RESEARCH ENVISAGED

β-Adrenergic blocking agents are used for a variety of cardiovascular and non-cardiovascular diseases including hypertension, ischemic heart disease, arrhythmias and prophylaxis of myocardial infarction.[333] β-Adrenergic blocking agents compete with catecholamines at β-adrenergic receptors[368] and this has been found responsible for their therapeutic action.[331] The β_1-receptor blockade tends to decrease heart rate, cardiac output, blood pressure while increasing peripheral vascular resistance, whereas β_2-receptor blockade tends to be disadvantageous in causing bronchoconstriction.[159, 369]

Ever since the introduction of β-adrenergic blocking agents into clinical practice various workers have been trying to obtain newer β-adrenergic blocking agents with better activity and cardioselectivity. The search for safe and effective β-adrenergic blocking agents still continues in order to develop drugs with maximal therapeutic benefits.

The aim of this study was to synthesize a number of aryloxypropanolamine class of compounds using vanillin and thymol as the starting material and test them for their β-adrenergic blocking activity and β-adrenergic binding affinity. Also aryloxypropanolamine compounds with *para*-amidic substituents were planned to be synthesized starting from 4-aminophenol and 5-amino-1-naphthol, so as to get cardioselective β-adrenergic blocking agents.

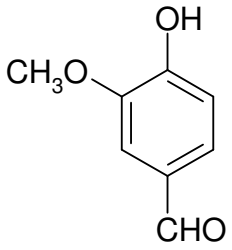
The work carried out by the present investigator is described in **Resumé and Discussion** section, which follows.

RESUMÉ AND DISCUSSION

The investigations carried out are discussed under the heads: Vanillin-derived aryloxypropanolamines; Thymol-derived aryloxypropanolamines; 4-Aminophenol-derived aryloxypropanolamines; 5-Amino-1-naphthol-derived aryloxypropanolamines; Miscellaneous compounds; β-Adrenoceptor binding assay; β-Adrenoceptor blocking activity; Local anaesthetic activity; and Partition coefficient.

VANILLIN-DERIVED ARYLOXYPROPANOLAMINES

Vanillin (**139**), a naturally occurring substance was used to synthesize a series of aryloxypropanolamines. The formyl group at 4-position allowed to introduce various substituents at the 4-position such as amino, oxime and enone functions. The phenolic group was elaborated to the oxypropanolamine side chain normally present in β-adrenergic blocking agents. The compounds prepared in this series have been divided into three structural groups: (i) Compounds with an isopropylamino substituent, (ii) *tert*-butylamino substituent and (iii) *N*-methylpiperazinyl substituent in the oxypropanol side chain.



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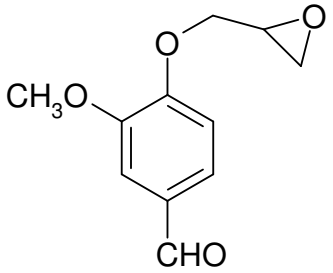


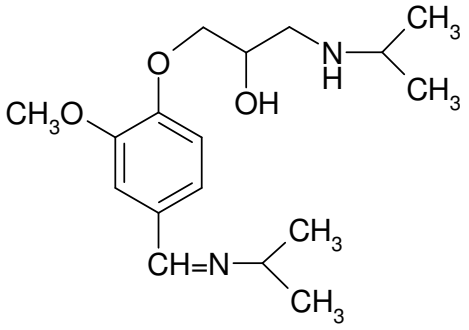
(140)

The key intermediate 4-(2,3-epoxypropoxy)-3-methoxybenzaldehyde (**140**) involved in the synthesis of all the compounds in this series was prepared by refluxing

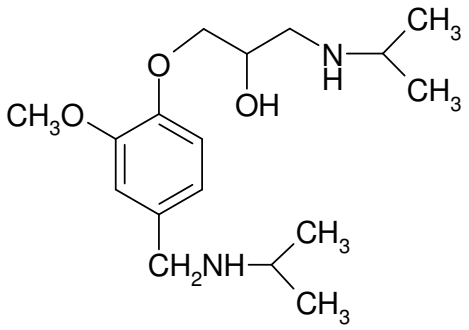
4-hydroxy-3-methoxybenzaldehyde (vanillin, **139**) in epichlorohydrin in the presence of anhydrous potassium carbonate. Removal of excess of epichlorohydrin under vacuum gave a solid product, which was purified by column chromatography using silica gel as stationary phase and chloroform as eluent to afford **140**. Carbonyl stretching vibration at 1695 cm^{-1} in infrared spectrum showed the presence of formyl (-CHO) group in the product. ^1H NMR spectrum showed at δ 2.78 a quartet and at 2.93 a triplet for two protons (-CH_2 of oxirane ring). Also there appeared a multiplet for one proton at δ 3.43 (-C*H* of oxirane ring).

