and **16**) showed marginal enhancement of MST in mice.

An increase in the global burden of tuberculosis with the worldwide mortality rate of 23% is a major cause of concern in the socioeconomic and health sectors.[1,2] The synergy of this disease with HIV infection and the emergence of MDR tuberculosis (TB) poses a threatening global challenge particularly in the developing countries.[3] Although a number of lead molecules exist today to develop new drugs, no new chemical entity has emerged for clinical use over the last 40 years for the treatment of this disease.[4,5] Therefore, there is an urgent need to develop new drugs, acting through a novel mechanism of action for the chemotherapy of TB. The incredible thickness of mycobacterial cell wall, absent in human cells, is responsible for longer period of treatment and the emergence of resistance against the known first line anti-TB drugs.[6–8] Therefore, it is a selective target and many crucial enzymes involved in the biosynthesis of cell wall macromolecules and their inhibitors are being looked at as future hope to develop new drugs against this disease. One such enzyme system is FAS-II required in the initial steps of mycolic acid biosynthesis.[9] Many inhibitors of FAS-II system are known and among them phenethyl alcohol[10] and triclosan[10] are important for lead optimization (Fig. 1). Recently, anti-mycobacterial activities have been reported in simple acetophenones,[11a] benzylideneacetophenones[11b] and *p*-nitro-α-acetylamino-β-hydroxypropiophenones.[11c,11d] We have also identified a glycosylated phenyl cyclopropyl methanone (Fig. 2) as a very good anti-tubercular agent active even against MDR strains of *M. tuberculosis* and in vivo



Triclosan Phenethyl alcohol

Figure 1. FAS-II inhibitors.

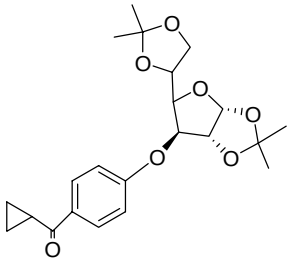


Figure 2. Glycosyl phenylcyclopropylmethanone.

Keywords: Tuberculosis; Tetrabutylammonium bromide; Phenyl cyclopropyl methanones; Wolf–Kishner reduction.
☆ CDRI Communication No. 6759.
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doi:10.1016/j.bmcl.2005.07.007

too.[12] Cyclopropyl ring is a common structural element of the mycobacterial cell wall[13] and its chemotherapeutic[14] importance is also well known. Further, aryl cyclopropyl ketones play a prominent role as intermediates in the synthesis of many other biologically active compounds.[15] Keeping in view the above, we were prompted to synthesize aryl cyclopropyl methanones and evaluate them for anti-mycobacterial activity.

A number of methods for the synthesis of cyclopropyl ring formation exist in the literature[16] and very recently, we have reported a rapid one-pot procedure for the synthesis of combinatorial library of phenyl cyclopropyl methanones on solid phase.[17] Requirements for larger quantity of material for biological evaluation led us to explore a new conventional approach for their synthesis.

Phenyl cyclopropylmethanones **1**–**12** were prepared by reaction of 4-chloro-4′-fluoro butyrophenone with furylmethyl-, phenylmethyl-, 4-methoxy phenylmethyl-, 3,4-dimethoxy phenylmethyl-, 2-chloro phenylmethyl-, 4- fluoro phenylmethyl-, 3-pyridylmethyl-, 4-pyridylmethyl-, 4-chlorophenylmethyl-, 3,4-dichloro phenylmethyl-, cyclohexyl and cyclopentyl alcohols in THF/DMF (1:1) in the presence of NaH and tetrabutylammonium bromide (TBAB) as phase transfer catalysts at 0–100 °C in very good yields (Scheme 1). The structures of all the compounds were determined on the basis of their spectroscopic data and microanalysis.[18]

The keto group in most of the active methanones has been partially or completely reduced to alcohol and methylene groups with sodium borohydride and Wolf–Kishner reduction, respectively, to see its effect on anti-tubercular activity profile. Thus, reduction of phenyl cyclopropyl ketones **1**–**8** and **11** with $NaBH_4$ in ethanol gave compounds **13**–**21**, respectively, in good yields.[19] However, reduction of compounds **1**–**6** and **8** with hydrazine hydrochloride followed by heating in the presence of KOH led to the respective phenyl cyclopropyl methanes **22**–**28** in moderate yields.[20]

In one of the most active compounds, **16**, the hydroxyl group was further derivatized as *O*-(epoxy-*n*-propyl) derivative **29** by its reaction with epichlorohydrin in THF in the presence of catalytic amount of tetrabutyl ammonium bromide following our earlier reported method[21] (Scheme 2).

