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Papers

Design, synthesis and antitubercular activity of compounds containing aryl and heteroaryl groups with alkylaminoethyl chains

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Aryl and heteroaryl derivatives with an alkylaminoethyl chain on the hydroxyl group of the benzene ring are prepared and evaluated against *Mycobacterium tuberculosis* $H_{37}R_v$ and showed the activity in the range of 3.12-25 μg/mL. The compounds containing alkylaminoethyl chains on aryl-chromeneyl carbinol do not show good activity. Similarly compounds with *bis* and *tris*-alkylaminoethyl chains on aryl and triarylmethane derivatives do not exhibit antitubercular activity. Among heteroaryl containing triarylmethanes (TRAMs), thiophene derivatives with alkylaminoethyl chain on aromatic hydroxyl group have exhibited good antitubercular activity. On the other hand, pyrrole containing TRAMs do not show good activity.

Keywords: Tuberculosis, pyrazinamide, alkylaminoethyl chains

Tuberculosis (TB) is a bacterial infection and is becoming alarming due to the appearance of multidrug resistance[1]. The WHO had estimated that if efforts to control TB are not further intensified then between 2000 and 2020, nearly one billion people will be newly infected, 200 million people will get sick, and 35 million will die from TB. Approximately 50% of India's population is reported to be tuberculin test positive. Every year about 0.4 million deaths and one million new cases of tuberculosis are reported. This led to the declaration of TB as a global emergency[2] by WHO in 1993. The regeneration of TB is closely linked to the emergence of HIV and total deficiency of the immune system[3]. Despite enormous efforts, no new drug has been introduced in the market for the past 40 years[4].

Ethambutol (EMB) **1**, a synthetic compound with profound antimycobacterial activity, is a first line anti-TB drug. Isoniazid (INH) **2** is a prodrug that requires activation by the mycobacterial catalase peroxidase enzyme (katG) to an active form, which then exerts a lethal effect on intracellular targets. INH is highly active against the MTB complex pathogens (*M. tuberculosis*, *M. bovis, M. africanum*) with very low MICs (0.02 to 0.06 μg/mL). Ethionamide **3**, the sulfur analogue of Isoniazide is also highly active against *M. tuberculosis*. Pyrazinamide (PZA) **4**, a structural analog of nicotinamide, is a first-line drug for short-course tuberculosis therapy. Recently, diarylquinoline **5**, (TMC 207, **Figure 1)** was discovered as a potent inhibitor of Mtb, M. smegmatis, and MDR-TB with ATP synthase target that appears to be essential to mycobacteria.

From our research group, several publications have appeared on design and synthesis of new compounds as antitubercular agents[5a-f]. Careful observation on the structure of the molecules revealed that the alkylaminoethyl chain played an important part in exhibiting antitubercular activity. Looking to the above mentioned structures of antitubercular drugs, it can also be inferred that a heteroaromatic moiety plays an important role in the activity. Therefore as a consequence of above facts and in continuation of our previous research work, we herein report the synthesis and antitubercular activity of several compounds containing aryl and heteroaryl moieties with alkylaminoethyl chains.

Initial synthesis of the target molecules **8a-d** having an alkylaminoethyl chain on the alkyl hydroxy group was carried out as follows. The reaction of 4-bromochromene **6** with 4-methoxybenzaldehyde using *n*-BuLi in THF furnished carbinol **7**. The reaction of **7** with four alkylaminoethyl chloride chains in the presence of K_2CO_3 and acetone led to

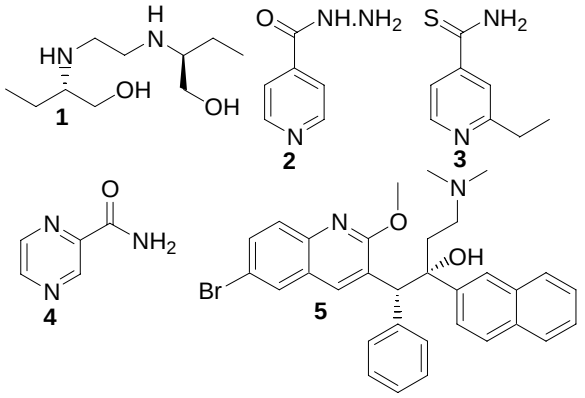
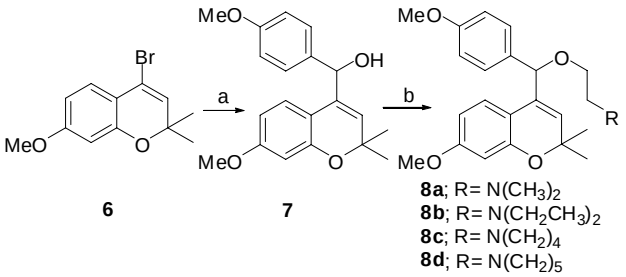
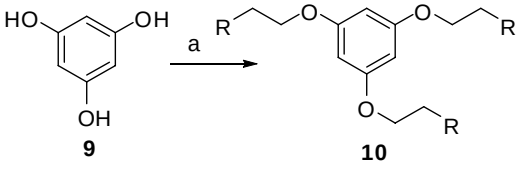


