European Journal of Medicinal Chemistry 45 (2010) 5965–5978

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and optimization of antitubercular activities in a series of 4-(aryloxy) phenyl cyclopropyl methanols

Surendra S. Bisht [a], Namrata Dwivedi [a], Vinita Chaturvedi [b], Namrata Anand [a], Mridul Misra [a], Rahul Sharma [a], Brijesh Kumar [c], Richa Dwivedi [b], Shyam Singh [b], Sudhir Kumar Sinha [b], Versha Gupta [d], P.R. Mishra [d], Anil K. Dwivedi [d], Rama P. Tripathi [a,*]

[a] Medicinal and Process Chemistry Division, CSIR, Lucknow-226001, India
[b] Drug Target Discovery and Development Division, CSIR, Lucknow-226001, India
[c] Sophisticated Advanced Instrumentation Facility Division, CSIR, Lucknow-226001, India
[d] Pharmaceutics Division, Central Drug Research Institute, CSIR, Lucknow-226001, India

ARTICLE INFO

Article history:
Received 28 July 2010
Received in revised form
7 September 2010
Accepted 28 September 2010
Available online 20 October 2010

Keywords:
Mycobacterium tuberculosis
Antitubercular agents
(Aryloxy)phenyl cyclopropyl methanone
(Aryloxy)phenyl cyclopropyl methanol
Cytotoxicty
Sodium hydride

ABSTRACT

A series of [4-(aryloxy)phenyl]cyclopropyl methanones were synthesized by reaction of different benzyl alcohols with 4-chloro-4′-fluorobutyrophenone in DMF in the presence of NaH/TBAB. The methanones were further reduced to respective methanols. The antitubercular activity of these compounds was evaluated *in vitro* against *Mycobacterium tuberculosis* H37Rv. Compounds **19**, **21**, **35**, **36** and **37** have shown minimum inhibitory concentration (MIC) of 3.12 μg/mL, while compounds **14**, **25** and **18** have shown MIC of 1.56 μg/mL and 0.78 μg/mL respectively. One of the compounds, cyclopropyl-4-[4-(2-piperidin-1-yl-ethoxy)benzyloxy]phenyl}methanol (**36**) showed 98% killing of intracellular bacilli in mouse bone marrow derived macrophages and was active against MDR, XDR and rifampicin clinical isolates resistant strains with MIC 12.5 μg/mL. Compound **36** was orally active *in vivo* in mice against *M. tuberculosis* H37Rv with an increase in MST by 6 days with 1 log reduction in the bacillary density in lungs as compared to control on 30th day after infection.

1. Introduction

Among chronic infectious diseases, tuberculosis (TB) a highly contagious, air-borne disease caused by *Mycobacterium tuberculosis* is a leading killer in the world and currently it represents the most threatening health problem globally. The emergence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug resistant (XDR-TB), coupled with HIV has aggravated the problem [1–3]. As per WHO estimate there are about 13.7 million chronic active cases, 9.4 million new cases, and 1.8 million deaths, mostly in developing countries [4]. More than 2 million people die of pulmonary TB every year [5–7]. The existing diagnostics, drugs and vaccines will be insufficient to achieve the objectives, set by STOP TB programme, to bring down the mortality of TB by 2015 and halve the incidence by 2050. A substantial effort in basic science, chemotherapy and epidemiology is necessary to develop better tools and strategies to control TB [8]. Although several molecules are known to be potent antitubercular agents [9–11] and at least 10 of them are in different stages of clinical trial [12] yet none of them are expected to be in the market before 2012. In the light of these, development of new chemical entities with novel mode of action is need of the hour to strengthen the armory of the anti-TB drugs.

Since past several years we have been involved in the discovery and development of new chemical entities as antitubercular agents that can improve the current therapeutic regimen and be effective in treatment of MDR-TB [13–21]. Simple acetophenones [22], benzylideneacetophenones [23] and *p*-nitro-α-acetylamino-β-hydroxypropiophenones [24] different chalcones and flavanoids [23] possess antimycobacterial activities. In this endeavor we have recently disclosed potent antimycobacterial activity in cyclopropylphenyl methanones (**1**) and methanols (**2**) as new chemical entities active *in vitro* against both the drug sensitive and MDR strains of *M. tuberculosis* (Fig. 1) [16]. However, the *in vivo* efficacies of these compounds were not very encouraging. From our preliminary studies, the key structural feature of this series was found to be a cyclopropylphenyl methanol unit (A) and variation in

* Corresponding author. Tel.: +91 0522 2612411; fax: +91 522 2623405/2623938/2629504.
E-mail address: rpt.cdri@gmail.com (R.P. Tripathi).

0223-5234/$ – see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2010.09.063

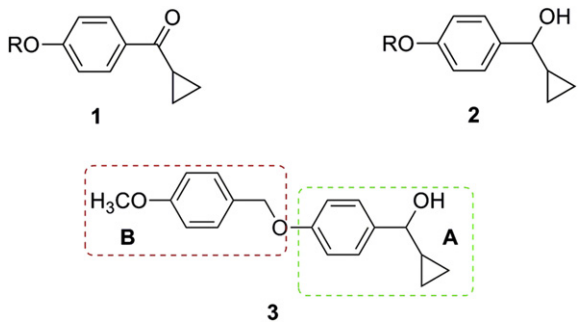


Fig. 1. Antitubercular cyclopropylphenyl methanones and methanols.

the activities was due to the substituents in the phenyl ring of 4-benzyloxy moiety (B). The most active compound of the series with marginal *in vivo* protection was found to be compound **3** (Fig. 1). Therefore, we were interested to optimize this potent antitubercular compound by keeping the cylopropylphenyl methanone and cyclopropylphenyl methanol unit constant and varying the 4-benzyloxy substituent.

Herein, we have reported the synthesis and antitubercular evaluation of [(aryloxy)phenyl]cyclopropyl methanones and methanols leading to identification of new scaffolds with improved activity against *M. tuberculosis* $H_{37}Rv$. Amongst the screened compounds, cyclopropyl-4-[4-(2-piperidin-1-yl-ethoxy)benzyloxy] phenyl}methanol (**36**) was found to be orally active.

2. Results and discussion

2.1. Chemistry

The starting benzyl alcohol derivatives (**4**–**10**) were prepared by sodium borohydride reduction of respective substituted benzaldehydes [16]. The [(benzyloxy)phenyl]cyclopropyl methanones (**12**–**18**) were prepared by reaction of the above benzyl alcohol derivatives (**4**–**10**) with 4-chloro-4′-fluorobutyrophenone (**11**) in presence of NaH and tetrabutylammonium bromide (TBAB) as phase transfer catalyst as per our earlier reported protocol [16] in 67–82% yields. Reduction of the cyclopropylphenyl methanones (**12**–**18**) with sodium borohydride at ambient temperature led to the formation of respective cyclopropylphenyl methanols (**19**–**25**) in 67–90% yields (Scheme 1).

The benzyl alcohol derivatives (**27**–**30**) on treatment with 4-chloro-4′-fluorobutyrophenone (**11**) separately in DMF in presence of NaH and tetrabutylammonium bromide as described above led to the formation of respective 4{[4-(aminoalkoxy)benzyloxy] phenyl}cyclopropyl methanones (**31**–**34**) respectively in 75–80% yields (Scheme 2).

Reduction of above methanones (**31**–**34**) with $NaBH_4$ afforded the respective 4{[4-(aminoalkoxy)benzyloxy]phenyl}cyclopropyl methanols (**35**–**38**) in 73–84% yields (Scheme 2).

In order to understand the positional importance of the hydrophilic chain (aminoalkoxy) in the terminal phenyl ring on activity, a positional isomer of most active compound **36** was prepared starting from 3-hydroxybenzaldehyde (**39**). The 3-aminoalkylated benzyl alcohol derivative (**40**) on reaction with 4-chloro-4′-fluorobutyrophenone (**11**) gave cyclopropyl-4-[3-(2-piperidin-1-yl-ethoxy)benzyloxy]phenyl} methanone (**41**) in 80% yield. The latter on reduction with $NaBH_4$ gave cyclopropyl-4-[3-(2-piperidin-1-yl-ethoxy)benzyloxy]phenyl}methanol (**42**) in 78% yield (Scheme 3).

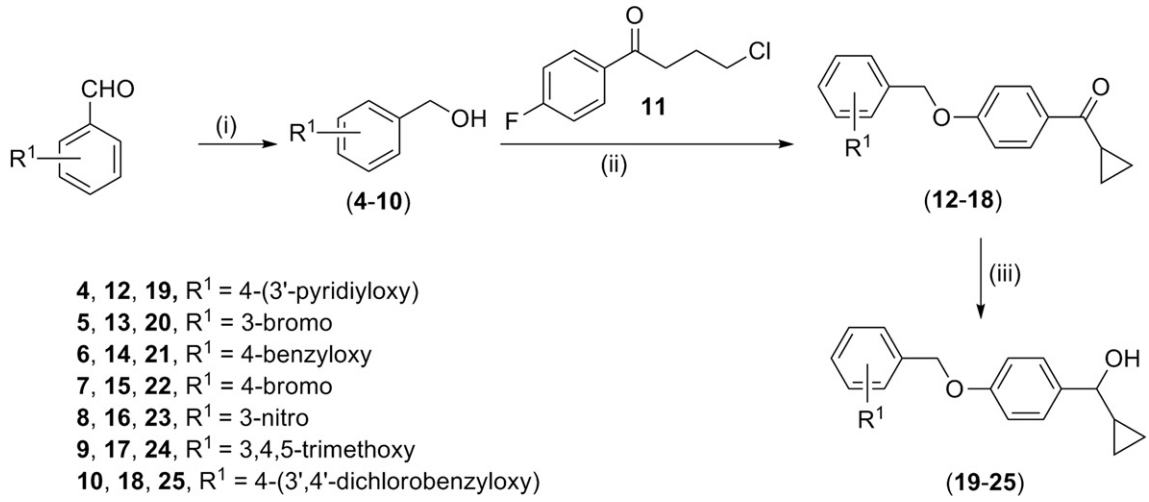
To see the effect of an additional substituent other than 4-aminoalkoxy group in the terminal phenyl ring methoxy substituent was introduced by selecting 3-methoxy-4-hydroxybenzaldehyde (**43**). The latter on reaction with different aminoalkyl halides hydrochlorides as described above gave respective 3-methoxy-4-ethoxyamino benzyl alcohols (**44**–**46**) in 71–79% yields, which on further reaction with 4-chloro-4′-fluorobutyrophenone (**11**) gave the respective cyclopropyl-4[3-(methoxy)-4-(aminoalkoxy)benzyloxy]phenyl methanones (**47**–**49**, Scheme 4). The cyclopropyl-4[3-(methoxy)-4-(aminoalkoxy)benzyloxy]phenyl methanols (**50**–**52**) were similarly prepared by sodium borohydride reduction of the respective methanones (**47**–**49**) in 75–79% yields (Scheme 4).

In order to see the importance of whole 4-benzyloxy moiety on antitubercular activity profiles we have synthesized {4-[2-(*N*,*N*-dibutylamino)ethoxy]phenyl}cyclopropyl methanone (**54**) by direct coupling of *N*,*N*-dibutylaminoethanol (**53**) with 4-chloro-4′-fluorobutyrophenone (**11**) in 75% yield. Compound **54** on sodium borohydride reduction afforded {4-[2-(*N*,*N*-dibutylamino)ethoxy] phenyl}cyclopropyl methanol (**55**) in 77% yield (Scheme 5).

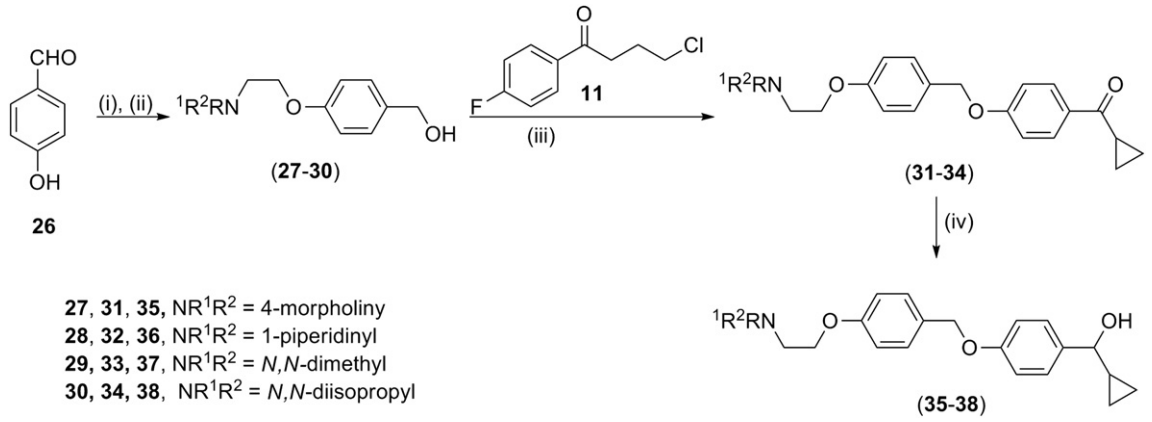
2.2. Biological activity

2.2.1. In vitro antimycobacterial activity

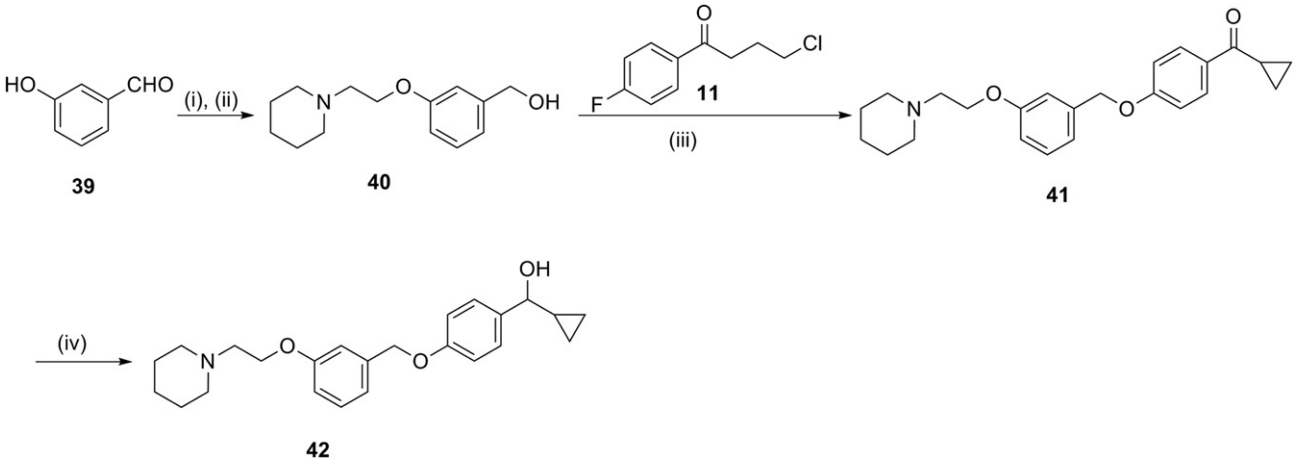
All the synthesized compounds were tested for their ability to inhibit the growth of *M. tuberculosis* by Agar-based proportion



Scheme 1. Reagents and conditions: (i) $NaBH_4$, MeOH, 0 °C-rt, 1–1.5 h; (ii) NaH, DMF, TBAB, 0 °C- reflux, 4–5 h; (iii) $NaBH_4$, MeOH, 0 °C-rt, 3–4 h.