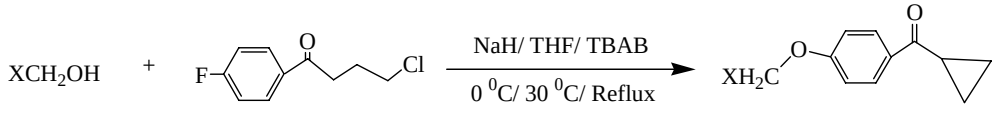
All the compounds synthesized were evaluated for their anti-tubercular activity against *M. tuberculosis* H37Ra by MABA method[22] while Agar Microdilution method[23] was used against *M. tuberculosis* H37Rv. Compound **16** was also screened against MDR strains, while the most active compounds **14** and **16** were also evaluated in mice model.[24]

As evident from Table 1, except compounds **9**, **10**, **12**, **15**, **17**–**19** and **28** all other compounds displayed activity with MIC ranging from 25 to 3.25 μg/mL against the virulent strain *M. tuberculosis* H37Rv. However, none of the compounds except compound **16** was active against avirulent strain H37Ra indicating that these compounds are specific for virulent strain. Further, compound **16**, having fluoro substituent, completely inhibited the growth of clinical isolates of MDR strains of *M. tuberculosis* H37Rv at 6.25 μg/mL while the standard first line anti-TB drugs were ineffective at their critical concentrations for MDR strains (Table 2).

A closer look into the structure–activity relationship in these compounds shows that cyclopropyl phenyl methanones **6**, **9**, **10** and **12** are inactive as their MICs are

Table 1. In vitro antimycobacterial activities of compounds **1**–**29**

Compound	X	MABA MIC (μg/ml) against *M. tuberculosis* H37Ra	Agar microdilution MIC (μg/ml) against *M. tuberculosis* H37Rv
1	Phenyl	25	6.25
2	4-Methoxy phenyl	>50	12.5
3	3,4-Methoxy phenyl	25	12.5
4	4-Fluoro phenyl	>25	12.5
5	Furfuyl	25	25
6	3-Pyridyl	>25	25
7	4- Pyridyl	>25	12.5
8	2-Chloro phenyl	>25	12.5
9	4-Chloro phenyl	>25	25
10	3,4-Dichloro phenyl	>25	25
11	Cyclopentyl	>25	25
12	Cyclohexyl	>25	>25
13	Phenyl	>50	25
14	4-Methoxy phenyl	>50	3.12
15	3,4-Methoxy phenyl	3.12	>50
16	4-Fluoro phenyl	25	6.25
17	Furyl	>25	>25
18	3-Pyridyl	>25	>25
19	4- Pyridyl	>25	>25
20	2-Chloro phenyl	>25	-
21	Cyclopentyl	25	3.12
22	Phenyl	>50	12.5
23	4-Methoxy phenyl	>25	25
24	3,4-Methoxy phenyl	12.5	25
25	4-Fluoro phenyl	nd	12.5
26	Furfuryl	25	25
27	3-Pyridyl	>25	25
28	2-Chloro phenyl	>25	>50
29	4-Fluoro phenyl	nd	3.12



1-12

Scheme 1.