Figure 1 — Some reported antitubercular agents



Scheme I

Reagents and conditions: (a) *n*-BuLi, THF, –78°C, *p*-anisaldehyde, 1h (b) alkylaminoethyl hydrochloride ($ClCH_2CH_2R.HCl$), anhy. K_2CO_3, dry acetone, reflux, 6-7 h, (yields are given in **Table I**)

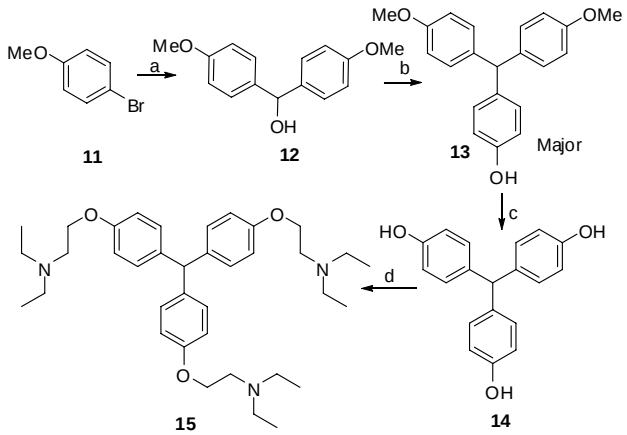


Scheme II

Reagents and conditions: alkylaminoethyl hydrochloride ($ClCH_2CH_2R.HCl$), anhy. K_2CO_3, dry acetone, reflux, 6-7 h

the formation of compounds **8a-d** (**Scheme I**). By treatment of amines **8a-d** with ethanolic hydrogen chloride, the corresponding salts were prepared. The ethanolic HCl salts were found to be inactive against *Mycobacterium tuberculosis* $H_{37}R_v$ *in vitro*.

The inactivity resulting from alkylaminoethyl chains on the hydroxyalkyl group prompted us to synthesize compounds having chains on an aromatic hydroxyl group. Towards this objective, phloroglucinol **9** was reacted with diethylamino ethyl



Scheme III

Reagents and conditions: Mg, THF, *p*-anisaldehyde, 0°C-rt, 2 h, (b) phenol, dry benzene, reflux, 2 h, (c) BBr_3, CH_2Cl_2, -78°C to RT, 1-2h (d) alkylaminoethyl hydrochloride ($ClCH_2CH_2R.HCl$), anhy. K_2CO_3, dry acetone, reflux, 6-7 h.

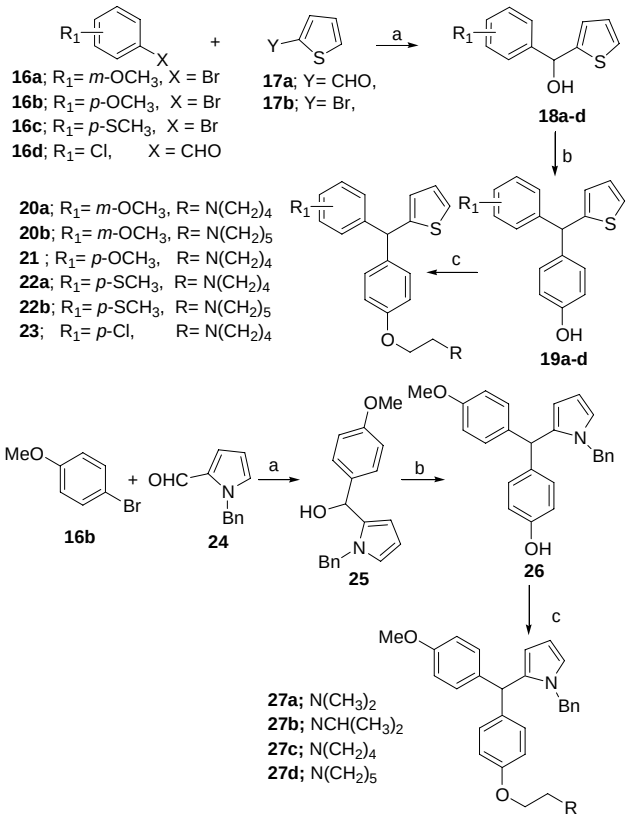
chloride chain in presence of K_2CO_3/acetone to furnish **10** (**Scheme II**) and was evaluated for its activity. The compound was moderately active with MIC 12.5 μg/mL.

It was anticipated that increasing chain length on the triarylmethane moiety might increase the activity. Towards this objective, Grignard reagent derived from 4-bromoanisole **11** was reacted with 4-methoxybenzaldehyde to furnish carbinol **12** (**Scheme III**). Friedel-Crafts reaction of **12** with anisole in presence of Conc. H_2SO_4/benzene furnished symmetric *para*-substituted trimethoxy triaryl methane **13**. Boron tribromide treatment of **13** in DCM at -78°C gave **14** having a *tris*-hydroxy functionality. The reaction of **14** with diethyl aminoethyl chroride chain in the presence of K_2CO_3 and acetone led to the formation of compounds **15** in 79% yield (**Scheme III**). By treatment of amine **15** with ethanolic hydrogen chloride the corresponding salts **15**·HCl were prepared. The ethanolic HCl salts were tested against *M. tuberculosis* $H_{37}R_v$ *in vitro* and were found to be active with MIC 12.5 μg/mL.