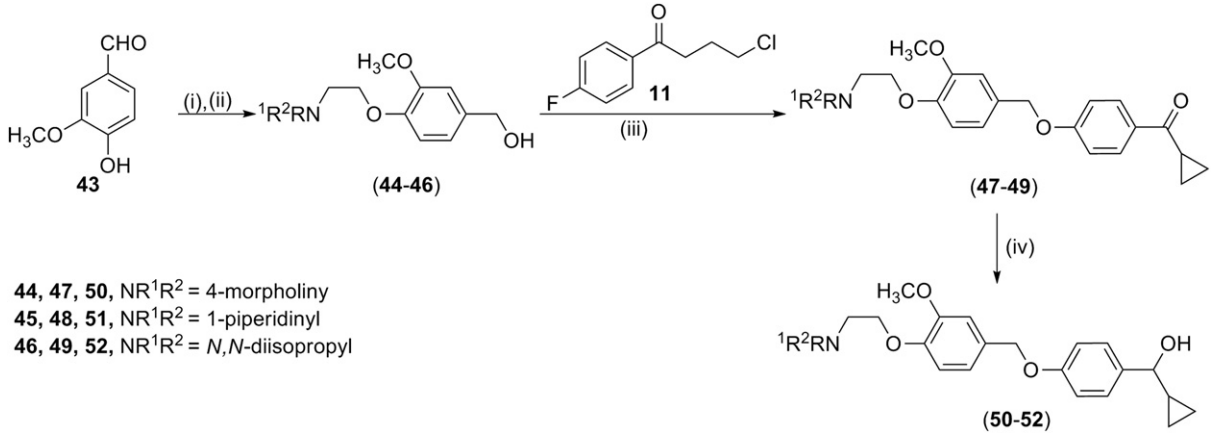


Scheme 2. Reagents and conditions: (i) $R^1R^2NCH_2CH_2Cl.HCl$, anhydrous THF, K_2CO_3, TBAB; (ii) $NaBH_4$, MeOH, 0 °C-rt, 1–1.5 h; (iii) NaH, DMF, TBAB, 0 °C- reflux, 4–5 h; (iv) $NaBH_4$, MeOH, 0 °C-rt, 3–4 h.

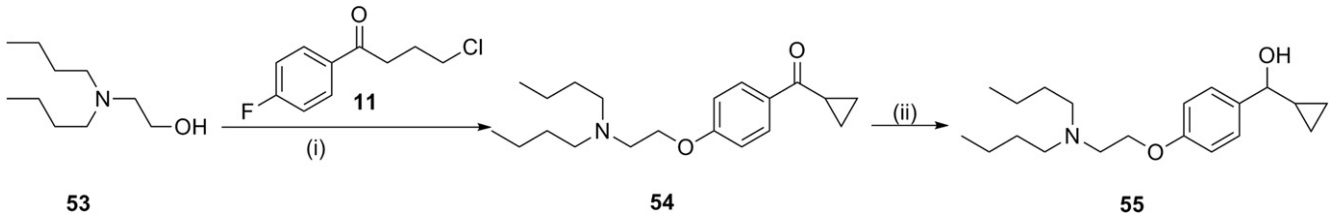


Scheme 3. Reagents and conditions: (i) 2-Chloroethylpiperidine hydrochloride, anhydrous THF, K_2CO_3, TBAB; (ii) $NaBH_4$, MeOH, 0 °C-rt, 1–1.5 h; (iii) NaH, DMF, TBAB, 0 °C- reflux, 4–5 h; (iv) $NaBH_4$, MeOH, 0 °C-rt, 3–4 h.

Assay using $H_{37}Rv$ strains [25]. Subsequently cytotoxicity evaluations of compounds showing antitubercular potential (MIC $\leq$ 3.12 μg/mL) against a mammalian cell line (VERO) and mouse bone marrow derived macrophages were carried out [26,27]. The compounds which were non-toxic and potentially active *in vitro* against *M. tuberculosis* H37Rv were evaluated for their effect to kill intracellular bacterium in *ex vivo* models of mouse bone marrow derived macrophages [28]. Most potent compound was then also tested for its *in vitro* efficacy (by proportion assay) against one multidrug resistant (MDR), one extensively drug resistant (XDR),



Scheme 4. Reagents and conditions: (i) $R^1R^2NCH_2CH_2Cl.HCl$, anhydrous THF, K_2CO_3, TBAB; (ii) $NaBH_4$, MeOH, 0 °C-rt, 1–1.5 h; (iii) NaH, DMF, TBAB, 0 °C- reflux, 4–5 h; (iv) $NaBH_4$, MeOH, 0 °C-rt, 3–4 h.



Scheme 5. Reagents and conditions: (i) NaH, DMF, TBAB, 0 °C- reflux, 4–5 h; (ii) $NaBH_4$, MeOH, 0 °C-rt, 3–4 h.

two rifampicin resistant and two drug susceptive clinical isolates of *M. tuberculosis* (procured from Central Jalma Institute Immunology and Leprosy at Agra).

The effect of the substituents of the benzyloxy ring on the antitubercular activity was investigated and shown in Table 1. As evident from Table 1 compounds **12**, **17**, **33**, **48**, **49**, **52**, **54** and **55** displayed MIC of >12.5 μg/mL while compounds **13**, **20**, **24**, **32**, **34**, **38**, **41**, and **50** displayed MIC of 12.5 μg/mL. The compounds, **15**, **16**, **22**, **23**, **31**, **42**, **47** and **51** displayed MIC of 6.25 μg/mL. Compounds **19**, **21**, **35**, **36** and **37** showed potent *in vitro* activity with MIC of 3.12 μg/mL against virulent strain *M. tuberculosis* $H_{37}Rv$ whereas the compounds **14** and **25** have MIC value of 1.56 μg/mL.

The compounds having MICs range between 0.78 and 3.12 μg/mL (**14**, **18, 19**, **21**, and **35**–**37**) were screened for their cytotoxicities with IC_{50} values up to 50 μg/mL concentration. Compounds were considered non-toxic if its IC_{50} was ≤10 times of its MIC. The SI (selectivity index) of the compounds was determined as ratio of IC_{50} against VERO cells or mouse bone marrow derived macrophage and MIC against *M. tuberculosis* H37Rv (SI = IC_{50}/MIC). For *in vivo* evaluation of any compound the SI should be ≥10 as it is considered to be safe.

As evident from the activity profiles few of the compounds showed quite good anti-TB activity *in vitro* as indicated by their low MICs, i.e., 0.78 μg/mL (compound **18**), 1.56 μg/mL (compounds **14** and **25**), and 3.12 μg/mL (compounds **19**, **21** and **35**–**37**). Compound **36** showed (MIC 12.5 μg/mL) against one multidrug resistant (MDR), one extensively drug resistant (XDR), two rifampicin resistant and two drug susceptive clinical isolates of *M. tuberculosis* (Table 2).

Table 1
In vitro antimycobacterial activities of synthesized compounds against *M. tuberculosis* $H_{37}Rv$.

Entry	Compounds	Clog *P*[a]	IC_{50} (μg/mL)	Selectivity index (SI)	MIC[b] (μg/ml) against $H_{37}Rv$
1	**12**	3.62	nd	nd	>12.5
2	**13**	4.13	nd	nd	12.5
3	**14**	4.70	>50	>10	1.56[c]
4	**15**	4.13	nd	nd	6.25[c]
5	**16**	3.31	nd	nd	6.25
6	**17**	3.12	nd	nd	>12.5
7	**18**	5.93	>50	>10	0.78[c]
8	**19**	3.54	>50	>10	3.12[c]
9	**20**	4.05	nd	nd	12.5
10	**21**	4.61	>50	>10	3.12[c]
11	**22**	4.05	nd	nd	6.25
12	**23**	3.22	nd	nd	6.25
13	**24**	3.03	nd	nd	12.5
14	**25**	5.84	nd	nd	1.56
16	**31**	2.94	nd	nd	6.25
17	**32**	4.14	nd	nd	12.5
18	**33**	3.02	nd	nd	>12.5
19	**34**	4.69	nd	nd	12.5
24	**35**	2.85	>50	>10	3.12[c]
25	**36**	4.06	>50	>10	3.12[c]
26	**37**	2.93	>50	>10	3.12[c]
27	**38**	4.61	nd	nd	12.5
20	**41**	4.14	nd	nd	12.5
28	**42**	4.06	nd	nd	6.25
21	**47**	2.83	nd	nd	6.25
22	**48**	4.04	nd	nd	>12.5
23	**49**	4.59	nd	nd	>12.5
29	**50**	2.74	nd	nd	12.5
30	**51**	3.94	nd	nd	6.25
31	**52**	4.5	nd	nd	>12.5
38	**54**	4.9	nd	nd	>12.5
39	**55**	4.81	nd	nd	12.5

[a] Clog *P* value calculated by using http://www.organic-chemistry.org/prog/peo/.
[b] MIC = Minimum inhibitory concentration, the lowest concentration of the compound which inhibits the growth of mycobacterium >90%; MIC of the drugs used as control, INH 0.02, rifampicin 0.20, ethambutol 2.00 μg/mL against M. tuberculosis $H_{37}R$.
[c] Non-toxic (at a dose of 10× MIC) against VERO and $BMDM_{\Phi}$.

2.2.2. Structure activity relationship

The SAR of the cyclopropyl[4-(4-methoxybenzyloxy)phenyl] methanols was carried out with respect to the above compound **3** (Fig. 1, MIC 3.12 μg/mL). In order to understand the importance of the substituents in benzyloxy ring on the activity, we prepared compounds cyclopropylphenyl methanone derivatives (**12**–**18**) and their methanoles (**19**–**25**). In general compounds having substituents at *para* position, either retained the activity (compounds **19**, **21** have shown MIC of 3.12 μg/mL, Table 1) as shown by compound **3** or increased the *in vitro* activity profile of the compounds (compounds **14**, **25** and **18** have shown MIC of 1.56 μg/mL and 0.78 μg/mL respectively, Table 1). This observation clearly established the importance of substituents at *para* position. Therefore, the effect polar and hydrophilic aminoalkoxy group as the *para* substitutent in the above series was sought in. Therefore, we prepared and evaluated the 4{[4-(aminoalkoxy)benzyloxy]phenyl}cyclopropyl methanones (**31**–**34**) and 4{[4-(aminoalkoxy)benzyloxy]phenyl} cyclopropyl methanols (**35**–**38**) against *M. tuberculosis*. As evident from the activity results compounds **35**, **36** and **37** with 2-(morpholinyl)-, 2-(piperidin-1-yl)-ethoxy and 2-(*N,N*-di-*methyl*)-ethoxy as *para* substitutent in the benzyloxy ring were equipotent (each MIC = 3.12 μg/mL) to the compound **3** (Table 1).

Compound **42** (MIC = 6.25 μg/mL) having [2-(piperidin-1-yl)-ethoxy**]** as the *meta* substitutent in the benzyloxy moiety (a positional isomer of compound **36**) was slightly less active (MIC 6.25 μg/mL) as compared to compound **36**. Thus compounds with *para* substitutents are more active than the *meta* substituents.

To understand the influence of methoxy group along with aminoalkoxy substituents of benzyloxy ring on the activity, we prepared cyclopropyl{4[3-(methoxy)-4-(aminoalkoxy)benzyloxy] phenyl} methanones (**47**–**49**) and their methanoles (**50**–**52**)

Table 2
In vitro activity of compound **36** against clinical isolates of *M. tuberculosis*.

Isolates	Drug susceptible		MDR	XDR	RMF resistant	
	1	2			1	2
MIC (μg/mL)	>12.5	>12.5	12.5	12.5	12.5	12.5

Table 3
Intracellular (*ex-vivo* activity) of non-toxic compounds against *M. tuberculosis* CFU in mouse bone marrow derived macrophages at a concentration of 5× MIC.

S. no.	Compounds	% Reduction in intracellular CFU of *M. tuberculosis*
1	**14**	0
2	**18**	24
3	**19**	67
4	**21**	54
5	**22**	88
6	**35**	89
7	**36**	98
8	**37**	80

(Scheme 4). This change does not improve the activity as none of the compounds exhibited MIC $\leq$ 3.12 μg/mL. This is clear that additional hydrophilic groups of benzyloxy ring did not improve the activity profile.

Finally to see the importance of benzyloxy ring on activity, we prepared and evaluated 4-{[2-(*N*,*N*-dibutylamino)ethoxy]phenyl} cyclopropyl methanone (**54**) and its alcohol derivative (**55**). The activity in these compounds (**54** and **55**) was significantly dropped as both of them showed MIC $\geq$ 12.5 μg/mL only. This observation again showed the significance of benzyloxy ring in antitubercular activity. On the basis of above structure activity relationship following generalization can be made (i) the maximum influence of substituents at *para* position on activity; (ii) activity decrease with increase hydrophilicity of benzyloxy ring; (iii) 4-benzyloxy ring play an important role for antitubercular action.

2.2.3. *Ex-vivo efficacy of compounds against intracellular M. tuberculosis in bone marrow derived mouse macrophages*

Among the non-toxic compounds showing potent *in vitro* activities two of the cyclopropyl methanones compounds **14** and **18** and six of the cylopropyl methanols **19**, **20**, **22**, **35**, **36** and **37** were evaluated further for their intracellular (*ex-vivo*) effect on CFU in mouse bone marrow derived macrophages at a concentration 5 times of their MIC values as per earlier reported method [28]. The results are presented in Table 3. It is evident that cyclopropyl methanones are not active as they reduce <50% of CFU count, while all the above aryloxyphenyl cyclopropyl methanols screened displayed >50% reduction in the CFU count. Compound **36** was the most active compound as it led to inhibition of 98% growth of intracellular bacilli.

2.2.4. *In vivo oral efficacy of compounds 22, 36 and 37 against M. tuberculosis $H_{37}Rv$ [29,30]*

Based on the above intracellular killing of the bacterium only aryloxyphenyl cyclopropyl methanols **22**, **36** and **37** were further evaluated for their *in vivo* oral efficacy against *M. tuberculosis* $H_{37}Rv$ in mice and the results were shown in Table 4. Among these compounds, compound **36** was the most potent compound with

Table 4
In vivo activity of aryloxyphenyl cyclopropyl methanols **22**, **36** and **37** and isoniazid against *M. tuberculosis* $H_{37}Rv$ in mice.

Compounds	MST[b] on day 30 (compound)	MST[b] on day 30 (Control)
22 [a] (100 mg/kg)	23.37	26.40
36 [a] (100 mg/kg)	27.50	23.37
37 [a] (100 mg/kg)	12.85	12.00
INH (25 mg/kg)	30.0	–

[a] Non-toxic against mammalian cell line, VERO and mouse bone marrow derived macrophages.
[b] MST, mean survival time.

Table 5
Detailed *in vivo* efficacy of compound **36** and isoniazid against *M. tuberculosis* $H_{37}Rv$ in mice.