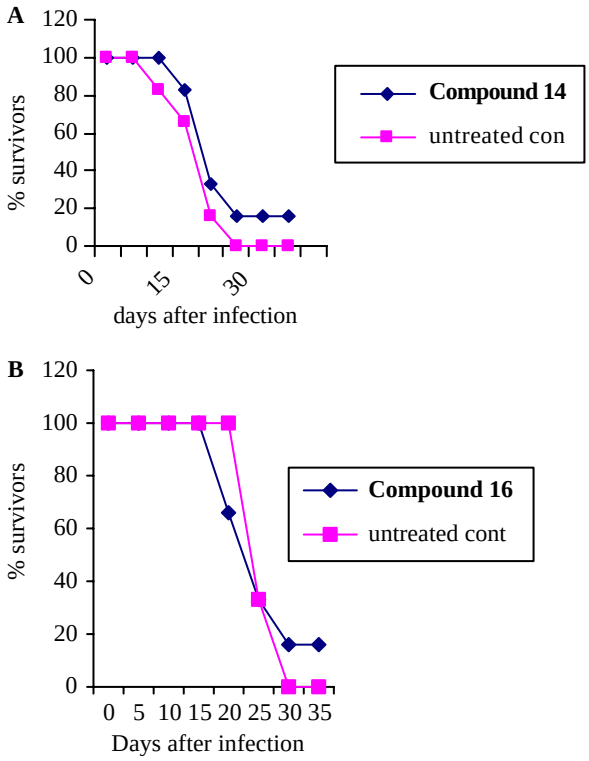
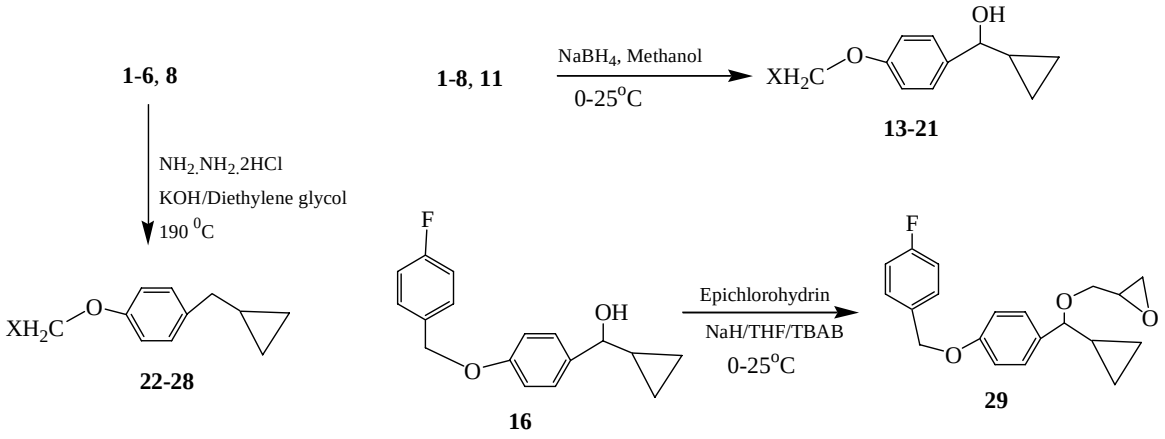


Figure 3. (A) Chemotherapeutic efficacy of compound **14** against *M. tuberculosis* H37Rv in mice. (B) Chemotherapeutic efficacy of Compound **16** against *M. tuberculosis* H37Rv in mice.

>25 μg/mL. However, compounds **1**–**4**, **7**–**8** have MICs in the range of 12.5–6.25 μg/mL. It is interesting to note that the partially reduced alcohols **14** (3.12 μg/mL), **16** (6.25 μg/mL) and **21** (3.12 μg/mL) of the corresponding phenyl cyclopropyl methanones **2** (12.5 μg/mL), **4** (12.5 μg/mL) and **11** (25 μg/mL) did offer better protection. Among the completely reduced cyclopropyl phenyl methanes, none of the compounds offer better inhibition than the parent ketones as the MICs were either retained or enhanced. Further, replacement of aryloxy moiety in these compounds with heteroaryloxy group did not improve the anti-tubercular efficacy. Replacement of aryloxy group with cyclopentyloxy moiety in the alcohols did offer a better result. However, in general, replacing the aryloxy group with cycloalkyloxy group gave compounds with comparable activities. Two of the cyclopropyl phenyl methanols, compounds **14** and **16** with 4-methoxybenzyloxy and 4-fluorobenzyloxy substituents offer very good protection (MICs 3.125 and 6.25 μg/mL, respectively). Since it is known that fluoro group plays a very important role in the biological activity profile of many biologically active molecules in vivo, therefore, compound **16** was further functionalized to the respective *O*-(*n*-epoxypropyl) derivative **29**, which has MIC of 3.12 μg/mL.

Cytotoxicity of the two compounds **14** and **16** in VERO cell line at different concentrations beginning from $10 \times$ MIC of the compounds was assayed and is expressed as inhibitory concentration (IC_{50}). On the basis



Scheme 2.

Table 2. In vitro activity of compound **16** and standard drugs against MDR strains of *M. tuberculosis* H37Rv

Compd. or drug	Growth of MDR strains after six weeks				
	BC-248(1)	BC-283 (1)	VA-101 (2)	BC-426 (3)	BC-437 (3)
Compound **16** (6.25 μg/ml)	--	--	--	--	--
INH (1 μg/ml)	++	++	++	++	++
Rifampicin (64 μg/ml)	++	++	++	++	++
Ethambutol (6 μg/ml)	++	++	++	--	--
No drug control	++	++	++	++	++

--, no growth; +, 1–20 growth (resistance), ++, heavy growth; (1) Strains resistant to rifampicin, isoniazid and ethambutol. (2) Strains resistant to rifampicin, isoniazid and ethambutol. (3) Strains resistant to rifampicin and isoniazid.

of IC_{50} values, selectivity index (SI) of these compounds was found to be 16 and 10, respectively, indicating that these compounds are suitable for in vivo evaluation.