Next, we intended to synthesize compounds having chains on heteroaryl substituted trisubstituted methane (TRSM) derivatives. Thiophene and pyrrole substituted compounds were synthesized and evaluated for their antitubercular activity (**Scheme IV**).

Methods for the determination of Anti-tubercular activity

Agar Micro Dilution Method: Drug susceptibility and determination of MIC of the test comp



Scheme IV

Reagents and conditions: (a) Mg, THF, 0°C-RT, 2 h, (b) Phenol, dry benzene, reflux, 2h, (c) alkylaminoethyl hydrochloride ($ClCH_2CH_2R.HCl$), anhy. K_2CO_3, dry acetone, reflux, 6-7 h, (yields are given in **Table I**)

ounds/drugs against *M. tuberculosis* $H_{37}R_v$ were performed by agar micro dilution method where serial twofold dilutions of each test compound were added into 7H10 agar and *M. tuberculosis* $H_{37}R_v$ was used as test organism. MIC is the concentration of the compound that completely inhibits the growth and colony forming ability of *M. tuberculosis*.

In 24 well plate, 3 mL middle brook 7H11 agar medium with OADC supplement is dispensed in each well. The test compound is added to the middle brook medium agar before in duplicate so that final concentration of test compound in each well is 25, 12.5, 6.25, 3.125 and 1.56 µg/mL, respectively. The known CFU of $H_{37}R_v$ culture was dispensed on top of agar in each well in negative pressure biosafety hood. The plates are then incubated at 37°C/5% CO_2 incubator. The concentration at which complete inhibition of colonies was observed was taken as MIC of test drug.

Table I — *In vitro* antitubercular activity of the synthesized compounds against *M. tuberculosis* $H_{37}R_v$

Serial No	Compound	R	Yield (%)[a]	MIC (µg/mL)
1	**8a**	$N(CH_3)_2$	71	>25
2	**8b**	$N(CH_2CH_3)_2$	86	>25
3	**8c**	$N(CH_2)_4$	81	>25
4	**8d**	$N(CH_2)_5$	79	>25
5	**10**	$N(CH_2CH_3)_2$	85	12.5
6	**15**	$N(CH_2CH_3)_2$	79	12.5
7	**20a**	$N(CH_2)_4$	83	3.12
8	**20b**	$N(CH_2)_5$	77	3.12
9	**21**	$N(CH_2)_4$	73	6.25
10	**22a**	$N(CH_2)_4$	74	3.12
11	**22b**	$N(CH_2)_5$	81	3.12
12	**23**	$N(CH_2)_4$	73	3.12
13	**27a**	$N(CH_3)_2$	76	12.5
14	**27b**	$NCH(CH_3)_2$	73	12.5
15	**27c**	$N(CH_2)_4$	79	12.5
16	**27d**	$N(CH_2)_5$	77	12.5
17	**27e**	$N(CH_2)_6$	87	12.5
18	**27f**		81	12.5

[a]Isolated yield after silica gel column chromatography

Biological results

All the compounds synthesized were evaluated for their antitubercular activity against *M. tuberculosis* $H_{37}R_v$ through Agar Micro Dilution Technique[6] and exhibited moderate to good activity (**Table I**). It is noteworthy that the activity was dependent on the heteroaryl substitution on TRSMs. Chroman containing trisubstituted methanes (TRSMs) **8a-d** did not exhibit any antitubercular activity, whereas pyrrole, thiophene containing TRSMs showed moderate to good activity. A closer look into the biological results of the above compounds reveals that in a given thiophene containing TRSMs, increasing the alkyl chain on nitrogen gave better activity, perhaps due to increase in hydrophobicity resulting into better penetration of the Mtb cell wall.

Experimental Section

General Procedure

All the reactions were monitored by TLC over silica gel coated TLC plates. IR spectra were recorded on a Perkin-Elmer 881 or FT IR 820/PC instrument and values are expressed in cm^{-1}. Electron impact

mass spectra were recorded on JEOL (Japan) /D-300 instrument and FAM mass spectra were recorded on JEOL SX 102/DA-6000 mass using Argon /Xenon (6 KV, 10 MA) as the FAB gas. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker Advance DPX 200 MHz using TMS as internal reference. Chemical shift value is expressed in δ ppm. Specific rotation was determined with Rudolph Autopol IIIrd polarimeter at 28°C. Elementary analysis was carried out on a Carlo ERBA-1108 analyzer. Commercially available grades of organic solvents of adequate purity are used in many reactions. Acetone was refluxed with $KMnO_4$ for 4 hr, after that it was distilled and stored in a bottle containing dried K_2CO_3. Benzene was refluxed with freshly cut and dried sodium metal pieces pressed in 3 Å sieves for 4-6 hr. It was distilled and stored in a dry bottle. Tetrahydrofuran first dried initially over calcium sulphate and then refluxed over lithium alimumium hydride. Peroxide was removed by passage through a column of aluminum and distilled and stored over molecular sieves 3Å.