Compound	On day 30		On day 40		Bacilli in lungs per g (on day 30)
	% survivors	MST	% survivors	MST	
Control	25	23.37	12	25.12	3.6×10^8
36 (100 mg/kg)	50	27.50	25	31.62	9.0×10^7
INH (25 mg/kg)	100	30.00	100	40	–

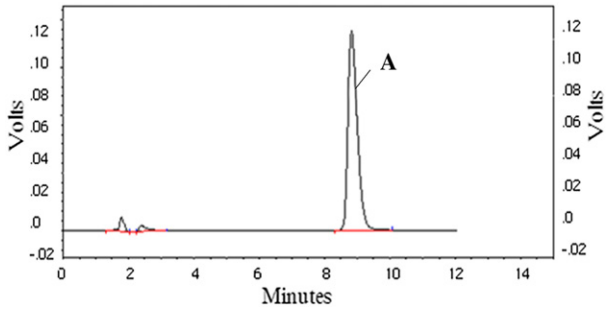


Fig. 2. HPLC chromatogram showing main peak (A) of compound **36** at 8.82 min.

acceptable MST. The other two compounds **22** and **37** could not protect the animals as compared to standard drug INH.

Based on the above results compound **36** was studied in detail for count of bacilli up to 40 days in mice [29,30]. The antitubercular activity was analyzed based on percentage of survivors, mean survival time and load of bacilli in lungs and the results are shown in Table 5. As evident from results the MST of the group of mice treated with the compound **36** was 27.50 (calculated on day 30) and 31.62 (calculated on day 40) as compared to untreated infected control group where the MST were respectively, 23.37 and 25.12. The percentages of mice survived on these days were 50 and 25 in the treated group as compared to control group in which 25 and 12 percent mice survived. In the group treated with INH, the MST was 30 on day 30 and 40 on day 40 as there was no mortality (100% survival) in this group.

2.2.5. *The stability study of compound **36** at gastric pH (0.1N HCl)*

Since the compound did not show expected *in vivo* activity, the stability of the compound **36** was studied at gastric pH and the results are depicted in Figs. 2–4. As shown in HPLC data (Fig. 2)

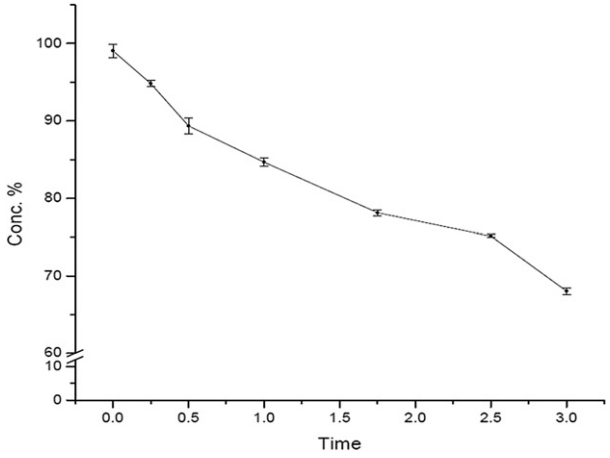


Fig. 3. Effect of 0.1N HCl on stability of compound **36** at ambient temperature.

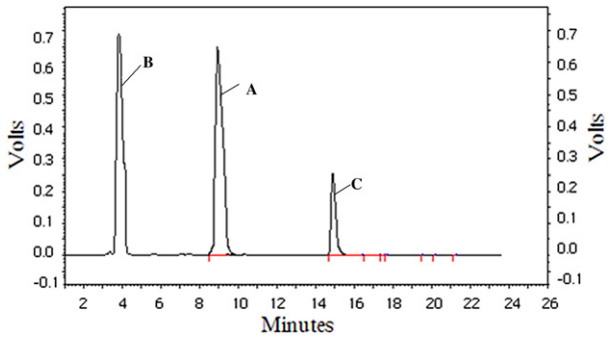


Fig. 4. HPLC chromatogram of compound **36** after incubation in 0.1N HCl for 3 h showing two degradation peaks (B and C) with retention time of 3.85 min and 14.87 min respectively. The peak of main compound (A) with retention time 8.82 min.

compound **36** is being degraded. After a time interval of 3 h <70% of the compound is left a major compound with retention time of 3 min.

In view of the instability of this compound under acidic pH, an enteric coating of the compound has been prepared and is being evaluated in detail.

3. Conclusion

In conclusion we have synthesized a library of [4-(aryloxy) phenyl] cyclopropyl methanones and methanols using simple and flexible synthetic chemistry in good yields. The compounds were evaluated against *M. tuberculosis* $H_{37}Rv$ *in vitro* with impressive MIC values. Compounds with potent *in vitro* activities were screened for their cytotoxicities against VERO cell line and mouse derived macrophages. The non-toxic compounds were further screened intracellulary against *M. tuberculosis* $H_{37}Rv$ in bone marrow derived muse macrophages. Several compounds showed good activity intracellulary too. The intracellulary active compounds **22**, **36** and **37** were screened for their *in vivo* protective efficacy in mouse model. The compound **36** possesses overall satisfactory drug-like properties. The mice treated with the compound **36** survived longer 4 days (calculated on day 30) and 6 days (calculated on day 40) as compared to untreated infected controls. The SAR from the series provided interesting consideration i.e., hydrophilic groups ethoxyamines, both aromatic rings were found to be suitable substituents in order to obtain good anti-TB activity. Further studies are in progress with this promising anti-TB compound with its formulation.

4. Experimental section

4.1. Chemistry

Commercially available reagent grade chemicals were used as received. All reaction was followed by TLC on E. Merck Kieselgel 60 F_{254}, with detection by UV light, spraying a 20% $KMnO_4$ aq. solution. Column chromatography was performed on silica gel (60–120 mesh and 100–200 mesh, E. Merck). IR spectra were recorded as thin films or on KBr pellets with a PerkinElmer Spectrum RX-1 (4000–450 cm^{-1}) spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Brucker DRX-300 in $CDCl_3$ or $CDCl_3$+CCl_4 chemical shift values are reported in ppm relative to TMS (tetramethylsilane) as internal reference, unless otherwise stated; s (singlet), d (doublet), dd (double doublet), t (triplet), m (multiplet); coupling constant (*J*) in hertz. FAB mass spectra were performed using a mass spectrometer Jeol SX-102, ES mass spectra were performed using Quattro II (Micromass) and HRMS were performed using JEOL MSRoute. The purity (>95%) of the compounds was determined either by HPLC or by combustion analyses. Elemental analyses were performed on a PerkinElmer 2400 II elemental analyzer.

4.1.1. General procedure for the synthesis of compounds (**12**–**18**)

To a stirring suspension of NaH (60% dispersion in mineral oil, 4 eq.) in DMF at 0 °C, was added benzyl alcohol (1 eq.), followed by the addition of 4-chloro-4′-fluorobutyrophenone **11** (1 eq.) dropwise. Tetrabutylammonium bromide (20 mol%) was added as catalyst to the stirring reaction mixture at ambient temperature for 30 min then transferred it to reflux and stirring continued till the consumption of the starting material (TLC) for given time. After the completion of reaction, the reaction mixture was filtered on celite pad. The filtrate was extracted with ethylacetate (3 × 25 mL) and then the organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified by simple column chromatography (using 60–120 mesh silica gel) to obtain the desired product.

*4.1.1.1. Cyclopropyl{4-[4-(pyridin-2-ylmethoxy)benzyloxy]phenyl} methanone (**12**).* To a stirring suspension of NaH (60% dispersion in mineral oil, 0.39 g, and 16.39 mmol) in DMF (12 mL) at 0 °C, was added benzyl alcohol derivative **4** (0.88 g, 4.09 mmol) dropwise. After 0.5 h, 4-chloro-4′-fluorobutyrophenone **11** (1.0 mL, 4.09 mmol) was added slowly through dropping funnel. Tetrabutylammonium bromide (0.26 g, 0.082 mmol) was added as catalyst to the stirring reaction mixture at ambient temperature for 30 min then transferred it to reflux and stirring continued till the consumption of the starting material (TLC) for given time. After completion of reaction, the reaction mixture was filtered on celite pad and the filtrate was extracted with ethylacetate (3 × 25 mL)/water (400 mL); the organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residual mass. The latter was purified by simple column chromatography (60–120 mesh silica gel) using ethyl acetate/hexane (4:6) as eluent to afford product **12** as a white solid yield 1.74 g (80%); mp 120–123 °C; ^1H NMR (200 MHz, $CDCl_3$) δ = 8.55 (d, *J* = 3.156 Hz, 1H, PyH), 7.93 (d, *J* = 8.8 Hz, 2H, ArH), 7.68 (m, 1H, PyH), 7.50 (d, *J* = 7.81 Hz, 2H, ArH), 7.28 (d, *J* = 8.5 Hz, 2H, ArH), 7.15 (m, 1H, PyH), 7.17 (d, *J* = 6.6 Hz, 2H, ArH), 6.95 (d, *J* = 8.7 Hz, 2H, ArH), 5.19 (s, 2H, OCH_2), 5.02 (s, 2H, OCH_2), 2.61 (m, 1H, cyclopropyl CH), 1.22 (m, 2H, cyclopropyl CH_2), 0.95 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 198.3 (CO), 162.7, 158.7, 157.6 (ArC), 149.4, 136.9 (PyCH.), 131.5, 129.1 (ArC), 130.5, 129.5 (ArCH), 122.8, 121.4 (PyCH), 115.3, 114.7 (ArCH), 70.8, 70.1 (OCH_2Ar), 16.8 (cyclopropyl CH), 11.3 (cyclopropyl CH_2′s); IR ν_{max} cm^{-1} 1651 (C=O); MS FAB *m*/*z* = 360.1 $[M + H]^+$; Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90; found C, 76.80; H, 5.85; N, 3.86.

*4.1.1.2. [4-(3-Bromobenzyloxy)phenyl](cyclopropyl)methanone (**13**).* It was obtained by the reaction of benzyl alcohol derivative **5** (0.75 g, 4.09 mmol), NaH (60% dispersion in mineral oil, 0.39 g, and 16.39 mmol), 4-chloro-4′-fluorobutyrophenone (11) (1.0 mL, 4.09 mmol) and tetrabutylammonium bromide (0.26 g, 0.082 mmol) by using the procedure as described for compound **12**, to give compound **13** as white solid, mp 85–86 °C; yield, 1.65 g (82%); R_f = 0.5 (ethylacetate/hexane, 4:6); ^1H NMR (200 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 8.5 Hz, 2H, ArH), 7.56 (s, 1H, ArH), 7.44 (d, *J* = 7.52 Hz, 1H, ArH), 7.30 (m, 2H, ArH), 6.96 (d, *J* = 8.6 Hz, 2H, ArH), 5.06 (s, 2H, OCH_2), 2.65–2.59 (m, 1H, cyclopropyl CH), 1.27 (m, 2H, cyclopropyl CH_2), 0.99 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 198.6 (CO), 162.3, 138.9, 131.9, 123.2 (ArC), 131.6, 130.6,

130.5, 126.1, 114.7 (ArCH), 69.4 (OCH_2), 16.9 (cyclopropyl CH), 11.6 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 1656 (C=O); MS FAB m/z = 331 $[M + H]^+$ Anal. Calcd for $C_{17}H_{15}BrO_2$: C, 61.65; H, 4.56; found C, 61.63; H, 4.52.

*4.1.1.3. [4-(4-(Benzyloxy)benzyloxy)phenyl](cyclopropyl)methanone (**14**).* It was obtained by the reaction of benzyl alcohol derivative **6** (0.87 g, 4.09 mmol), NaH (60% dispersion in mineral oil, 0.39 g, and 16.39 mmol), 4-chloro-4′-fluorobutyrophenone (**11**) (1.0 mL, 4.09 mmol) and tetrabutylammonium bromide (0.26 g, 0.082 mmol) by using the procedure as described for compound **12**, to give compound **14** as liquid; yield 1.46 g (67%); R_f = 0.5 (ethylacetate/hexane, 3:7); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.99 (d, J = 8.7. Hz, 2H, ArH), 7.32 (m, 7H ArH), 7.20 (d, J = 8.4 Hz, 2H ArH), 6.94 (m, 2H ArH), 5.07 (s, 4H, 2× OCH_2), 2.66 (m, 1H, cyclopropyl CH), 1.24 (m, 2H, cyclopropyl CH_2), 1.03 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 199.4 (CO), 162.9, 159.2, 156.9, 137.2, 132.4 (ArC), 130.6, 129.7, 129.4, 129.0, 128.9, 128.7, 128.4, 128.2, 127.8, 127.8, 115,4, 114.9, 112.2 (ArCH's), 70.4, 70.3 (2× OCH_2), 17.0 (cyclopropyl CH), 11.6 (cyclopropyl CH_2's); IR ν_{max} cm^{-1}, 1659.6 (C=O); MS FAB m/z = 359 $[M + H]^+$ Anal. Calcd for $C_{24}H_{22}O_3$: C, 80.42; H, 6.19; found C, 80.54; H, 6.31.

*4.1.1.4. [4-(4-Bromobenzyloxy)phenyl](cyclopropyl)methanone (**15**).* It was obtained by the reaction of benzyl alcohol derivative **7** (0.76 g, 4.09 mmol), NaH (60% dispersion in mineral oil, 0.39 g, and 16.39 mmol), 4-chloro-4′-fluorobutyrophenone (**11**) (1.0 mL, 4.09 mmol) and tetrabutylammonium bromide (0.26 g, 0.082 mmol) by using the procedure as described for compound **12**, to give compound **15** as white solid, mp 130–131 °C; yield 1.5 g (75%); R_f = 0.5 (ethylacetate/hexane, 4:6); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.99 (d, J = 9.71 Hz, 2H, ArH), 7.51 (d, J = 8.34 Hz, 2H, ArH), 7.29 (d, J = 8.46 Hz, 2H, ArH), 6.90 (d, J = 9.68 Hz, 2H, ArH), 5.06 (s, 2H, OCH_2), 2.62 (m, 1H, cyclopropyl CH), 1.23 (m, 2H, cyclopropyl CH_2), 1.00 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 198.8 (CO) 162.4 (ArC), 153.4, 135.6 (ArC), 132.2, 131.2, 131.8, 130.6, 129.4, 122.5, (ArCH's), 114.8 (ArC), 70.1 (OCH_2) 69.6 (OCH_2's), 16.9 (cyclopropyl CH), 11.6 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 2943 (C–H stretching), 1651 (C=O); HRMS (JEOL MSRoute) m/z calcd for $C_{17}H_{15}BrO_2$ (M^+) 330.0255, found 330.0249; MS FAB m/z = 331 $[M + H]^+$; Anal. Calcd for $C_{17}H_{15}BrO_2$: C, 69.75; H, 7.02; found C, 69.70; H, 7.18.

*4.1.1.5. Cyclopropyl[4-(3-nitrobenzyloxy)phenyl]methanone (**16**).* It was obtained by the reaction of benzyl alcohol derivative **8** (0.63 g, 4.09 mmol), NaH (60% dispersion in mineral oil, 0.39 g, and 16.39 mmol), 4-chloro-4′-fluorobutyrophenone (**11**) (1.0 mL, 4.09 mmol) and tetrabutylammonium bromide (0.26 g, 0.082 mmol) by using the procedure as described for compound **12**, to give compound **16** as liquid; yield 1.48 g (82%); R_f = 0.5 (ethylacetate/hexane, 1:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.33 (s, 1H, ArH), 8.23 (d, J = 7.9 Hz, 1H, ArH), 8.05 (m, 2H, ArH), 7.80 (d, J = 7.5 Hz, 1H, ArH), 7.63 (t, 1H, J = 7.9 Hz, ArH), 7.06 (d, J = 8.6 Hz, 2H, ArH), 5.23 (s, 2H, OCH_2), 2.67 (m, 1H, cyclopropyl CH), 1.26 (m, 2H, cyclopropyl CH_2) 1.04 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 199.43 (CO) 162.09, 148.90, 138.89, 132.18 (ArC), 133.51, 130.76, 130.12, 123.55, 122.58, 114.87 (ArCH), 69.10 (OCH_2), 17.14 (cyclopropyl CH), 11.75 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 1653 (C=O), 1599; Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71; found, C, 68.64; H, 5.02; N, 4.68; MS FAB m/z = 298 $[M + H]^+$.