The efficacy of compounds **14** and **16** against challenge of *M. tuberculosis* H37Rv was also seen at 100 mg/kg in vivo in the mouse model. As evident from Figures 3A and B, there were 27% and 17% enhancements in MST of the mice as compared to control by compounds **14** and **16**, respectively.

In conclusion, we have developed a novel one-pot synthesis of aryloxyphenyl cyclopropyl methanones and their derivatives, which have shown very good activity against *M. tuberculosis*. It will be interesting to prepare an analogue of the active compound, which may be non-toxic to eukaryotes but strongly anti-tubercular.

Acknowledgments

The authors thank Mr. R. Grover and Mr. R. C. Mishra for their partial contribution during this work. N. D. and N. T. are thankful to CSIR, New Delhi, for fellowships. We also thank Dr. B. S. Srivastava and Dr. R. Srivastava, Microbiology Division, CDRI, for their constructive suggestions.

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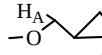
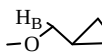
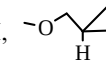
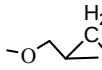
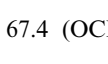
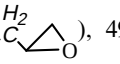
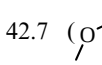
18. General procedure for the synthesis of phenyl cyclopropyl methanones: To a stirring slurry of NaH (2.8 g, 118.8 mmol) in anhydrous THF (20 mL), 4-fluorobenzyl alcohol (5 mL, 39.6 mmol) was added at 0 °C. 4-Chloro-4′-fluorobutyrophenone (7.9 mL, 39.6 mmol) was added to this stirring reaction mixture followed by the addition of TBAB (0.8 g) and stirring continued for further 18 h at ambient temperature. The excess of NaH was quenched with aq NH_4Cl solution and filtered on Cellite and the filtrate was evaporated and the crude product, thus obtained, was extracted with ethyl acetate and washed with water. The organic layer was dried (Na_2SO_4) and evaporated to give a crude mass, which was purified over SiO_2 column using hexane/ethyl acetate (5:1) as eluent to give compound **4**. Colourless granules, mp 116–118 °C. Yield 90%, FAB MS *m/z* = 271 $[M+H]^+$, IR ν_{max} cm^{-1} 2945 (C–H stretching), 1600 (C–O); ^1H NMR (200 MHz, $CDCl_3$) δ = 8.03 and 7.90 (each d, *J* = 8.80 Hz, each 2H, Ar-H), 7.34 and 7.01 (each m, each 2H, ArH), 5.04 (s, 2H, OCH_2Ar), 2.60 (m, 1H, cyclopropyl CH), 1.21 and 0.98 (each m, each 2H, cyclopropyl CH_2s); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 199.2 (C=O), 165.4, 162.6, 132.5, 132.4, (ArC), 130.6, 129.8, 129.6, 116.2, 115.7, 114.9 (Ar-CH), 69.8 (OCH_2Ar), 17.0 (cyclopropyl CH), 11.5 (cyclopropyl CH_2s). Anal. Calcd for $C_{17}H_{15}O_2F$ (270): C, 75.55; H, 5.55; Found: C, 75.31; H, 5.64.
19. General procedure for the partial reduction of ketones with $NaBH_4$: To the stirring solution of cyclopropyl methanone **4** (4.0 g, 14.81 mmol) in methanol (20 mL) at 0 °C, $NaBH_4$ (0.56 g, 14.81 mmol) was added and the stirring was continued for next 3 h at an ambient temperature. The reaction was quenched with aq NH_4Cl at 0 °C and the solvent was evaporated under reduced pressure. The residue obtained was extracted with ethyl acetate (50 mL) and washed with water. The organic layer was dried (anhydr. Na_2SO_4) and concentrated to give a

crude mass, which was chromatographed over SiO_2 column using hexane/ethyl acetate (3:1) as eluent to afford the compound **16** as colourless powder. Yield 85%, mp 82–83 °C. FAB MS $m/z = 273$ $[M+H]^+$, IR ν_{max} cm^{-1} 3339.7 (OH stretching), 2933.4 (C–H stretching), 1609.7 (C–O); ^1H NMR (200 MHz, $CDCl_3$) $\delta = 8.07$ and 7.98 (d, 8.80 Hz, 2H, Ar-H), 7.41 and 7.47 (m, 2H, ArH), 7.25 and 7.07 (m, 4H, ArH), 5.08 (s, 2H, OCH_2Ar), 3.80 (s, 3H, OCH_3) 2.60 (m, 1H, cyclopropyl CH), 1.73 (s, 1H, OH exchangeable with D_20) 1.20and 0.98 (each m, each 2H, cyclopropyl CH_2s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.4, 136.9, 135.8, 135.1, (ArC), 129.8, 129.6, 127.7, 116.1, 115.6, 115.0, (Ar-CH), 82.5 (CHOH), 69.7 (OCH_2Ar), 19.5 (cyclopropyl CH), 3.1, 2.0 (cyclopropyl CH_2s). Anal. Calcd for $C_{17}H_{17}O_2F$ (272): C, 75.00; H, 6.25; Found: C, 74.89; H, 6.50.