(7-Methoxy-2,2-dimethyl-2*H*-chromen-4-yl)(4-methoxyphenyl)methanol 2. To a stirred solution of the **1** (1.2 g, 4.46 mmole) in dry THF (30 mL), at –78°C and under N_2, *n*-butyl lithium (4.18 mL of 1.6 *M* in hexane, 6.69 mmole), was added *via* a syringe in a single portion. The resulting orange solution was stirred at –78°C for 15-20 minutes after which the 4-methoxy benzaldehyde (0.61 g, 4.46 mmole) in THF (2 mL) was added in a single portion at the same temperature. The resulted pale yellow solution was stirred at RT for 1 hr. The reaction-mixture was quenched by gradual addition of saturated aq. NH_4Cl (~10 mL) and THF was removed in vacuo. The mixture was extracted thrice with ethyl acetate, the extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuo. The residue was chromatographed over silica gel and elution with 15% ethyl acetate in hexane (R_f= 0.5) furnishing 2 (1.02 g, 70%) as yellow oil. R_f = 0.5 (15% ethyl acetate in hexane). IR (Neat): 3420, 2974, 1612, 1507, 1249, 1169, 1146, 1030, 754 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.32 (d, 2H, *J* = 8.6 Hz, Ar*H*), 6.89-6.83 (m, 3H, Ar*H*), 6.38 (d, 1H, *J* = 2.5 Hz, Ar*H*), 6.27 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.5 Hz, Ar*H*), 5.70 (s, 1H, 3*H*), 5.56 (s, 1H, C*H*OH), 3.76 (s, 3*H*, OCH_3), 3.70 (s, 1H, OCH_3), 2.35 (bs, 1H, CHO*H*), 1.46 (s, 6H, 2-CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 160.7, 159.6, 154.9, 134.5, 133.7, 128.8, 125.3, 125.2, 114.4, 114.1, 106.8, 102.7, 76.7, 72.6, 55.5, 28.2; MS (FAB): *m/z* (%): 326 (50, [M$^+$]), 311 (100, [M$^+$-CH_3]), 309 (55, [M$^+$-OH]). Anal. Calcd for $C_{20}H_{22}O_4$; C, 73.60; H, 6.79. Found: C, 73.62; H, 6.74%.

2-((7-Methoxy-2,2-dimethyl-2*H*-chromen-4-yl)(4-methoxyphenyl)methoxy)-*N*,*N*-dimethylethanamine 3a. A mixture of compounds **2** (0.20 g, 0.674 mmole), anhydrous K_2CO_3 (0.28 g, 2.02 mmole), 1-(2-chloroethyl)-dimethyl amine hydrochloride (0.12 g, 0.81mmole) and dry acetone (7 mL) was refluxed for 7 hr. K_2CO_3 was filtered off and acetone was removed. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Column chromatography over basic alumina and elution with 35% ethyl acetate in hexane furnished the compound **3a** (0.18 g, 71%) as light yellow oil. IR (KBr): 3431, 2937, 2836, 1613, 1507, 1461, 1249, 1147, 1034, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.30 (t, 2H, *J* = 8.6 Hz, Ar*H*), 7.02 (d, 1H, *J* = 8.5 Hz Ar*H*), 6.84 (d, 2H, *J* = 8.6 Hz, Ar*H*), 6.36 (d, 1H, *J* = 2.5 Hz Ar*H*), 6.26 (dd, 1H, J_1 = 2.7 Hz, J_2 = 8.6 Hz Ar*H*), 5.60 (s, 1H, =C*H*), 5.11 (s, 1H, C*H*OH), 3.77 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.61-3.56 (m, 2H), 2.57 (t, 2H, *J* = 6.0 Hz), 2.25 (s, 6H), 1.46 (s, 3H), 1.44 (s, 3H); MS: 398 (M$^+$+ H), 309. Anal. Calcd. for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.59; H, 6.81; N, 3.46%.

***N*,*N*-diethyl-2-((7-methoxy-2,2-dimethyl-2*H*-chromen-4-yl)(4-methoxyphenyl)methoxy)ethanamine 3b**: IR (KBr): 3402, 2969, 2840, 1612, 1507, 1461, 1249, 1147, 1035, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.32 (t, 2H, *J* = 8.6 Hz, Ar*H*), 7.02 (d, 1H, *J* = 8.5 Hz, Ar*H*), 6.84 (d, 2H, *J* = 8.6 Hz, Ar*H*), 6.37 (d, 1H, *J* = 2.4 Hz Ar*H*), 6.27 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.5 Hz, Ar*H*), 5.61 (s, 1H, =C*H*), 5.11 (s, 1H, C*H*OH), 3.76 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.59-3.51 (m, 2H), 2.70 (t, 2H, *J* = 6.2 Hz), 2.56 (q, 2H, J_1 = 7.14 Hz, J_2 = 12.1 Hz), 1.47 (s, 3H), 1.45 (s, 3H), 1.02 (t, 6H, *J* = 7.10 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 160.7, 159.5, 155.0, 132.7, 131.7, 128.8, 126.6, 125.7, 114.1, 106.7, 102.5, 81.4, 78.1, 70.0, 67.8, 55.6, 52.8, 48.0, 28.3, 12.2; MS: 426 (M$^+$+ H), 310. Anal. Calcd. for $C_{26}H_{35}NO_4$: C, 73.38; H, 8.29; N, 3.29. Found: C, 73.29; H, 8.35; N, 3.24%.