*4.1.1.6. Cyclopropyl[4-(3,4,5-trimethoxybenzyloxy)phenyl]methanone (**17**).* It was obtained by the reaction of benzyl alcohol derivative **9** (0.81 g, 4.09 mmol), NaH (60% dispersion in mineral oil, 0.39 g, and 16.39 mmol), 4-chloro-4′-fluorobutyrophenone (**11**) (1.0 mL, 4.09 mmol) and tetrabutylammonium bromide (0.26 g, 0.082 mmol) by using the procedure as described for compound **12**, to give compound **17** as white solid, mp 90–92 °C; yield 1.56 g (75%); R_f = 0.5 (ethylacetate/hexane, 4:6); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.02 (d, J = 8.8 Hz, 2H, ArH), 7.05 (d, J = 8.8 Hz, 2H, ArH), 6.66 (s, 2H, ArH), 5.05 (s, 2H, OCH_2), 3.87 (s, 9H, 3× OCH_3), 2.66 (m, 1H, cyclopropyl CH), 1.23 (m, 2H, cyclopropyl CH_2), 1.03 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 198.7 (CO) 162.2, 153.4, 137.8, 131.7, 131.2 (ArC), 130.2, 114,4, 104.5 (ArCH), 70.3 (OCH_2), 60.7(OCH_3), 56.0 (2× OCH_3), 16.5 (cyclopropyl CH), 11.2 (cyclopropyl CH_2's); Anal. Calcd for $C_{20}H_{22}O_5$ (345): C, 70.16; H, 6.48; found C, 70.10; H, 6.45; IR ν_{max} cm^{-1} 1651 (C=O); MS FAB m/z = 343 $[M + H]^+$; HRMS (JEOL MSRoute) m/z calcd for $C_{20}H_{22}O_5$ (M^+) 342.1467, found 342.1467.

*4.1.1.7. Cyclopropyl{4-[3-(3,4-dichlorobenzyloxy)benzyloxy]phenyl}methanone (**18**).* It was obtained by the reaction of compound **10** (1.15 g, 4.09 mmol), NaH (60% dispersion in mineral oil, 0.39 g, and 16.39 mmol), 4-chloro-4′-fluorobutyrophenone (**11**) (1.0 mL, 4.09 mmol) and tetrabutylammonium bromide (0.26 g, 0.082 mmol) by using the procedure as described for compound **12**, to give compound **18** as white solid, mp 80–82 °C; yield 1.95 g (75%); R_f = 0.5 (ethylacetate/hexane, 4:6); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.10 (d, J = 8.8 Hz, 2H, ArH), 7.65 (s, 1H, ArH), 7.56 (d, J = 8.2 Hz, 1H, ArH), 7.43 (m, 1H, ArH), 7.05 (m, 6H, ArH), 5.23 (s, 2H, OCH_2), 5.13 (s, 2H, OCH_2), 2.63 (m, 1H, cyclopropyl CH), 1.25 (m, 2H, cyclopropyl CH_2), 0.92 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 199.3 (CO), 159.5, 157.6, 139.5, 136.9, 134.6, 133.8, 132.1 (ArC), 130.9, 130.6, 130.3, 129.6, 126.9, 120.6, 115.3, 114.9, 114.8, 114.7 (ArCH), 70.2, 68.9 (OCH_2Ar), 17.0 (cyclopropyl CH), 11.7 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 1696 (C=O); HRMS (JEOL MSRoute) m/z calcd for $C_{24}H_{20}Cl_2O_3$ (M^+) 426.0781, found 426.0790, MS FAB m/z = 449 $[M + Na]^+$ Anal. Calcd for $C_{24}H_{20}Cl_2O_3$: C, 67.46; H, 4.72; found C, 67.45; H, 4.65.

*4.1.2. General procedure for synthesis of compounds **19–25***

To a stirred solution of the above 4-(benzyloxy)phenyl cyclopropyl methanones (**12–18**)(1 eq.) in MeOH (5 mL), $NaBH_4$ (0.10 g, 2.78 mmol) was slowly added at 0 °C. The reaction mixture was brought at ambient temperature and stirring continued until the disappearance of the starting material (TLC). The reaction mixture was quenched by adding saturated aqueous ammonium chloride in order to remove the unused $NaBH_4$ and the reaction mixture was evaporated under reduced pressure to give a crude mass. The latter was extracted with chloroform several times. The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a crude material which was chromatographed over silica (silica gel 60–120 mesh) to afford desired products (**19–25**).

*4.1.2.1. Procedure for the synthesis of cyclopropyl{4-[4-(pyridin-2-ylmethoxy)benzyloxy]phenyl}methanol (**19**).* To a stirred solution of cyclopropyl{4-[4-(pyridin-2-ylmethoxy)benzyloxy]phenyl}- methanone **12** (1.0 g, 2.78 mmol) in MeOH (5 mL), $NaBH_4$ (0.10 g, 2.78 mmol) was slowly added at 0 °C. The reaction mixture was brought at ambient temperature and stirring continued tills the disappearance of the starting material (TLC). The reaction mixture was quenched by adding saturated aqueous ammonium chloride in order to remove the unused $NaBH_4$ and the reaction mixture was evaporated under reduced pressure to give a crude mass. The latter was extracted with chloroform several times. The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a crude material which was chromatographed (SiO_2, 60–12-mesh) over to afford desired product **19** as white solid, mp 120–123 °C; yield 0.80 g (80%); R_f = 0.5 (methanol/chloroform, 2:98); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.55

(d, $J = 4.156$ Hz, 1H, PyH), 7.65 (m, 2H, PyH), 7.31 (m, 5H, PyH, ArH), 6.91 (m, 4H, ArH), 5.18 (s, 2H, OCH_2), 4.95 (s, 2H, OCH_2), 3.96 (d, $J = 7.9$ Hz, 1H, CHOH), 1.50 (bs, 1H, OH), 1.18 (m, 1H, cyclopropyl CH), 0.55 (m, 2H, cyclopropyl CH_2), 0.33 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 158.6, 157.5$ (ArC), 149.5, 137.3 (ArCH), 136.9, 130.0 (ArC), 129.6, 127.6, 123.0, 121.7, 115.3, 115.0 (ArCH), 70.9, 70.1 (OCH_2Ar), 31.3 (CHOH), 19.4 (cyclopropyl CH), 3.9, 3.1 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 3413 (O–H stretching), 2903 (C–H stretching); MS FAB $m/z = 361$ $[M + H]^+$; Anal. Calcd for $C_{23}H_{23}NO_3$ (361): C, 76.43; H, 6.41; N, 3.88; found C, 76.63; H, 6.31; N, 3.78.

*4.1.2.2. [4-(3-Bromobenzyloxy)phenyl](cyclopropyl)methanol (**20**).* It was obtained by the reaction of compound **13** (1.0 g, 3.03 mmol), $NaBH_4$ (0.12 g, 3.03 mmol), by using the procedure as described for compound **19**, to give compound **20** as white solid, mp 70–72 °C; yield 0.90 g (90%); $R_f = 0.5$ (methanol/chloroform, 2:98); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.59$ (s, 1H, ArH), 7.46 (d, $J = 7.7$ Hz, 1H, ArH), 7.32 (m, 4H, ArH), 6.93 (d, $J = 8.6$ Hz, 2H, ArH), 5.06 (s, 2H, OCH_2), 3.94 (d, 1H, CHOH), 2.03 (brs exchangeable with D_2O), 1.21 (m, 1H, cyclopropyl CH), 0.55 (m, 2H, cyclopropyl CH_2), 0.33 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 158.3, 139.8, 137.0, 123.1$ (ArC), 131.4, 130.7, 130.5, 126.2, 115.0 (ArCH), 78.5 (CHOH), 69.5 (OCH_2), 19.5 (cyclopropyl CH), 4.0, 3.2 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 3380 (OH stretching); HRMS (JEOL MSRoute) m/z calcd for $C_{17}H_{17}BrO_2$ (M^+) 332.0412, found 332.0421, MS FAB $m/z = 333$ $[M + H]^+$; Anal. Calcd for $C_{17}H_{17}BrO_2$: C, 61.28; H, 5.14; found C, 61.25; H, 5.10.

*4.1.2.3. 4-{4-[Benzyloxy)benzyloxy]phenyl}(cyclopropyl)methanol (**21**).* It was obtained by the reaction of compound **14** (1.0 g, 3.87 mmol), $NaBH_4$ (0.15 g, 3.87 mmol), by using the procedure as described for compound **19**, to give compound **21**, as liquid; yield 0.67 g (67%); $R_f = 0.5$ (methanol/chloroform, 2:98); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.40$ (m, 4H, ArH), 7.23 (m, 5H, ArH), 7.99 (m, 4H ArH), 5.05 (s, 4H, 2× OCH_2), 4.59 (m, 1H, cyclopropyl CHOH), 2.14 (m, 1H, cyclopropyl CH), 1.30 (m, 2H, cyclopropyl CH_2), 1.19 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 158.78, 137.36, 131.08$ (ArC), 130.18, 130.03, 129.63, 129.02, 128.41, 127.87, 127.56 (ArCH's), 70.48, 70.24 (2×OCH_2), 17.0 (cyclopropyl CH), 11.6 (cyclopropyl CH_2's); IR ν_{max} cm^{-1}, 3387, 1610, 1586; MS FAB $m/z = 343$ $[M - OH]^+$; Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71; found C, 79.95; H, 6.67.

*4.1.2.4. [4-(4-Bromobenzyloxy)phenyl](cyclopropyl)methanol (**22**).* It was obtained by the reaction of compound **15** (1.0 g, 3.03 mmol), $NaBH_4$ (0.12 g, 3.03 mmol), by using the procedure as described for compound **19**, to give compound **22** as white semisolid; yield 0.90 g (90%); $R_f = 0.5$ (methanol/chloroform, 2:98); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.49$ (d, $J = 8.3$ Hz, 2H, ArH), 7.30 (m, 4H, ArH), 7.29 (d, $J = 8.6$ Hz, 2H ArH), 5.00 (s, 2H, OCH_2), 3.93 (d, $J = 8.15$ Hz, 1H, CHOH), 1.91 (brs exchangeable with D_2O, 1H, OH), 1.20 (m, 1H, cyclopropyl CH), 0.55 (m, 2H, cyclopropyl CH_2), 0.33 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 158.3, 137.0, 136.5, 122.2$ (ArC), 132.1, 129.3, 121.7, 115.0 (ArCH), 78.3 (CHOH), 69.2 (OCH_2) 19.5 (cyclopropyl CH), 3.9, 3.1 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 3405 (O–H stretching); HRMS (JEOL MSRoute) m/z calcd for $C_{17}H_{17}BrO_2$ (M^+) 332.0412, found 332.0417, MS FAB $m/z = 334$ $[M + 2H]^+$; Anal. Calcd for $C_{17}H_{17}BrO_2$: C, 61.28; H, 5.14; found C, 61.53; H, 5.21.

*4.1.2.5. Cyclopropyl[4-(3-nitrobenzyloxy)phenyl]methanol (**23**).* It was obtained by the reaction of compound **16** (1 g, 3.36 mmol), $NaBH_4$ (0.13 g, 3.36 mmol), by using the procedure as described for compound **19**, to give compound **23**. It was obtained as liquid; yield 0.83 g (82%); $R_f = 0.5$ (methanol/chloroform, 2:98); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 8.32$ (s, 1H, ArH), 8.20 (d, $J = 7.7$ Hz, 1H, ArH), 7.79 (d, $J = 7.4$ Hz, 1H, ArH), 7.60 (t, 1H, $J = 7.9$ Hz, ArH), 7.40 (d, $J = 8.5$ Hz, 2H, ArH), 6.98 (d, $J = 8.6$ Hz, 2H, ArH), 5.16 (s, 2H, OCH_2), 3.99 (d, 1H, CHOH), 1.25 (m, 1H, cyclopropyl CH), 0.62 (m, 2H, cyclopropyl CH_2), 0.35 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 158.00, 148.88, 139.73, 137.46$, (ArC), 133.51, 129.97, 127.84, 123.28, 122.52, 115.09 (ArCH), 69.13 (OCH_2), 19.53 (cyclopropyl CH), 3.94, 3.17 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 1527, 1350, 1236; MS FAB $m/z = 282$ $[M - 18]^+$; Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68; found, C, 68.18; H, 5.70; N, 4.65.

*4.1.2.6. Cyclopropyl[4-(3,4,5-trimethoxybenzyloxy)phenyl]methanol (**24**).* It was obtained by the reaction of compound **17** (1.0 g, 2.92 mmol), $NaBH_4$ (0.11 g, 2.92 mmol), by using the procedure as described for compound **19**, to give compound **24** as liquid; yield 0.85 g (85%); $R_f = 0.5$ (methanol/chloroform, 3:97); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.35$ (d, $J = 8.5$ Hz, 2H, ArH), 6.95 (d, $J = 8.5$ Hz, 2H, ArH), 6.66 (s, 2H, ArH), 4.95 (s, 2H, OCH_2), 3.95 (m, 10H, OCH_3, CHOH), 2.01 (brs exchangeable with D_2O, 1H, OH), 1.24 (m, 1H, cyclopropyl CH), 0.55 (m, 2H, cyclopropyl CH_2), 0.36 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 158.4, 153.8, 1385, 137.1, 132.7$(ArC), 127.5, 114.8, 105.0 (ArCH's), 77.5 (CHOH), 70.4 (OCH_2), 60.7, 56.3 (OCH_3), 19.5 (cyclopropyl CH), 3.7, 3.1 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 3492 (O–H stretching), 2937 (C–H stretching), 1597 (C=C stretching); HRMS (JEOL MSRoute) m/z calcd for $C_{20}H_{24}O_5$ (M^+) 344.1624, found 344.1612, MS FAB $m/z = 345$ $[M + H]^+$; Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02; found C, 69.83; H, 7.21.

*4.1.2.7. Cyclopropyl{4-[3-(3,4-dichlorobenzyloxy)benzyloxy]phenyl} methanol (**25**).* It was obtained by the reaction of compound **18** (1.0 g, 2.23 mmol), $NaBH_4$ (0.08 g, 2.23 mmol), by using the procedure as described for compound **19**, to give compound **25** as liquid; yield 0.85 g (85%); $R_f = 0.5$ (methanol/chloroform, 2:98); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.51–7.21$ (m, 6H, ArH), 6.99–6.97 (m, 2H, ArH), 6.90–6.85 (m, 3H ArH), 5.01 (s, 2H, OCH_2), 4.99 (s, 2H, OCH_2), 3.97 (d, 1H, $J = 7.96$ Hz, cyclopropyl CHOH), 1.18 (m, 1H, cyclopropyl CH), 0.58 (m, 2H, cyclopropyl CH_2), 0.31 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 158.95, 158.51, 130.94, 130.13, 129.61, 127.66, 126.82$ (ArC), 139.34, 137.60, 136.87, 133.23, 132.40, 120.57, 115.07, 114.66, 113.99 (ArCH's), 70.10, 68.86 (2× OCH_2), 19.54 (cyclopropyl CH), 3.96, 3.19 (cyclopropyl CH_2's); IR ν_{max} cm^{-1}, 3445 (O–H stretching), 1595 (C=C stretching); MS FAB $m/z = 451$ $[M + H]^+$; Anal. Calcd for $C_{24}H_{22}Cl_2O_3$: C, 67.14; H, 5.16; Cl, 16.52; found C, 67.10; H, 5.13; Cl, 16.44.