20. General procedure for the complete reduction of ketones: Compound **4** (2 g, 7.35 mmol), $NH_2NH_2{\cdot}2HCl$ (0.27 g, 7.35 mmol) and KOH (0.5 g) in diethylene glycol (15 mL) were refluxed at 200 °C for 4 h. The reaction was quenched and extracted with $CHCl_3$ and washed with water. The organic layer was evaporated and the residue obtained purified over SiO_2 using hexane/ethyl acetate (60:40) as eluent to give compound **25** as colourless solid, mp 46–48 °C . FAB MS $m/z = 256$ $[M+H]^+$, IR ν_{max} cm^{-1} 2916.6 (C–H stretching), 1607.3 (C–O); ^1H NMR (200 MHz, $CDCl_3$) $\delta = 7.25$ and 7.21 (d, $J = 8.2$, 2H, Ar-H), 7.15 and 7.05 (m, 2H, ArH), 6.95 and 6.92 (m, 2H, ArH), 6.74 and 6.70 (d, $J = 8.5$, 2H, ArH), 4.80 (s, 2H, OCH_2Ar), 2.32 (d, 2H, $–CH_2$) 1.22 (m, 1H, cyclopropyl CH), 0.78, .02 (m, each 2H, cyclopropyl CH_2s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.3, 160.4, 157.3, 135.1, (ArC), 129.8, 129.7 128.6, 116.1, 115.6,115.0 (Ar-CH), 69.8 (OCH_2Ar), 39.8 (CH_2), 12.5 cyclopropyl (CH), 5.03 (both cyclopropyl CH_2s). Anal. Calcd for $C_{17}H_{17}OF$ (256): C, 79.68; H, 6.64; Found: C, 79.80; H, 6.89.

21. General procedure for the epoxy derivative of compound **16**: To a stirring slurry of NaH (0.39 g, 16.53 mmol) in anhydr. THF (5 mL) at 0 °C compound **16** (1.5 g, 5.51 mmol) was added slowly and after 15 min epichlorohydrin (0.35 mL, 5.51 mmol) in anhydr. THF (10 mL) was added slowly followed by the addition of TBAB (0.20 g). The stirring was continued for next 10 h at an ambient temperature. After disappearance of the starting material, excess of NaH was quenched with aq NH_4Cl solution and filtered on Cellite and the filtrate was concentrated. The residue, thus obtained, was extracted with ethyl acetate (50 mL) and washed with water. The organic layer was dried (anhydr. Na_2SO_4) and concentrated to give a crude mass, which was purified over SiO_2 column using hexane/ethyl acetate (4:1) as eluent to give compound **29**. Colourless flakes. Yield 85%, mp 90–92 °C FAB MS $m/z = 328$ $[M+H]^+$, IR ν_{max} cm^{-1} 3338.7 (OH stretching), 2930.4 (C–H stretching), 1608.7 (C–O); ^1H NMR (200 MHz, $CDCl_3$) $\delta = 7.42$ and 7.38 (each d, $J = 8.60$ Hz, each 2H, Ar-H), 7.28 (m, 4H, ArH), 7.10 and 6.96 (each d, $J = 8.60$ each 2H, ArH), 5.01 (s, 2H, OCH_2Ar), 3.72 (m, 1H, ) 3.54 (m, 1H, ), 3.39 (m, 1H, ), 2.74 (m, 2H, ), 1.25 (m, 1H, cyclopropyl-CH), 0.48, 0.44 and 0.42 (m, 4H, cyclopropyl CH_2s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.3, 158.6, 134.6, 133.2 (ArC), 127.4, 127.3, 126.2, 126.1, 113.7, 113.3, 112.7 (Ar-CH), 83.8 (CHOH), 67.4 (OCH_2Ar), 66.9 (), 49.1 (), 42.7 (), 15.5 (cyclopropyl CH), 2.3, 0.1 (cyclopropyl CH_2s). Anal. Calcd for $C_{20}H_{20}O_3F$ (327): C, 73.39; H, 6.11; Found: C, 73.50; H, 6.31.

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