1-(2-((7-Methoxy-2,2-dimethyl-2*H*-chromen-4-yl)(4-methoxyphenyl)methoxy)ethyl)pyrrolidine 3c: IR (KBr): 3436, 2928, 2858, 1678, 1506, 1299, 1147, 1033, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.24 (t, 2H, *J* = 8.6 Hz, Ar*H*), 6.96 (d, 1H, *J* = 8.5 Hz, Ar*H*), 6.77 (d, 2H, *J* = 8.6 Hz, Ar*H*), 6.29 (d, 1H, *J* = 2.5 Hz, Ar*H*), 6.21 (dd, 1H, J_1 = 2.5 Hz, J_2 = 8.5 Hz,

Ar*H*), 5.51 (s, 1H, =C*H*), 5.05 (s, 1H, C*H*OH), 3.70 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.54-3.51 (m, 2H), 2.68 (t, 2H, *J* = 6.2 Hz), 2.49-2.46 (m, 2H),1.70-1.66 (m, 2H), 1.39 (s, 3H), 1.37 (s, 3H); MS: 424 (M^++ H), 309. Anal. Calcd. for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85; N, 3.31. Found: C, 73.69; H, 7.93; N, 3.34%.

1-(2-((7-Methoxy-2,2-dimethyl-2*H*-chromen-4-yl) (4-methoxyphenyl)methoxy)ethyl)piperidine 3d: IR (KBr): 2934, 2855, 1613, 1507, 1248, 1149, 1031, 764 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.31 (t, 2H, *J* = 8.6 Hz, Ar*H*), 7.04 (d, 1H, *J* = 8.5 Hz, Ar*H*), 6.84 (d, 2H, *J* = 8.6 Hz, Ar*H*), 6.37 (d, 1H, *J* = 2.5 Hz, Ar*H*), 6.28 (dd, 1H, J_1 = 2.5 Hz, J_2 = 8.5 Hz Ar*H*),, 5.56 (s, 1H, =C*H*), 5.13 (s, 1H, C*H*OH), 3.77 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.61-3.55 (m, 2H), 2.59 (t, 2H, *J* = 6.1 Hz), 2.25 (s, 6H), 1.46 (s, 3H), 1.43 (s, 3H); MS: 438 (M^++ H), 309. Anal. Calcd. for $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06; N, 3.20. Found: C, 74.19; H, 8.05; N, 3.24%.

2,2',2''-(Benzene-1,3,5-triyltris(oxy))tris(*N*,*N*-diethylethanamine) 5: ^1H NMR ($CDCl_3$, 200 MHz): δ 6.08 (s, 3H), 3.98 (t, 6H, *J* = 6.2 Hz), 2.84 (t, 6H, *J* = 6.2 Hz), 2.62 (q, 12H, J_1 = 7.0 Hz, J_2 =14.2 Hz), 1.06 (t, 18H, *J* =7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 161.0, 94.5, 66.9, 52.0, 48.1, 12.2; MS: 424 (M^++ H). Anal. Calcd. for ($C_{24}H_{45}N_3O_3$): C, 68.04; H, 10.71; N, 9.92. Found: C, 68.11; H, 10.68; N, 9.83%.

***Bis*(4-Methoxyphenyl)methanol 7**: A solution of 4-bromoanisole **6** (8.2 mL, 70.74 mmole) in dry THF (40 mL) was added to activated magnesium (1.93 g, 80.2 mmole) in dry THF and was stirred at RT under dry nitrogen for 0.5 hr. To Grignard reagent thus formed was added *p*-anisaldehyde (7 g, 51.56 mmole) in THF (10 mL) and stirring was continued for another 1-2 hr. The reaction-mixture was quenched by gradual addition of saturated NH_4Cl (~10mL) and THF was removed in vacuo. The mixture was extracted thrice with ethyl acetate, washed with brine and dried over sodium sulphate. It was concentrated and charged over silica gel. Elution with 10% ethyl acetate in hexane furnished carbinol product **7** (5.5 g, 73.3%) as viscous pale yellow liquid. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.24-7.20 (d, 4H, *J* = 8.6 Hz), 6.84-6.80 (m, 4H), 5.68 (s, 1H), 3.74 (s, 6H); MS: 245 (M^++ H). Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.69; H, 6.54%.

4-(*Bis*(4-Methoxyphenyl)methyl)phenol 8: To a solution of carbinol 7 (1.0 g, 4.09 mmole) and phenol (0.39 g, 4.09 mmole) in dry benzene (15 mL) was added catalytic amount of Conc. H_2SO_4 and the mixture was heated at 80°C for 1h. After cooling, the reaction- mixture was neutralized with saturated aq. $NaHCO_3$ and extracted with ethyl acetate. The concentrated extract was subjected to column chromatography on silica gel and elution with 15% ethyl acetate in hexane furnishing 8 (0.82 g, 61%) as brown viscous oil. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.02-6.92 (m, 6H), 6.82-6.69 (m, 6H), 5.37 (s, 1H), 3.77 (s, 6H); MS: 321 (M^++H). Anal. Calcd. for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, C, 78.79; H, 6.21%.