*4.1.3. Preparation of benzyl alcohols (**27**–**30**)*

*4.1.3.1. Procedure for preparation of 4-(2-morpholinoethoxy)phenyl methanol (**27**).* A mixture of the 4-hydroxybenzaldehyde **26** (1.0 g, 8.19 mmol), anhydrous K_2CO_3 (3.3 g, 24.58 mmol), TBAB (0.26 g, 0.819 mmol) and 4-(2-chloroethyl) morpholine hydrochloride (1.82 g, 9.83 mmol), in anhydrous THF (10 mL) was refluxed with stirring at till the disappearance of the starting materials (TLC). The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give the crude mass which was used as such in the subsequent step of reduction with sodium borohydride.

To the stirring solution of the above crude 4-(2-morpholinoethoxy)benzaldehyde in methanol (10 mL), was added $NaBH_4$ (0.31 g, 8.19 mmol) slowly at 0 °C and the stirring was continued at an ambient temperature till the complete reduction (TLC). The excess amount of $NaBH_4$ was quenched with aq. NH_4Cl at 0 °C and the reaction mixture was evaporated under reduced pressure to remove the solvent. The crude product, thus obtained was extracted with ethyl acetate/water (50 mL/200 mL). The organic layer was

dried over anhydrous Na_2SO_4 and concentrated to give a crude mass, which was chromatographed over SiO_2 column using ethyl acetate/hexane (3:7) as eluent to afford the compound **27** as colourless liquid; yield 1.5 g (78%); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.23$ (d, $J = 8.5$ Hz, 2H, ArH), 6.86 (d, 2H, $J = 8.5$ Hz, ArH), 4.54 (s, 2H, OCH_2), 4.07 (t, 2H, $J = 5.74$ Hz, OCH_2), 3.72 (m, 4H, OCH_2), 2.80 (t, $J = 5.72$ Hz, 2H, NCH_2), 2.57 (m, 4H, 2× NCH_2 morpholine protons); IR ν_{max} cm^{-1} 3437 (OH stretching), 1603 (C=C stretching); MS FAB $m/z = 237$ $[M]^+$.

*4.1.3.2. 4-[2-(Piperidin-1-yl)ethoxy]phenyl methanol (**28**).* It was obtained by the reaction of 4-hydroxybenzaldehyde **26** (1.0 g, 8.19 mmol), anhydrous K_2CO_3 (3.39 g, 24.58 mmol), TBAB (0.26 g, 0.819 mmol), 1-(2-chloroethyl)piperidine hydrochloride (1.79 g, 9.83 mmol) and $NaBH_4$ (0.31 g, 8.19 mmol) by using the procedure as described for compound **27**, to give compound **28** as colourless liquid, yield 1.64 g (85%); $R_f = 0.5$ (ethylacetate/hexane, 4:6); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.19$ (d, 2H, $J = 8.0$ Hz, ArH), 6.79 (d, $J = 8.0$ Hz, 2H, ArH), 4.54 (s, 2H, OCH_2), 4.02 (t, $J = 6.1$ Hz, 2H, OCH_2), 3.03 (bs, 1H, OH), 2.72 (t, $J = 6.1$ Hz, 2H, NCH_2), 2.45 (m, 4H, 2× NCH_2 piperidine protons), 1.54 (m, 4H, CH_2 piperidine protons), 1.44 (m, 2H, CH_2 piperidine protons); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 158.6$, 134.0 (ArC), 128.8, 114.8 (ArCH's), 66.1, 64.9 (OCH_2), 58.3, 55.4 (NCH_2), 26.2 (2× CH_2), 24.6 (CH_2); IR (KBr), ν_{max} cm^{-1} 3404 (OH stretching), 1611 (C=C stretching); ESMS $m/z = 236$ $[M + H]^+$.

*4.1.3.3. 4-[2-(Dimethylamino)ethoxy]phenyl methanol (**29**).* It was obtained by the reaction of 4-hydroxybenzaldehyde **26** (1.0 g, 8.19 mmol), anhydrous K_2CO_3 (3.39 g, 24.58 mmol), TBAB (0.26 g, 0.819 mmol), 2-chloro-*N,N*-dimethylethanamine hydrochloride (1.40 g, 9.83 mmol) and $NaBH_4$ (0.31 g, 8.19 mmol) by using the procedure as described for compound **27**, to give compound **29**, as yellow liquid, yield 1.08 g (68%); $R_f = 0.5$ (ethylacetate/hexane, 4:6); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.18$ (d, $J = 8.3$ Hz, 2H, ArH), 6.78 (d, $J = 8.3$ Hz, 2H, ArH), 4.38 (s, 2H, OCH_2), 4.04 (t, 2H, $J = 5.6$ Hz, OCH_2), 3.22 (bs, 1H OH), 2.72 (t, $J = 5.6$ Hz, 2H, NCH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 158.6$, 129.9 (ArC), 127.8, 114.9 (ArCH), 690, 66.2 (OCH_2), 23.9 (CH_3); IR ν_{max} cm^{-1} 3416 (OH stretching), 1611 (C=C stretching); ESMS $m/z = 196$ $[M + H]^+$.

*4.1.3.4. 4-[2-(Diisopropylamino)ethoxy]phenyl methanol (**30**).* It was obtained by the reaction of 4-hydroxybenzaldehyde **26** (1 g, 8.19 mmol), anh. K_2CO_3 (3.39 g, 24.58 mmol), TBAB (0.26 g, 0.819 mmol), 2-chloro-*N,N*-diisopropylethanamine hydrochloride (1.95 g, 9.83 mmol) and $NaBH_4$ (0.31 g, 8.19 mmol) by using the procedure as described for compound **27**, to give compound **30** as yellow liquid, yield 1.44 g (70%); $R_f = 0.5$ (ethylacetate/hexane, 4:6); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.24$ (d, $J = 8.0$ Hz, 2H, ArH), 6.84 (d, $J = 8.0$ Hz, 2H, ArH), 4.55 (s, 2H, OCH_2), 3.90 (t, 2H, $J = 7.3$ Hz, OCH_2), 3.10 (m, 2H, 2× NCH), 2.84 (t, $J = 7.3$ Hz, 2H, NCH_2), 2.25 (bs, 1H, OH), 1.06, 1.03 (each singlet, 6H, 2× CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 158.8$, 133.5 (ArC), 128.9, 114.8 (ArCH), 69.4, 65.1 (OCH_2), 50.1 (2× CHN), 44.8 (CH_2N), 21.3 (4× CH_3); IR ν_{max} cm^{-1} 3344 (OH stretching), 1612(C=C stretching); ESI MS $m/z = 252$ $[M + H]^+$.

*4.1.3.5. Cyclopropyl{4-[4-(2-morpholin-4-yl-ethoxy)benzyloxy] phenyl}methanone (**31**).* It was obtained by the reaction of benzyl alcohol derivative **27** (0.97 g, 4.09 mmol), NaH (60% dispersion in mineral oil, 0.39 g, and 16.39 mmol), 4-chloro-4′-fluorobutyrophenone (**11**) (1.0 mL, 4.09 mmol) and tetrabutylammonium bromide (0.26 g, 0.082 mmol) by using the procedure as described for compound **12**, to give compound **31** as white solid; mp 90–91 °C; yield 1.86 g (80%); $R_f = 0.5$ (methanol/chloroform, 2:8); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.97$ (d, $J = 8.8$ Hz, 2H, ArH), 7.30 (d, 2H, $J = 8.6$ Hz, Ar–H), 6.97 (d, $J = 9.3$ Hz, 2H, ArH), 6.89 (d, 2H, $J = 8.6$ Hz, ArH), 5.04 (s, 2H, OCH_2), 4.07 (t, 2H, $J = 6.0$ Hz, OCH_2), 3.17 (m, 4H, OCH_2), 2.73 (t, $J = 6.0$ Hz, 2H, NCH_2), 2.58 (m, 5H, 2× NCH_2 morpholine protons, m cyclopropyl CH), 1.18 (m, 2H, cyclopropyl CH_2), 0.96 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 198.9$ (C=O), 162.8, 159.2 (ArC), 131.0, 128.8 (ArC), 130.5, 129.4, 115.0, 114.8 (ArCH's), 70.2 (OCH_2), 67.2 (OCH_2CH_2), 66.1 (2× CH_2's), 58.3 (NCH_2CH_2O), 55.4 (2× CH_2), 16.9 (cyclopropyl CH), 11.5 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 1661(C=O); HRMS (JEOL MSRoute) m/z calcd for $C_{23}H_{27}NO_4$ (M^+) 381.1940, found 381.1938, MS FAB $m/z = 382$ $[M + H]^+$; Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.31; N, 3.67; found C, 72.63; H, 7.11; N, 3.78.

*4.1.3.6. Cyclopropyl{4-[4-(2-piperidin-1-yl-ethoxy)benzyloxy] phenyl}methanone (**32**).* It was obtained by the reaction of benzyl alcohol derivative **28** (0.96 g, 4.09 mmol), NaH (60% dispersion in mineral oil, 0.39 g, and 16.39 mmol), 4-chloro-4′-fluorobutyrophenone (**11**) (1.0 mL, 4.09 mmol) and tetrabutylammonium bromide (0.26 g, 0.082 mmol) by using the procedure as described for compound **12**, to give compound **32** as white solid, mp 87–90 °C; yield 1.85 g (80%); $R_f = 0.5$ (methanol/chloroform, 2:8); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.96$ (d, 2H, $J = 8.0$ Hz, ArH), 7.30 (d, $J = 8.0$ Hz, 2H, ArH), 6.95 (m, 4H, ArH), 5.01 (s, 2H, OCH_2), 4.07 (t, $J = 6.0$ Hz, 2H, OCH_2), 2.73 (t, $J = 6.0$ Hz, 2H, NCH_2), 2.50 (m, 1H, cyclopropyl CH), 2.45 (m, 4H, 2× NCH_2 piperidine protons), 1.62 (m, 4H, piperidine protons), 1.44 (m, 2H, CH_2 piperidine protons), 1.18 (m, 2H, cyclopropyl CH_2), 0.96 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 198.5$ (C=O), 162.8, 159.2 (ArC), 131.0, 128.6 (ArC), 130.5, 129.4, 115.0, 114.8 (ArCH's), 70.2 (OCH_2), 66.3 (OCH_2CH_2), 58.3 (NCH_2CH_2O), 55.4 (2× CH_2), 26.2 (2× CH_2), 24.6 (CH_2), 16.8 (cyclopropyl CH), 11.4 (cyclopropyl CH_2's); IR (KBr), ν_{max} cm^{-1} 1656 (C=O); HRMS (JEOL MSRoute) m/z calcd for $C_{24}H_{29}NO_3$ (M^+) 379.2147, found 379.2172, MS FAB $m/z = 380$ $[M + H]^+$; Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69; found, C, 75.90; H, 7.65; N, 3.65.

*4.1.3.7. Cyclopropyl{4-[4-(2-(dimethylamino)ethoxoy]benzyloxy} phenyl methanone (**33**).* It was obtained by the reaction of benzyl alcohol derivative **29** (0.8 g, 4.09 mmol), NaH (60% dispersion in mineral oil, 0.39 g, 16.39 mmol), 4-chloro-4′-fluorobutyrophenone (**11**) (1.0 mL, 4.09 mmol) and tetrabutylammonium bromide (0.26 g, 0.082 mmol) by using the procedure as described for compound **12**, to give compound **33** as white solid, mp 118–119 °C; yield 1.55 g (75%); $R_f = 0.5$ (methanol/chloroform, 2:8); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.97$ (d, $J = 8.3$ Hz, 2H, ArH), 7.31 (d, $J = 8.3$ Hz, 2H, ArH), 7.96 (d, $J = 8.4$ Hz, 2H, ArH), 6.90 (d, $J = 8.4$ Hz, 2H, ArH), 5.03 (s, 2H, OCH_2), 4.07 (t, 2H, $J = 5.62$ Hz, OCH_2), 2.71 (t, $J = 5.62$ Hz, 2H, NCH_2), 2.59 (m, cyclopropyl CH), 1.19 (m, 2H, cyclopropyl CH_2), 0.97 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 199.4$ (CO), 162.9, 159.3, 129.3, 128.0 (ArC), 115.8, 115.1, 115.0, 114.8, (ArCH), 70.6, 66.4, 58.6 (OCH_2Ar), 17.0 (cyclopropyl CH), 11.6, 11.5 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 1657 (C=O stretching); HRMS (JEOL MSRoute) m/z calcd for $C_{21}H_{25}NO_3$ (M^+) 339.1834, found 339.1837, MS FAB ESI MS $m/z = 340$ $[M + H]^+$; Anal. Calcd for $C_{21}H_{25}NO_3$; C, 74.31; H, 7.42; N, 4.13; found, C, 74.28; H, 7.39; N, 4.10.

*4.1.3.8. Cyclopropyl{4-[4-(2-diisopropylamino)ethoxy)benzyloxy] phenyl}methanone (**34**).* It was obtained by the reaction of benzyl alcohol **30** derivative (1.01 g, 4.09 mmol), NaH (60% dispersion in mineral oil, 0.39 g, 16.39 mmol), 4-chloro-4′-fluorobutyrophenone (**11**) (1.0 mL, 4.09 mmol) and tetrabutylammonium bromide (0.26 g, 0.082 mmol) by using the procedure as described for compound **12**, to give compound **34** as white solid, mp 107–108 °C; yield 1.8 g (75%); $R_f = 0.5$ (methanol/chloroform, 2:8); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.96$ (d, $J = 8.8$ Hz, 2H, ArH), 7.30 (d, $J = 8.6$ Hz, 2H, ArH), 7.97 (d, $J = 8.8$ Hz, 2H, ArH), 6.87 (d, $J = 8.6$ Hz, 2H, ArH), 5.03

(s, 2H, OCH_2), 3.87 (t, 2H, $J = 7.3$ Hz, OCH_2), 3.03 (m, 2H, 2× NCH), 2.80 (t, $J = 7.3$ Hz, 2H, NCH_2), 2.50 (m, 1H, cyclopropyl CH), 1.19 (m, 2H, cyclopropyl CH_2), 1.05 (s, 6H, 2× CH_3), 1.02 (s, 6H, 2× CH_3), 0.97 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 199.5$ (CO), 162.8, 159.4, 131.5, 128.3 (ArC), 131.5, 130.5, 115.0, 114.8, (ArCH), 70.3, 69.6, (OCH_2Ar), 50.0 (2× CHN), 44.7 (CH_2N), 21.3 (4× CH_3), 16.9 (cyclopropyl CH), 11.5 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 1658 (C═O stretching); HRMS (JEOL MSRoute) m/z calcd for $C_{25}H_{33}NO_3$ (M^+) 395.2450, found 395.2461, ESI MS $m/z = 396$ $[M + H]^+$; Anal. Calcd for $C_{25}H_{33}NO_3$; C, 75.91; H, 8.41; N, 3.54; found, C, 75.86; H, 8.38; N, 3.50.