4,4',4''-Methanetriyltriphenol 9: ^1H NMR ($CDCl_3$, 200 MHz): δ 7.22-7.11 (m, 6H), 7.08-6.85 (m, 6H), 5.59 (s, 1H); MS: 293 (M^++ H). Anal. Calcd. for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.13; H, 5.43%.

2,2',2''-(4,4',4''-Methanetriyltris(benzene-4,1-diyl)-tris(oxy))tris(*N*,*N*-diethylethanamine) 10: ^1H NMR ($CDCl_3$, 200 MHz): δ 6.91-6.87 (m, 6H), 6.74-6.69 (m, 6H), 5.28 (s, 1H), 3.93 (t, 6H, *J* = 6.3 Hz), 2.77 (t, 6H, *J* = 6.3 Hz), 2.54 (q, 12H, J_1 = 7.1 Hz, J_2 = 14.2 Hz), 0.97 (t, 2H, *J* = 7.1 Hz); MS: 587 (M^++H). Anal. Calcd. for ($C_{40}H_{58}O_3$): C, 81.86; H, 9.96. Found: C, 81.93; H, 9.91%.

(3-Methoxyphenyl)-thiophen-2-yl-methanol 13a: IR (Neat): 3436, 2926, 1597, 1352, 1039, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.27-7.21 (m, 2H), 7.05-7.02 (m, 2H), 6.97-6.92 (m, 2H), 6.88-6.84 (m, 1H), 6.03 (s, 1H), 3.82 (s, 3H).^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.5, 146.6, 143.4, 128.2, 125.3, 124.1, 123.6, 117.3, 112.3, 110.5, 71.0, 53.9; MS: 203 (M^+-OH).

4-[(3-Methoxyphenyl)-thiophen-2-yl-methyl]-phenol 14a: IR (Neat): 3334, 2369, 1600, 1510, 1259 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.24-7.18 (m, 2H), 7.05 (d, 2H, *J* = 8.2), 6.92-6.88 (m, 1H), 6.81-6.69 (m, 5H), 6.77 (s, 1H), 5.56 (s, 1H), 5.24 (s, 1H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.3, 153.0, 146.8, 144.4, 134.8, 128.7, 128.0, 125.3, 124.9, 123.2, 120.1, 113.9, 113.6, 110.5, 53.9, 50.0; MS: 296 (M^+).

1-(2-{4-[(3-Methoxyphenyl)-thiophen-2-yl-methyl]-phenoxy}-ethyl)-pyrrolidine 15a: As described for 3a, compound 14a (0.10g, 0.34 mmole), K_2CO_3 (0.14 g, 1.01 mmole), 1-(2-chloroethyl)-pyrrolidine hydrochloride (0.06 g, 0.37 mmole) furnished 12d (0.11g, 83%) as a brown semi solid. IR (Neat): 2932, 1603, 1508, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.25-7.09 (m, 4H), 6.94-6.09 (m, 7H), 5.58 (s, 1H), 4.09 (t, 2H, *J* = 5.8), 3.74 (s, 3H), 2.90 (t, 2H, *J* = 5.8), 2.65-2.63 (m, 4H); 2.03-1.81 (m, 4H); MS: 394 (M^++H).

1-(2-{4-[(3-Methoxyphenyl)-thiophen-2-yl-methyl]-phenoxy}-ethyl)-piperidine 15b: As described for 3a, compound **10a** (0.10 g, 0.34 mmole), K_2CO_3 (0.14 g, 1.01 mmole), 1-(2-chloroethyl)-piperidine hydrochloride (0.07 g, 0.37 mmole) furnished **12e** (0.10 g, 77 %) as a red semi solid. IR (neat): 2927, 1596, 1351 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.28-7.19 (m, 2H), 7.13 (d, 2H, *J* = 8.0), 6.95-6.92 (m, 1H), 6.87-6.80 (m, 4H), 6.77 (s, 1H), 6.70 (d, 1H, *J* = 6.8), 5.60 (s, 1H), 4.11 (t, 2H, *J* = 5.7), 3.77 (s, 3H), 3.74 (t, 4H, *J* = 5.7), 2.81 (t, 2H, *J* = 5.7), 2.61-2.57 (m, 4H); MS: 410 (M^++H).

1-(2-{4-[(4-Methoxyphenyl)-thiophen-2-yl-methyl]-phenoxy}-ethyl)-pyrrolidine 16: IR (Neat): 3440, 1635, 1245, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.08-7.00 (m, 5H), 6.78-6.72 (m, 6H), 5.48 (s, 1H), 3.98 (t, 2H), 3.69 (s, 3H), 2.79 (t, 2H), 2.61-2.56 (m, 4H), 1.92-1.73 (m, 4H); MS: 394 (M^++H).