*4.1.3.9. Cyclopropyl{4-[4-(2-morpholin-4-yl-ethoxy)benzyloxy] phenyl}methanol (**35**).* It was obtained by the reaction of compound **31** (1.0 g, 2.62 mmol), $NaBH_4$ (0.09 g, 2.62 mmol), by using the procedure as described for compound **19**, to give compound **35** as white solid, mp 114–115 °C; yield 0.84 g (84%); $R_f = 0.5$ (methanol/chloroform, 4:6); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.29$ (d, $J = 8.2$ Hz, 4H, ArH), 6.89 (d, $J = 7.9$ Hz, 4H, ArH), 4.97 (s, 2H, OCH_2), 3.97 (t, $J = 5.6$ Hz, 2H, OCH_2CH_2), 3.93 (d, $J = 8.0$ Hz, 2H, CHOH), 3.68 (m, 4H, OCH_2's morpholine protons), 2.78 (t, $J = 5.6$ Hz, 2H, OCH_2CH_2), 2.54 (m, 4H, NCH_2's morpholine protons), 1.59 (bs, 1H, OH), 1.17 (m, 1H, cyclopropyl CH), 0.55 (m, 2H, cyclopropyl CH_2), 0.34 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 158.9$, 158.6, 136.9, 129.7 (ArC), 129.7, 127.6, 115.0 (ArCH's), 78.2, (CHOH), 70.1 (OCH_2) 67.1 (OCH_2's), 66.1 (OCH_2CH_2), 57.9 (NCH_2CH_2O) 54.4 (CH_2's), 19.4 (cyclopropyl CH), 4.0, 3.0 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 3196 (OH stretching), 2927 (C–H stretching), 1608 (C–O); HRMS (JEOL MSRoute) m/z calcd for $C_{23}H_{29}NO_4$ (M^+) 383.2097, found 383.2081, MS FAB $m/z = 383$ $[M + H]^+$; Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65; found C, 72.03; H, 7.31; N, 3.78.

*4.1.3.10. Cyclopropyl-4-[4-(2-piperidin-1-yl-ethoxy)benzyloxy] phenyl}methanol (**36**).* It was obtained by the reaction of compound **32** (1.0 g, 2.63 mmol), $NaBH_4$ (0.10 g, 2.63 mmol), by using the procedure as described for compound **19**, to give compound **36** as a white solid mp 125–126 °C, yield 0.78 g (78%); $R_f = 0.5$ (methanol/chloroform, 4:6); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.32$ (d, $J = 8.2$ Hz, 4H, ArH), 6.91 (d, $J = 8.7$ Hz, 4H, ArH), 4.96 (s, 2H, OCH_2), 4.96 (t, 2H, $J = 5.9$ Hz, OCH_2), 3.95 (d, $J = 8.2$ Hz, 1H, CHOH), 2.74 (t, $J = 5.9$ Hz, 2H, NCH_2CH_2O), 2.49 (m, 4H, 2× NCH_2 piperidine protons), 2.37 (s, 1H, OH), 1.59 (s, 4H, piperidine protons), 1.44 (m, 2H, CH_2 piperidine protons), 1.18 (m, 1H, cyclopropyl CH), 0.44 (m, 2H, cyclopropyl CH_2), 0.34 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 159.0$, 158.6, 136.0 (ArC), 129.5, 127.6, 115.0 (ArCH's), 78.4 (CHOH), 70.2 (OCH_2), 66.2 (OCH_2CH_2), 58.2 (NCH_2CH_2O), 55.4 (2× CH_2), 26.2 (2× CH_2), 24.5 (CH_2), 19.4 (cyclopropyl CH), 4.0, 3.1 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 3422 (O–H stretching); HRMS (JEOL MSRoute) m/z calcd for $C_{24}H_{31}NO_3$ (M^+) 381.2304, found 381.2302, MS FAB $m/z = 382$ $[M + H]^+$; Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67; found C, 75.50; H, 8.13; N, 3.64.

*4.1.3.11. Cyclopropyl{4-[4-(2-(dimethylamino)ethoxy]benzyloxy} phenyl)methanol (**37**).* It was obtained by the reaction of compound **33** (1.0 g, 2.53 mmol), $NaBH_4$ (0.1 g, 2.53 mmol), by using the procedure as described for compound **19**, to give compound **37** as white solid, mp 118–119 °C; yield 0.77 g (77%); $R_f = 0.5$ (methanol/chloroform, 3:7); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.23$ (m, 4H, ArH), 6.85 (m, 4H, ArH), 4.89 (s, 2H, OCH_2), 3.96 (t, 2H, $J = 5.4$ Hz, OCH_2), 3.86 (d, $J = 8.1$ Hz, 1H, CHOH), 2.63 (t, $J = 5.4$ Hz, 2H, NCH_2), 2.63 (t, $J = 5.4$ Hz, 2H, 2× CH_3), 1.13 (m, cyclopropyl CH), 0.52 (m, 2H, cyclopropyl CH_2), 0.22 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 159.0$, 158.6, 136.8, 129.3, 128.0 (ArC), 127.6, 115.0, 78.4, 70.2, 66.3, 58.5, 46.2, 19.4 (cyclopropyl CH), 3.9, 3.0 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 1601 (C═O stretching), 3429 (OH stretching); HRMS (JEOL MSRoute) m/z calcd for $C_{21}H_{27}NO_3$ (M^+) 341.1991, found 341.1928, ESI MS $m/z = 342$ $[M + H]^+$; Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10; found C, 73.82; H, 7.91; N, 4.06.

*4.1.3.12. Cyclopropyl{4-[4-(2-diisopropylamino)ethoxy)benzyloxy] phenyl}methanol (**38**).* It was obtained by the reaction of compound **34** (1.0 g, 2.94 mmol), $NaBH_4$ (0.11 g, 2.94 mmol), by using the procedure as described for compound **19**, to give compound **38** as white solid, mp 84–85 °C; yield 0.73 g (73%); $R_f = 0.5$ (methanol/chloroform, 3:7); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.20$ (m, 4H, ArH), 6.81 (m, 4H, ArH), 5.20 (s, 2H, OCH_2), 3.87 (d, $J = 8.1$ Hz, 1H, CHOH), 3.79 (t, 2H, $J = 7.4$ Hz, OCH_2), 2.96 (m, 2H, 2× NCH), 2.73 (t, $J = 7.4$ Hz, 2H, CH_2), 1.81 (s, 1H, OH), 1.08 (m, cyclopropyl CH), 0.98 (s, 6H, 2× CH_3), 0.95 (s, 6H, 2× CH_3), 0.51 (m, 2H, cyclopropyl CH_2), 0.25 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 159.2$, 158.7, 136.8, 129.2 (ArC), 129.4, 127.5, 115.0, 114.9 (ArC), 78.4 (CHOH), 70.2 (OCH_2), 69.6 (OCH_2), 50.0 (2× CHN), 44.7 (NCH_2), 21 (4× CH_3), 19.4, (cyclopropyl CH), 3.9, 3.1 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 3413 (OH stretching); HRMS (JEOL MSRoute) m/z calcd for $C_{25}H_{35}NO_3$ ($M + H^+$) 398.2695, found 398.2692, ESI MS $m/z = 398$ $[M + H]^+$; Anal Calcd for $C_{25}H_{35}NO_3$: C, 75.53; H, 8.87; N, 3.52; found C, 75.50; H, 8.82; N, 3.48.

*4.1.3.13. 3-[2-(Piperidin-1-yl)ethoxy]phenyl methanol (**40**).* It was obtained by the reaction of 3-hydroxybenzaldehyde **39** (1.0 g, 8.19 mmol), anhydrous K_2CO_3 (3.39 g, 24.58 mmol), TBAB (0.26 g, 0.819 mmol), 1-(2-chloroethyl)piperidine hydrochloride (1.79 g, 9.83 mmol) and NaBH4 (0.31 g, 8.19 mmol) by using the procedure as described for compound **27**, to give compound **40**, as yellow liquid, yield 1.54 g (80%); $R_f = 0.5$ (methanol/chloroform, 3:7); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.19$ (m, 2H, ArH), 6.91 (m, 2H, ArH), 6.86 (m, 1H, ArH), 5.76 (bs, 1H, OH), 4.58 (s, 2H, OCH_2), 4.17 (t, $J = 5.3$ Hz, 2H, OCH_2), 2.94 (t, $J = 5.3$ Hz, 2H, NCH_2), 2.84 (m, 4H, 2× NCH_2 piperidine protons), 1.69 (m, 4H, CH_2 piperidine protons), 1.46 (m, 2H, CH_2 piperidine protons); IR ν_{max} cm^{-1} 3404 (OH stretching), 1611 (C═C stretching); ESMS $m/z = 236$ $[M + H]^+$.

*4.1.3.14. Cyclopropyl{4-[3-(2-piperidin-1-yl-ethoxy)benzyloxy]phenyl} methanone (**41**).* It was obtained by the reaction of benzyl alcohol **40** (1.05 g, 4.09 mmol), NaH (60% dispersion in mineral oil, 0.39 g, 16.39 mmol), 4-chloro-4′-fluorobutyrophenone (**11**) (1.0 mL, 4.09 mmol) and tetrabutylammonium bromide (0.26 g, 0.082 mmol) by using the procedure as described for compound **12**, to give compound **41** as white solid, mp 79–80 °C; yield 1.84 g (80%); $R_f = 0.5$ (methanol/chloroform, 4:6); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.98$ (d, 2H, $J = 8.8$ Hz, ArH), 7.23 (m, 1H, ArH), 6.96 (m, 4H, ArH), 6.86 (m, 1H, ArH), 5.08 (s, 2H, OCH_2), 4.09 (t, $J = 6.0$ Hz, 2H, OCH_2), 2.75 (t, $J = 6.0$ Hz, 2H, NCH_2), 2.60 (m, 1H, cyclopropyl CH), 2.50 (m, 4H, 2× CH_2 piperidine protons), 1.62 (m, 4H, piperidine protons), 1.46 (m, 2H, CH_2 piperidine protons), 1.18 (m, 2H, cyclopropyl CH_2), 0.96 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 198.4$ (C═O), 162.3, 159.1, 137.8, 131.2 (ArC), 130.1, 129.6, 114.4, 114.2, 113.5 (ArCH's), 69.9, (OCH_2), 65.8 (OCH_2CH_2), 57.8 (NCH_2CH_2O), 55.0 (2× CH_2), 29.6 (2× CH_2), 24.1 (CH_2), 16.5 (cyclopropyl CH), 11.0 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 1659(C═O); HRMS (JEOL MSRoute) m/z calcd for $C_{24}H_{29}NO_3$ (M^+) 380.2225, found 380.2215, MS FAB $m/z = 380$ $[M + H]^+$; Anal. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69; found, C, 75.89; H, 7.67; N, 3.63.

*4.1.3.15. Cyclopropyl{4-[3-(2-piperidin-1-yl-ethoxy)benzyloxy] phenyl}methanol (**42**).* It was obtained by the reaction of compound **41** (1.0 g, 2.63 mmol), $NaBH_4$ (0.1 g, 2.63 mmol), by using the procedure as described for compound **19**, to give compound **42** as liquid; yield 0.78 g (78%); $R_f = 0.5$ (methanol/chloroform, 4:6); ^{1}H

NMR (200 MHz, $CDCl_3$) δ = 7.30 (m, 3H, ArH), 6.95 (m, 4H, ArH), 6.85 (m, 1H, ArH), 5.03 (s, 2H, OCH_2), 4.11 (t, 2H, J = 6.0 Hz, OCH_2), 3.98 (d, J = 8.0 Hz, 1H, CHOH), 2.76 (t, J = 6.0 Hz, 2H, NCH_2CH_2O), 2.54 (m, 4H, 2× NCH_2 piperidine protons), 2.37 (s, 1H, OH), 1.62 (s, 4H, piperidine protons), 1.48 (m, 2H, CH_2 piperidine protons), 1.19 (m, 1H, cyclopropyl CH), 0.65 (m, 2H, cyclopropyl CH_2), 0.33 (m, 2H, cyclopropyl CH_2); IR ν_{max} cm^{-1} 3350 (OH stretching); HRMS (JEOL MSRoute) m/z calcd for $C_{24}H_{31}NO_3$ ($M + H^+$) 382.2382, found 382.2371, MS FAB m/z = 382 $[M + H]^+$; Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67; found C, 75.52; H, 8.15; N, 3.65.

*4.1.3.16. 3-Methoxy[4-(2-morpholinoethoxy)phenyl]methanol (**44**).* It was obtained by the reaction of 4-hydroxy-3-methoxybenzaldehyde **43** (1.0 g, 6.57 mmol), anhydrous K_2CO_3 (2.72 g, 19.73 mmol), TBAB (0.21 g, 0.657 mmol), 4-(2-chloroethyl)morpholine hydrochloride (1.46 g, 7.89 mmol) and $NaBH_4$ (0.25 g, 6.57 mmol) by using the procedure as described for compound **27**, to give compound **44**, as colourless liquid, yield 1.37 g (79%); R_f = 0.5 (methanol/chloroform, 3:7); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 6.86 (s, 1H, ArH), 6.78 (m, 2H, ArH), 4.54 (s, 2H, OCH_2), 4.09 (t, J = 5.8 Hz, 2H, OCH_2), 3.80 (s, 3H, OCH_3), 3.70 (t, J = 5.9 Hz, 2H, NCH_2), 2.80 (m, 4H, 2× OCH_2 morpholine protons), 2.56 (m, 4H, 2× NCH_2 morpholine protons); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 148.7, 129.6 (ArC), 119.5, 113.8, 111.3 (ArCH's), 66.9, 65.1 (OCH_2), 57.9, 54.3 NCH_2CH_2O), 56.0 (OCH_3); IR ν_{max} cm^{-1} 3421 (OH stretching), 1600 (C═C stretching); ESI MS m/z = 268 $[M + H]^+$.

*4.1.3.17. 3-Methoxy-4-[2-(piperidin-1-yl)ethoxy]phenyl methanol (**45**).* It was obtained by the reaction of 4-hydroxy-3-methoxybenzaldehyde **43** (1.0 g, 6.57 mmol), anhydrous K_2CO_3 (2.72 g, 19.73 mmol), TBAB (0.21 g, 0.657 mmol), 4-(2-chloroethyl)piperidine hydrochloride (1.44 g, 7.89 mmol) and $NaBH_4$ (0.25 g, 6.57 mmol) by using the procedure as described for compound **27**, to give compound **45**, as yellow liquid, yield 1.34 g (77%); R_f = 0.5 (methanol/chloroform, 4:6); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 6.91 (s, 1H, ArH), 6.78 (m, 2H, ArH), 5.50 (bs, 1H, OH), 4.56 (s, 2H, OCH_2), 4.22 (t, J = 5.46 Hz, 2H, OCH_2), 3.80 (s, 3H, OCH_3), 3.06 (t, J = 5.4 Hz, 2H, NCH_2), 2.83 (m, 4H, 2× NCH_2 piperidine protons), 1.77 (m, 4H, CH_2 piperidine protons), 1.54 (m, 2H, CH_2 piperidine protons); IR ν_{max} cm^{-1} 3425 (OH stretching), 1632 (C═C stretching); ESI MS m/z = 266 $[M + H]^+$.