1-(2-{4-[(4-Methylsulfanyl-phenyl)-thiophen-2-yl-methyl]-phenoxy}-ethyl)-pyrrolidine 17a: IR (Neat): 2925, 1602, 1351 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.26-7.07 (m, 7H), 6.94-6.90 (m, 1H), 6.84 (d, 2H, *J* = 8.0), 6.66 (d, 1H, *J* = 3.6), 5.57 (s, 1H), 4.10 (t, 2H, *J* = 5.8), 2.91 (t, 2H, *J* = 5.8), 2.94-2.88 (m, 4H); 2.46 (s, 3H), 1.98-1.82 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 157.9, 148.6, 141.5, 136.9, 130.1, 129.6, 127.0, 126.9, 126.5, 124.8, 114.8, 67.2, 55.4, 55.0, 51.2, 23.8, 16.3; MS: 409 (M^++H).

1-(2-{4-[(4-Methylsulfanyl-phenyl)-thiophen-2-yl-methyl]-phenoxy}-ethyl)-piperidine 17b: IR (Neat): 2930, 1607, 1506, 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.19-7.00 (m, 7H), 6.87-6.85 (m, 1H), 6.75 (d, 2H, *J* = 8.0), 6.60-6.58 (m, 1H), 5.50 (s, 1H), 4.03 (t, 2H, *J* = 5.8), 2.72(t, 2H, *J* = 5.8), 2.47-2.45 (m, 4H), 2.38 (s, 3H), 1.56-1.18 (m, 6H); MS: 424 (M^++H).

1-(2-{4-[(4-Chloro-phenyl)-thiophen-2-yl-methyl]-phenoxy}-ethyl)-pyrrolidine 18: IR (Neat): 2929, 1595, 1511, 1351 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.28-7.05 (m, 7H), 6.94-6.82 (m, 3H), 6.66-6.64 (m, 1H), 5.58 (s, 1H), 4.13 (t, 2H, *J* = 5.6 Hz), 2.95 (t, 2H, *J* = 5.6 Hz), 2.71-2.69 (m, 4H), 1.88-1.84 (m, 4H), 1.33-1.25 (m, 2H); MS: 398 (M^++H).

4-((1-Benzyl-1*H*-pyrrol-2-yl)(4-methoxyphenyl)-methyl)phenol 21: As described for 8, carbinol 20 (1.77 g, 4.51 mmole) and phenol (0.52 mL, 6.32 mmole) in dry benzene (20 mL) cat. amount Conc. H_2SO_4 furnished 21 (1.31 g, 62%) as brown viscous oil. IR (KBr): 3021, 2361, 1601, 1427, 1216, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.31-7.25 (m, 3H), 6.95-6.65 (m, 11H), 6.11-6.08 (m, 1H), 5.57 (d, 1H, *J* = 0.8 Hz), 5.04 (s, 1H), 4.78 (s, 2H), 3.78 (s, 3H); MS: 369 (M^+). Anal. Calcd. for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79. Found: C, 81.19; H, 6.31; N, 3.73%.

2-(4-((1-Benzyl-1*H*-pyrrol-2-yl)(4-methoxyphenyl)methyl)phenoxy)-*N*,*N*-dimethylethanamine 22a. A mixture of compounds 21 (0.22 g, 1.028 mmole), anhydrous K_2CO_3 (0.71 g, 5.14 mmole), 1-(2-chloroethyl)-dimethyl amine hydrochloride (0.284 g, 1.54 mmole) and dry acetone (20 mL) was refluxed for 7 hr. K_2CO_3 was filtered off and acetone was removed. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Column chromatography over basic alumina and elution with 35% ethyl acetate in hexane furnished the compound 22a (0.26 g, 76%) as brown viscous oil. IR (Neat): 3021, 2360, 1601, 1430, 1216, 760. cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.32-7.24 (m, 3H), 6.93-6.88 (m, 6H), 6.77-6.72 (m, 4H), 6.64-6.63 (m, 1H), 6.07 (t, 1H, *J* = 3.11 Hz), 5.57-5.56 (m, 1H), 5.05 (s, 1H), 4.78 (s, 2H), 4.04 (t, 2H, *J* = 6.2 Hz), 3.77(s, 3H), 2.89 (t, 2H, *J* = 6.2 Hz), 2.32(s, 2H); MS: 441 (M^++ H). Anal. Calcd. for $C_{29}H_{32}N_2O_2$: C, 79.06; H, 7.32; N, 6.36. Found: C, 79.12; H, 7.19; N, 6.27%.

1-Benzyl-2-((4-methoxyphenyl)(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)methyl)-1*H*-pyrrole 22b: IR (Neat): 2924, 2372 1606, 1508, 1246, 1035, 757. cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.34-7.25 (m, 3H), 6.94-6.89 (m, 6H), 6.80-6.76 (m, 4H), 6.67-6.65 (m, 1H), 6.09 (t, 1H, *J* = 3.10 Hz), 5.58-5.57 (m, 1H), 5.04 (s, 1H), 4.79 (s, 2H), 4.04 (t, 2H, *J* = 6.1 Hz), 3.77(s, 3H), 2.89 (t, 2H, *J* = 6.2 Hz), 2.72-2.61 (m, 4H), 1.08 (t, 4H, *J* = 7.12 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.5, 157, 139.0, 136.0, 135.7, 135.6, 130.1, 129.1, 127.7, 126.8, 122.3, 114.6, 114.0, 110.2, 107.1, MS: 467 (M^++ H). Anal. Calcd. for $C_{31}H_{34}N_2O_2$: C, 79.79; H, 7.34; N, 6.00. Found: C, 79.84; H, 7.29; N, 6.08%.