*4.1.3.18. 3-Methoxy-4-[2-(diisopropylamino)ethoxy]phenyl methanol (**46**).* It was obtained by the reaction of 4-hydroxy-3-methoxybenzaldehyde (1.0 g, 6.57 mmol), anhydrous K_2CO_3 (2.72 g, 19.73 mmol), TBAB (0.21 g, 0.657 mmol), 2-chloro-*N*,*N*-dimethylethanamine hydrochloride (1.12 g, 7.89 mmol) and $NaBH_4$ (0.25 g, 6.57 mmol) by using the procedure as described for compound **27**, to give compound **46**, as yellow liquid; yield, 1.31 g (71%); R_f = 0.4 (methanol/chloroform, 3:7); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 6.83 (s, 1H, ArH), 6.76 (s, 2H, ArH), 4.51 (s, 2H, OCH_2), 3.88 (t, J = 7.7 Hz, 2H, OCH_2), 3.79 (s, 3H, OCH_3), 3.05 (m, 2H, CHN ×2), 2.86 (t, J = 7.7 Hz, 2H, NCH_2), 1.03, 1.00 (each singlet, 6H, 2× CH_3); IR ν_{max} cm^{-1} 3420 (OH stretching), 1635 (C═C stretching); ESI MS m/z = 282 $[M + H]$+.

*4.1.3.19. Cyclopropyl{4-[3-methoxy-4-(2-morpholino)ethoxy)benzyloxy]phenyl} methanone (**47**).* It was obtained by the reaction of benzyl alcohol derivative **44** (1.09 g, 4.09 mmol), NaH (60% dispersion in mineral oil, 0.39 g, 16.39 mmol), 4-chloro-4′-fluorobutyrophenone **11** (1.0 mL, 4.09 mmol) and tetrabutylammonium bromide (0.26 g, 0.082 mmol) by using the procedure as described for compound **12**, to give compound **47** as white solid, mp 69–70 °C; yield 2.05 g (82%), R_f = 0.4 (methanol/chloroform, 3:7); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.99 (d, 2H, J = 8.8 Hz, ArH), 6.92 (m, 5H, ArH), 5.28 (s, 2H, OCH_2), 4.14 (t, J = 6.0 Hz, 2H, OCH_2), 3.86 (s, 3H, OCH_3), 3.72 (t, J = 4.8 Hz, 4H, $-CH_2OCH_2-$), 2.83 (t, J = 5.9 Hz, 2H, NCH_2), 2.55–2.65 (m, 5H, 2× NCH_2 morpholine protons and cyclopropyl CH), 1.20 (m, 2H, cyclopropyl CH_2), 0.99 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 199.0 (C═O), 162.7, 148.7, 131.6, 129.6 (ArC), 130.6, 120.6, 114.2, 113.9, 111.8 (ArCH's), 70.5 (OCH_2), 67.2 (OCH_2CH_2), 57.9 NCH_2CH_2O), 56.3 (2× CH_2), 54.6 (OCH_3), 53.7 (CH_2), 16.9 (cyclopropyl CH), 11.5 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 1658 (C═O); HRMS (JEOL MSRoute) m/z calcd for $C_{24}H_{29}NO_5$ (M^+) 411.2046, found 411.2041, ESI MS m/z = 412 $[M + H]^+$; Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40; found, C, 70.00; H, 7.06; N, 3.33.

*4.1.3.20. Cyclopropyl{4-[3-methoxy-4-(2-piperidin-1-yl)ethoxy)benzyloxy]phenyl} methanone (**48**).* It was obtained by the reaction of benzyl alcohol derivative **45** (1.09 g, 4.09 mmol), NaH (60% dispersion in mineral oil, 0.39 g, 16.39 mmol), 4-chloro-4′-fluorobutyrophenone **11** (1.0 mL, 4.09 mmol) and tetrabutylammonium bromide (0.26 g, 0.082 mmol) by using the procedure as described for compound **12**, to give compound **48** as white solid, mp 70–71 °C; yield 2.12 g (85%); R_f = 0.4 (methanol/chloroform, 4:6); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.98 (d, 2H, J = 8.7 Hz, ArH), 6.98 (d, J = 8.7 Hz, 2H, ArH), 6.90 (m, 3H, ArH), 5.02 (s, 2H, OCH_2), 4.10 (t, J = 6.3 Hz, 2H, OCH_2), 2.80 (s, 3H, OCH_3), 2.77 (t, J = 6.3 Hz, 2H, NCH_2), 2.49–2.60 (m, 5H, 2× NCH_2 piperidine protons and cyclopropyl CH), 1.61 (m, 4H, piperidine protons), 1.44 (m, 2H, CH_2 piperidine protons), 1.21 (m, 2H, cyclopropyl CH_2), 0.98 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ (C═O), 162.2149.5, 148.2, 131.0, 128.8 (ArC), 130.5, 120.1, 114.2, 113.4, 113.0, 111.3 (ArCH's), 69.9 (OCH_2), 66.7 (OCH_2CH_2), 58.3 (NCH_2CH_2O), 57.5 (2× CH_2), 55.6 (OCH_3), 54.8(CH_2), 25.7 (2× CH_2), 24.0 (CH_2), 16.3 (cyclopropyl CH), 10.9 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 1658 (C═O); HRMS (JEOL MSRoute) m/z calcd for $C_{25}H_{31}NO_4$ (M^+) 409.2253, found 409.2245, ESI MS m/z = 410 $[M + H]^+$; Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42; found, C, 73.27; H, 7.60; N, 3.38.

*4.1.3.21. Cyclopropyl{4-[4-(2-diisopropylamino)ethoxy)-3-methoxybenzyloxy]-phenyl}methanone (**49**).* It was obtained by the reaction of benzyl alcohol derivative **46** (1.15 g, 4.09 mmol), NaH (60% dispersion in mineral oil, 0.39 g, 16.39 mmol), 4-chloro-4′-fluorobutyrophenone 11 (1.0 mL, 4.09 mmol) and tetrabutylammonium bromide (0.26 g, 0.082 mmol) by using the procedure as described for compound **12**, to give compound **49** as white solid, mp 64–65 °C; yield 1.97 g (76%); R_f = 0.4 (methanol/chloroform, 4:6); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.98 (d, J = 8.8 Hz, 2H, ArH), 7.00 (d, J = 8.8 Hz, 2H, ArH), 6.90 (m, 3H, ArH), 5.02 (s, 2H, OCH_2), 3.91 (m, 5H, OCH_2 and OCH_3), 3.03 (m, 2H, 2× NCH), 2.87 (t, J = 7.5 Hz, 2H, NCH_2), 2.70 (m, 1H, cyclopropyl CH), 1.19 (m, 2H, cyclopropyl CH_2), 1.05 (s, 6H, 2× CH_3), 1.02 (s, 6H, 2× CH_3), 0.96 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 198.7 (CO), 162.8, 149.8, 149.0, 131.5, 128.8 (ArC), 130.5, 120.6, 114.8, 112.9, 111.6 (ArCH), 70.5, 70.3 (OCH_2Ar), 56.2 (OCH_3), 50.0 (2× CHN), 44.6 (CH_2N), 21.3 (4× CH_3), 16.9 (cyclopropyl CH), 11.5 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 1611 (C═O stretching); HRMS (JEOL MSRoute) m/z calcd for $C_{26}H_{35}NO_4$ ($M + H^+$) 426.2644, found 426.2651, ESI MS m/z = 426 $[M + H]^+$. Anal. Calcd for $C_{26}H_{35}NO_4$ C, 73.38; H, 8.29; N, 3.29; found C, 73.34; H, 8.25; N, 3.26.

*4.1.3.22. Cyclopropyl{4-[3-methoxy-4-(2-morpholino)ethoxy)benzyloxy]phenyl} methanol (**50**).* It was obtained by the reaction of compound **47** (1.0 g, 2.43 mmol), $NaBH_4$ (0.09 g, and 2.43 mmol), by using the procedure as described for compound **19**, to give compound **50** as white solid, mp 72–73 °C; yield 0.79 g (79%); R_f = 0.4 (methanol/chloroform, 4:6); ^{1}H NMR (200 MHz, $CDCl_3$)

δ = 7.33 (d, J = 8.6 Hz, 2H, ArH), 6.91 (m, 5H, ArH), 4.97 (s, 2H, OCH_2), 4.13 (t, 2H, J = 5.9 Hz, OCH_2), 3.95 (d, J = 8.2 Hz, 1H, CHOH), 3.86 (s, 3H, OCH_3), 3.71 (t, J = 4.4 Hz, 4H, $-CH_2OCH_2-$), 2.82 (t, J = 5.9 Hz, 2H, NCH_2CH_2O), 2.59–2.55 (m, 4H, 2× NCH_2 morpholine protons), 2.16 (s, 1H, OH protons), 1.21 (m, 1H, cyclopropyl CH), 0.56 (m, 2H, cyclopropyl CH_2), 0.43 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 158.6, 150.1, 148.4, 136.8, 130.5 (ArC), 127.6, 120.5, 115.0, 113.9, 111.8, 109.9 (ArCH's), 78.3 (CHOH), 70.4 (OCH_2), 67.2 (OCH_2CH_2), 57.9 (NCH_2CH_2O), 56.2 (OCH_3), 54.4 (2× CH_2), 19.5 (cyclopropyl CH), 3.9, 3.1 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 3449 (OH stretching); HRMS (*JEOL* MSRoute) m/z calcd for $C_{24}H_{31}NO_5$ (M^+) 413.2202, found 413.2192, ESI MS m/z = 414 $[M + H]^+$; Anal. Calcd $C_{24}H_{31}NO_5$ found C, 69.71; H, 7.56; N, 3.39; found C, 69.68; H, 7.50; N, 3.33.

*4.1.3.23. Cyclopropyl{4-[3-methoxy-4-(2-(piperidin-1-yl)ethoxy) benzyloxy]phenyl} methanol (**51**).* It was obtained by the reaction of compound **48** (1.0 g, 2.44 mmol), $NaBH_4$ (0.09 g, and 2.44 mmol), by using the procedure as described for compound **19**, to give compound **51** as white solid, mp 119–121 °C; yield 0.78 g (78%); R_f = 0.5 (methanol/chloroform, 4:6); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.30 (d, J = 8.4 Hz, 2H, ArH), 6.89 (m, 5H, ArH), 4.94 (s, 2H, OCH_2), 4.10 (t, 2H, J = 6.4 Hz, OCH_2), 3.93 (d, J = 8.0 Hz, 1H, CHOH), 3.8 (s, 3H, OCH_3), 2.90 (s, 1H, OH), 2.77 (t, J = 6.3 Hz, 2H, NCH_2), 2.49–2.60 (m, 5H, 2× NCH_2 piperidine protons and cyclopropyl CH), 1.61 (m, 4H, piperidine protons), 1.44 (m, 2H, CH_2 piperidine protons), 1.21 (m, 2H, cyclopropyl CH_2), 0.98 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 198.1 (C=O), 162.2149.5, 148.2, 131.0, 128.8 (ArC), 130.5, 120.1, 114.2, 113.4, 113.0, 111.3 (ArCH's), 69.9 (OCH_2), 66.7 (OCH_2CH_2), 58.3 NCH_2CH_2O), 57.5 (2× CH_2), 55.6 (OCH_3), 54.8 (CH_2), 25.7 (2× CH_2), 24.0 (CH_2), 16.3 (cyclopropyl CH), 10.9 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 3566 (OH stretching); HRMS (*JEOL* MSRoute) m/z calcd for $C_{25}H_{33}NO_4$ (M^+) 411.2410, found 411.2398, ESI MS m/z = 412 $[M + H]^+$; Anal. Calcd for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08; N, 3.40; found C, 72.96; H, 8.08; N, 3.40.

*4.1.3.24. Cyclopropyl{4-[4-(2-diisopropylamino)ethoxy)-3-methoxybenzyloxy] phenyl}methanol (**52**).* It was obtained by the reaction of compound **49** (1.0 g, 2.35 mmol), $NaBH_4$ (0.08 g, 2.35 mmol), by using the procedure as described for compound **19**, to give compound **52** as white solid, mp 84–85 °C; yield 0.75 g (75%); R_f = 0.5 (methanol/chloroform, 4:6); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.23 (m, 2H, ArH), 6.88 (m, 5H, ArH), 4.94 (s, 2H, OCH_2), 3.90 (m, 5H, OCH_2 and OCH_3), 3.57 (d, J = 8.1 Hz, 1H, CHOH), 3.00 (m, 2H, 2× NCH), 2.87 (t, 2H, J = 7.8 Hz, NCH_2), 1.81 (s, 1H, OH), 1.18 (m, cyclopropyl CH), 1.05 (s, 6H, 2× CH_3), 1.02 (s, 6H, 2× CH_3), 0.57 (m, 2H, cyclopropyl CH_2), 0.30 (m, 2H, cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 159.9, 158.6, 149.7, 148.7, 141.0, 129.7 (ArC), 127.8, 127.6, 120.6, 115.6, 115.2, 115.0, 112.9, 111.6 (ArCH), 78.2 (CHOH), 70.4, 70.1 (OCH_2), 56.2 (OCH_3), 50.0 (2× CHN), 44.7 (NCH_2), 21.2 (4× CH_3), 19.4, (cyclopropyl CH), 3.9, 3.1 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 3430 (OH stretching); HRMS (*JEOL* MSRoute) m/z calcd for $C_{26}H_{37}NO_4$ (M^+) 428.2800 found 428.2788, ESI MS m/z = 428 $[M + H]^+$; Anal. Calcd, for $C_{26}H_{37}NO_4$: C, 73.03; H, 8.72; N, 3.28; found C, 73.00; H, 8.70; N, 3.25.

*4.1.3.25. {4-[2-(N,N-Dibutylamino)ethoxy]phenyl}cyclopropyl methanone (**54**).* It was obtained by the reaction of 2-(*N,N*-dibutylamino) ethanol **53** (0.82 g, 4.09 mmol), NaH (60% dispersion in mineral oil, 0.39 g, 16.39 mmol), 4-chloro-4′-fluorobutyrophenone (**11**) (1.0 mL, 4.09 mmol) and tetrabutylammonium bromide (0.26 g, 0.082 mmol) by using the procedure as described for compound **12**, to give compound **54** as liquid; yield 1.45 g (75%); R_f = 0.4 (methanol/chloroform, 3:7); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.99 (dd, J_1 = 1.9 Hz, J_2 = 6.9 Hz, 2H, ArH), 6.90 (dd, J_1 = 1.9 Hz, J_2 = 6.9 Hz, 2H, ArH), 4.07 (t, 2H, J = 6.3 Hz, OCH_2), 2.83 (t, J = 6.3 Hz, 2H, NCH_2), 2.60 (m, 1H, cyclopropyl CH), 2.51 (m, 4H, 2× NCH_2), 145–1.18 (m, 10H, n-butyl 2× CH_2CH_2 and cyclopropyl CH_2), 1.00–0.88 (m, 8H, 2× CH_3 and cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 198.9 (CO), 163.0, 131.3 (ArC), 130.5, 130.5, 114.5 (ArCH), 67.3 (OCH_2Ar), 55.1, 53.1, 29.8, 21.0, 14.4 (4× CH_3), 16.9 (cyclopropyl CH), 11.9, 11.4 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 1671 (C=O stretching); HRMS (*JEOL* MSRoute) m/z calcd for $C_{20}H_{31}NO_2$ ($M + H^+$) 318.2433 found 318.2435, ESI MS m/z = 318 $[M + H]^+$; Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41; found C, 75.60; H, 9.80; N, 4.39.