***N*-(2-(4-((1-Benzyl-1*H*-pyrrol-2-yl)(4-methoxyphenyl)methyl)phenoxy)ethyl)-*N*-isopropylpropan-2-amine 22c**: IR (KBr): 3021, 2360, 1599, 1425, 1216, 1044, 761. cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.32-7.26 (m, 3H), 6.95-6.88 (m, 6H), 6.80-6.75 (m, 4H), 6.67-6.65 (m, 1H), 6.10 (t, 1H, *J* = 3.10 Hz), 5.56-5.55 (m, 1H), 5.04 (s, 1H), 4.79 (s, 2H), 4.01 (t, 2H, *J* = 6.9 Hz), 3.77 (s, 3H), 3.07-3.00 (m, 2H), 2.80 (t, 2H, *J* = 6.9 Hz), 2.72-2.61 (m, 4H), 1.04 (d, 12H, *J* = 6.4 Hz); MS: 497 (M^++ H). Anal. Calcd. for $C_{33}H_{40}N_2O_2$: C, 79.80; H, 8.12; N, 5.64. Found: C, 79.69; H, 8.16; N, 5.61%.

1-(2-(4-((1-Benzyl-1*H*-pyrrol-2-yl)(4-methoxyphenyl)methyl)phenoxy)ethyl)piperidine 22d: IR (KBr): 3020, 2401, 1643, 1423, 1216, 1040, 760. cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.31-7.25 (m, 3H), 6.93-6.88 (m, 6H), 6.80-6.75 (m, 4H), 6.66-6.65 (m, 1H), 6.09 (t, 1H, *J* = 3.1 Hz), 5.56-5.55 (m, 1H), 5.05 (s, 1H), 4.79 (s, 2H), 4.08 (t, 2H, *J* = 6.0 Hz), 3.77 (s, 3H). 2.78 (t, 2H, *J* = 5.9 Hz), 2.53 (t, 4H, *J* = 4.5 Hz), 1.68-1.59 (m, 4H), 1.46-1.44 (m, 2H); MS: 481 (M^++ H). Anal. Calcd. for $C_{32}H_{36}N_2O_2$: C, 79.96; H, 7.55; N, 5.83. Found: C, 79.91; H, 7.56; N, 5.75%.

1-(2-(4-((1-Benzyl-1*H*-pyrrol-2-yl)(4-methoxyphenyl)methyl)phenoxy)ethyl)azepane 22e: IR (KBr): 3020, 2401, 1642, 1510, 1216, 1038, 760. cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.31-7.25 (m, 3H), 6.94-6.88 (m, 6H), 6.80-6.76 (m, 4H), 6.66-6.64 (m, 1H), 6.10 (t, 1H, *J* = 3.0 Hz), 5.58-5.56 (m, 1H), 5.05 (s, 1H), 4.79 (s, 2H), 4.03 (t, 2H, *J* = 6.2 Hz), 3.77 (s, 3H). 2.93 (t, 2H, *J* = 6.2 Hz), 2.79-2.74 (m, 4H), 1.61-1.38 (m, 8H); MS: 495 (M^++H). Anal. Calcd. for $C_{33}H_{38}N_2O_2$: C, 80.13; H, 7.74; N, 5.66. Found: C, 80.07; H, 7.80; N, 5.58%.

4-(2-(4-((1-Benzyl-1*H*-pyrrol-2-yl)(4-methoxyphenyl)methyl)phenoxy)ethyl)morpholine 22f: IR (KBr): 3020, 2400, 1638, 1510, 1216, 1041, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.32-7.21 (m, 3H), 6.95-6.89 (m, 6H), 6.80-6.76 (m, 4H), 6.67-6.65 (m, 1H), 6.21-6.16 (m, 1H), 6.09 (t, 2H, *J* = 3.1 Hz), 5.05 (s, 1H), 4.79 (s, 2H), 4.07 (t, 2H, *J* = 6.1 Hz), 3.77 (s, 3H). 3.75-3.71 (m, 4H), 2.78 (t, 2H, *J* = 6.1 Hz), 2.59-2.25 (m, 4H); MS: 483 (M^++H). Anal. Calcd. for $C_{31}H_{34}N_2O_3$: C, 77.15; H, 7.10; N, 5.80. Found: C, 77.08; H, 7.05; N, 5.86%.

Conclusion

The synthesis of the aminoalkyl derivatives of aryl and heteroaryl comprising compounds through Grignard reaction, Friedel-Crafts arylation is reported and aminohydrochloride chain formation reactions and these compounds were active in the range of 3.12-25 μg/mL against *Mycobacterium tuberculosis* $H_{37}R_v$. All these results suggest that it will be interesting to prepare the analogues of active molecules for finding new compounds that possess better activity and bioavailability.

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