*4.1.3.26. {4-[2-(N,N-Dibutylamino)ethoxy]phenyl}cyclopropyl methanol (**55**).* It was obtained by the reaction of cyclopropyl{4-[2-(dibutylamino)ethoxy]phenyl}methanone **54** (0.5 g, 1.57 mmol), $NaBH_4$ (0.06 g, 1.57 mmol), by using the procedure as described for compound **12**, to give compound **55** as yellow liquid; yield 0.39 g, (77%); R_f = 0.5 (methanol/chloroform, 2:8); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.31 (dd, J_1 = 1.9 Hz, J_2 = 6.7 Hz, 2H, ArH), 6.87 (dd, J_1 = 1.9 Hz, J_2 = 6.7 Hz, 2H, ArH), 4.02 (t, 2H, J = 6.4 Hz, OCH_2), 3.92 (d, J = 7.3 Hz, 1H, CHOH), 2.83 (t, J = 6.4 Hz, 2H, NCH_2), 2.53 (m, 4H, 2× NCH_2), 2.12 (bs, 1H, OH), 145–1.18 (m, 9H, n-butyl 2× CH_2CH_2 and cyclopropyl CH), 1.00–0.88 (m, 8H, 2× CH_3 and cyclopropyl CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 158.7, 136.5 (ArC), 127.5, 114.6 (ArCH), 78.2 (CHOH), 67.0, (OCH_2Ar), 55.1, 53.1, 30.1, 29.7, 21.0 (CH_2), 19.4 (cyclopropyl CH), 14.5 (CH_3), 3.9, 3.0 (cyclopropyl CH_2's); IR ν_{max} cm^{-1} 3428 (OH stretching); HRMS (*JEOL* MSRoute) m/z calcd for $C_{20}H_{33}NO_2$ ($M + H^+$) 320.2589 found 320.2592, ESI MS m/z = 320 $[M + H]^+$. Anal. Calcd for $C_{20}H_{33}NO_2$: C, 75.19; H, 10.41; N, C, 75.15; H, 10.37; N, 75.10.

4.2. Bio-evaluation methods

4.2.1. Determination of antitubercular activity against *M. tuberculosis* $H_{37}Rv$ strain (agar microdilution method) [25]

Drug susceptibility and determination of MIC of the test compounds/drugs against *M. tuberculosis* $H_{37}Rv$ was done by agar microdilution method. The MIC of the test compounds was determined by incorporating two-fold dilution of this suspension were added to (in tubes) 7H10 middle brook's medium (containing 1.7 mL medium and 0.2 mL OADC supplement) at different concentration of the test compounds keeping the volume constant i.e. 0.1 mL. Medium was allowed to cool keeping the tubes in slanting position. A culture of *M. tuberculosis* $H_{37}Rv$ growing on *L–J* medium was harvested in 0.85% saline with 0.05% Tween-80. A suspension of 1 μg mL^{-1} concentration of extracts/compounds was prepared in dimethyl sulphoxide (DMSO). These tubes were then incubated at 37 °C for 24 h followed by streaking of *M. tuberculosis* $H_{37}Rv$ (5×10^5 bacilli per tube). The tubes were then incubated at 37 °C. Growth of bacilli was seen after 30 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with $H_{37}Rv$. The lowest concentration of the compound at which complete inhibition of colonies occurred was taken as minimum inhibitory concentration (MIC) of test compound.

4.2.2. Cytotoxicity evaluation [26,27]

4.2.2.1. In VERO cell line. Cell line was procured from laboratory animal division of CDRI. The cell suspension was plated in 96-well tissue culture plates at a density of 10,000 cells per well (in 200 μL) in Dulbecco's minimal essential medium (DMEM) with antibiotics + 10% fetal bovine serum (FBS). The monolayers were then incubated overnight at 37 °C and 5% CO_2 for allowing adherence of cells. Compounds of different concentrations (minimum 10× MIC) were added in DMEM + 10% FBS. As a positive control, a known toxic compound was used. DMSO was used as negative control. After 24 h incubation, 20 μL of MTS solution (tetrazolium

compound, Owen's reagent) was added to each well and incubated for 2 h at 37 °C, 5% CO_2. Reading was taken at 490 nm using a plate reader. Absorbance shown by DMSO containing wells was taken as 100% survivors. A compound is considered toxic if it causes 50% inhibition at concentration 10-fold higher than its MIC.

4.2.2.2. In mouse bone marrow derived macrophages. Prior permission of the institute's ethics committee (CPCSEA registration no. 34/1999 dated 11.3.99, extended up to 2012) had been taken for performing *in vivo* experiments.

Mouse was euthanized by exposure to CO_2 and the femur bones were dissected out. The bones were trimmed at each end, and the marrow was flushed out (using 26-gauge needle) with 5 mL of Dulbecco's minimal essential medium (DMEM) supplemented with 10% FBS, 15% L-929 fibroblast conditioned supernatant (prepared as described below), and non-essential amino acids. Cells were washed twice and plated in 96-well tissue culture plates at a concentration of 10^5 cells per well (100 μL) in supplemented DMEM. The monolayers were then incubated at 37 °C in 5% CO_2 with the medium change every 3rd day. Macrophages were used 5 days later. Different concentrations of compounds were added in antibiotic free, FBS supplemented, DMEM and incubated at 37 °C in 5% CO_2. After 48 h, 20 μL of MTS solution was added to each well and incubated for 2 h at 37 °C in 5% CO_2. Reading was taken at 490 nm using a plate reader. Absorbance shown by DMSO containing wells is taken as 100% survivors. A compound is considered toxic if it causes 50% inhibition at concentration 10-fold higher than its MIC.

4.2.3. Ex vivo (macrophage) model of TB

4.2.3.1. Ex vivo assay for intracellular killing of M. tuberculosis H37Rv [28]. Mouse macrophages were used after 5 days in culture as described above. They were infected with 1ml suspension containing 5×10^6 *M. tuberculosis* ($H_{37}R_v$) in antibiotic-free DMEM (with 10% FBS) and incubated for 3 h. After incubation, the wells were thoroughly washed to remove the extracellular bacteria and were later replenished with 1 mL antibiotic-free DMEM (with 10% FBS) containing 5× MIC of compounds being tested. In order to determine the number of bacilli that were phagocytosed during the 3-h incubation period, 1 well was lysed with 0.1% saponin (20 min), and plated 50 μL of 1:100 dilutions on 7H11 agar plate. After 4 days of incubation at 37 °C in 5% CO_2, each well was gently washed and the cells were lysed with 0.1% saponin. The lysates were serially diluted in normal saline and plated on 7H11 agar plates. Bacterial colonies were counted after 4 weeks incubation at 37 °C in humidified air.

4.2.3.2. In vivo activity of compounds in mouse model [29,30]. Outbred female swiss mice weighing 18–20 g were be infected via lateral vein (i.v.) with 10^7 colony forming units of *M. tuberculosis* $H_{37}Rv$. Next day mice were divided in groups of 10 mice each. Experimental groups were be given the aqueous suspension of the test samples (alone or in combination with suboptimal doses of Std. Anti-TB drugs) at the dose 100 mg/kg body weight, positive control groups received ED_{90} dose of standard Anti-Tb drugs INH, while the negative control (No drug) group were given placebo, orally, daily for 28 days. Mice were kept under observation for 30 days. Anti-tubercular efficacy was assessed by monitoring (1) the general health of mice, (2) the mean survival time, (3) percent survivors at different time intervals, (4) lesions in lung, (5) enlargement of spleen and (6) bacillary load in lung/spleen.

4.2.4. Experiment conditions for HPLC of compound ***36***

4.2.4.1. Materials and reagents. Acetonitrile (HPLC grade) was obtained from Merck Limited (Mumbai, India). Triple distilled water from all glass apparatus was used. Potassium dihydrogen orthophosphate (analytical reagent grade) was purchased from SD fine chemicals Limited (Mumbai, India).

4.2.4.2. HPLC conditions. The HPLC system (Shimadzu, Kyoto, Japan) was equipped with a pump (LC-10 ATvp), a PDA detector (LC-10MAvp), a Rheodyne (Cotati, CA, USA) model 7125 in Jector with a 20 μL loop. HPLC separation was achieved on a Lichrosphere® Lichrocart® CN column (250 mm, 4 mm, 5 μm; Merck Ltd., Mumbai, India) at 25 ± 3 °C.

The mobile phase was consisted of mixture of potassium dihydrogen phosphate buffer (0.01 M) and acetonitrile (30:70 *v/v*) at a flow rate of 1 mL/min. Column effluent was monitored at 240 nm. Data was acquired and processed using CLASS-VP software (version 6.14).

Acknowledgment

This is a CDRI communication no. 7973. Surendra and Mridul thank CSIR New Delhi for SRF, Namrata to UGC New Delhi for SRF and Rahul to DRDO New Delhi for PA. We sincerely acknowledge the financial assistance from DRDO and DBT New Delhi. SAIF CDRI is also acknowledged for providing the spectral and microanalytical data of the compounds.

Appendix. Supporting Information

All experimental details, biological assays, HPLC result, ^1H NMR and ^{13}C NMR, HRMS spectral data of prototype compounds are available free of charge via the internet at doi:10.1016/j.ejmech.2010.09.063.

References

[1] Y. Zhang, Annu. Rev. Pharmacol. Toxicol. 45 (2005) 529–564.
[2] J.S. Freundlich, F. Wang, C. Vilchèze, G. Gulten, R. Langley, G.A. Schiehser, D.P. Jacobus, W.R. Jacobs Jr., J.C. Sacchettini, Chem. Med. Chem. 4 (2009) 241–248.
[3] A. Nayyar, R. Jain, Curr. Med. Chem. 12 (2005) 1873–1886.
[4] World health organization, Global Tuberculosis Control; Surveillance, Planning, Financing. World Health Organization, Geneva, 2008.http://www.who.int/tb/publications/global_report/en/index.html [accessed February 2009].
[5] C. Dye, S. Scheele, P. Dolin, V. Pathania, M.C. Raviglione, J. Am. Med. Assoc. 282 (1999) 677–686.
[6] J.B. Bass, L.S. Farer, P.C. Hopewell, R. O'Brein, R.F. Jacob, F. Ruben, D.E. Snider Jr., G. Thornton, Am. J. Respir. Crit. Care Med. 149 (1994) 1359–1374.
[7] P. Farmer, J. Bayona, M. Becerra, J. Furin, C. Henry, H. Hiatt, J.Y. Kim, C. Mitnick, E. Nardell, S. Shin, Int. J. Tuberc. Lung Dis. 2 (1998) 869–876.
[8] E.C. Rivers, R.L. Mancera, Drug Discov. Today 13 (2008) 23–24.
[9] R.E. Chaisson, Am. J. Respir. Crit. Care Med. 167 (2003) 1461–1466.
[10] The Global Plan to Stop TB, 2006–2015. World Health Organization and Stop TB Partnership, Geneva, 2006, O/HTM/STB/2006.35.
[11] R.P. Tripathi, N. Tewari, N. Dwivedi, V.K. Tiwari, Med. Res. Rev. 25 (2005) 93–131.
[12] C.E. Rivers, R.L. Mancera, Drug Discov. Today 13 (2008) 1090–1098.
[13] D. Katiyar, V.K. Tiwari, N. Tewari, S.S. Verma, S. Sinha, A. Gaikwad, A. Srivastava, V. Chaturvedi, R. Srivastava, B.S. Srivastava, R.P. Tripathi, Eur. J. Med. Chem. 40 (2005) 351–360.
[14] D. Katiyar, V.K. Tiwari, R.P. Tripathi, A. Srivastava, V. Chaturvedi, R. Srivastava, B.S. Srivastava, Bioorg. Med. Chem. 11 (2003) 4369–4375.
[15] N. Dwivedi, N. Tewari, V.K. Tiwari, V. Chaturvedi, Y.K. Manju, A. Srivastava, A. Giakwad, S. Sinha, R.P. Tripathi, Bioorg. Med. Chem. Lett. 15 (2005) 4526–4530.
[16] R.P. Tripathi, S.S. Verma, J. Pandey, K.C. Agarwal, V. Chaturvedi, Y.K. Manju, A.K. Srivastva, A. Gaikwad, S. Sinha, Bioorg. Med. Chem. Lett. 16 (2006) 5144–5147.
[17] N. Tewari, V.K. Tiwari, R.P. Tripathi, V. Chaturvedi, A. Srivastava, R. Srivastava, P.K. Shukla, A.K. Chaturvedi, A. Gaikwad, S. Sinha, B.S. Srivastava, Bioorg. Med. Chem. Lett. 15 (2004) 329–332.
[18] R.P. Tripathi, V.K. Tiwari, N. Tewari, D. Katiyar, N. Saxena, S. Sinha, A. Gaikwad, A. Srivastava, V. Chaturvedi, Y.K. Manju, R. Srivastava, B.S. Srivastava, Bioorg. Med. Chem. 13 (2005) 5668–5679.
[19] R.P. Tripathi, N. Saxena, V.K. Tiwari, S.S. Verma, V. Chaturvedi, Y.K. Manju, A.K. Srivastva, A. Gaikwad, S. Sinha, Bioorg. Med. Chem. 14 (2006) 8186–8196.
[20] R.P. Tripathi, R. Tripathi, V.K. Tiwari, L. Bala, S. Sinha, A. Srivastava, R. Srivastava, B.S. Srivastava, Eur. J. Med. Chem. 37 (2002) 773–781.

[21] J. Pandey, V.K. Tiwari, S.S. Verma, V. Chaturvedi, S. Bhatnagar, S. Sinha, A.N. Gaikwad, R.P. Tripathi, Eur. J. Med. Chem. 44 (2009) 3350–3355.
[22] L. Rajabi, C. Courreges, J. Montoya, R.J. Aguilera, T.P. Primm, Lett. Appl. Microbiol. 40 (2005) 212–217.
[23] Y.M. Lin, Y. Zhou, M.T. Flavin, L.M. Zhou, W. Nie, F.C. Chen, Bioorg. Med. Chem. 10 (2002) 2795–2802.
[24] M.A. Morgan, K.A. Doerr, H.O. Hampel, N.L. Goodman, G.D. Roberts, J. Clin. Microbiol. 21 (1985) 634–635.
[25] J.K. McClatchy, Lab. Med. 9 (1978) 47–52.
[26] A.H. Cory, T.C. Owen, J.A. Barltrop, J.G. Cory, Cancer Commun. 3 (1991) 207–212.
[27] T. Mosmann, J. Immunol. Methods 65 (1983) 55–63.
[28] P.S. Skinner, S.K. Furney, D.A. Kleinest, I.M.M. Orme, Antimicrob. Agents Chemother. 39 (1995) 750–753.
[29] G. Canetti, F. Grumbach, J. Grosset, Am. Rev. Respir. Dis. 82 (1960) 295–313.
[30] F. Fenner, Am. Rev. Tuberc. Dis. 64 (1951) 252–383.