(i) Compounds with isopropylamino substituent in the oxypropanol side chain

Refluxing the epoxy compound **140** with excess of isopropylamine, gave 1-(isopropylamino)-3-(4-isopropyliminomethyl-2-methoxyphenoxy)propan-2-ol (**141**), which could not be crystallized. Proton signals were observed in the NMR spectrum at



(141)



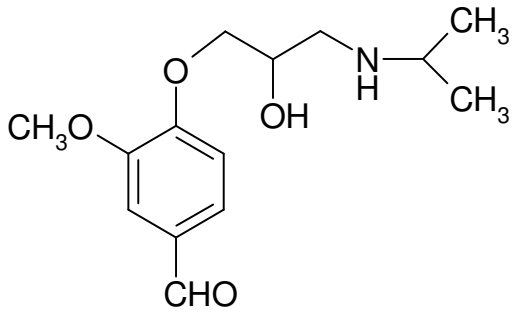
(142)

δ 1.08 (d, 6H, -NHCH(CH_3)$_2$) and at 1.25 (d, 6H, ArCH=NCH(CH_3)$_2$) indicating the presence of two isopropyl groups. Also there appeared a one proton singlet at δ 8.2 (ArC*H*=N-).

The imine **141** was reduced with sodium borohydride in methanol at low temperature

(5°C) to give 1-(isopropylamino)-3-(4-isopropylaminomethyl-2-methoxyphenoxy)propan-2-ol (**142**), which could not be crystallized. The ^{1}H NMR spectrum of **142** showed signals at δ 1.08 (q, 12H) indicating the presence of two isopropyl groups. Also there appeared a two proton singlet at δ 3.68 (ArC*H*$_2$-). The compound **142** was converted into its oxalate by refluxing with oxalic acid in methanol. Oxalate of **142** in ^{1}H NMR spectrum displayed signals at δ 7.01 (d, 3H) for aromatic protons in addition to other usual signals.

Hydrolysis of the imine **141** by refluxing in acetic acid (5%) gave 4-(2-hydroxy-3-isopropylaminopropoxy)-3-methoxybenzaldehyde (**143**), which was used for the preparation



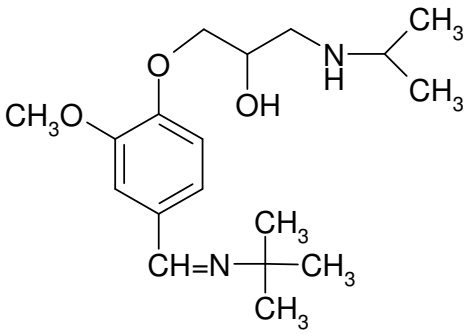
(143)

of oxalate as such. In ^{1}H NMR spectrum signals were displayed at δ 9.83 (s, 1H, ArC*H*O), indicating the presence of aldehyde function in the product. Also there appeared a proton signal at δ 1.09 (d, 6H, -CH(C*H*$_3$)$_2$). The compound **143** was converted to its oxalate by refluxing with oxalic acid in methanol. Proton signals showed a multiplet at δ 4.02 (2H, -OC*H*$_2$-) and a singlet at 3.70 ppm (3H, -OC*H*$_3$).

Refluxing **143** with excess of *tert*-butylamine in methanol gave 1-(4-*tert*-butyliminomethyl-2-methoxyphenoxy)-3-(isopropylamino)propan-2-ol **(144)**, which was oily in nature. Signals at δ 1.0 (d, 6H, -CH(C*H*$_3$)$_2$) and 1.2 ppm (s, 9H, -C(C*H*$_3$)$_3$)

indicated the presence of both isopropyl and *tert*-butyl groups in **144**. Also there appeared a singlet at δ 8.2 (1H, ArC*H*=N-).

Reduction of the imine **144** with sodium borohydride at low temperature gave 1-(4-*tert*-butylaminomethyl-2-methoxyphenoxy)-3-(isopropylamino)propan-2-ol (**145**),



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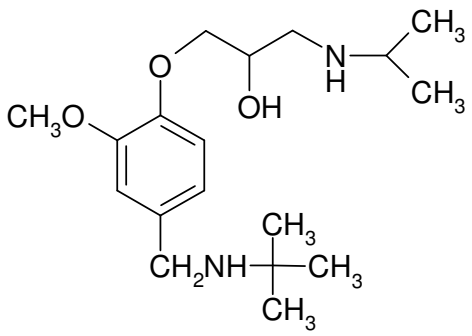
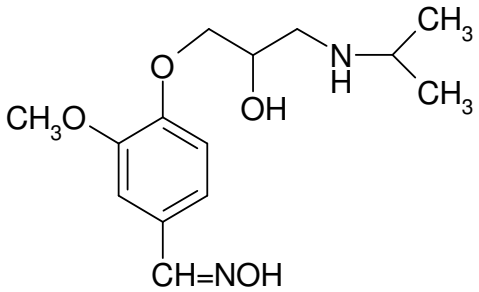


(145)

which could not be crystallized . ^{1}H NMR of **145** exhibited proton signals at δ 1.07 (d, 6H, -CH(CH_3)$_2$) and 1.19 (s, 9H, -C(CH_3)$_3$) for both isopropyl and *tert*-butyl groups. Also there appeared a singlet at δ 3.62 (2H, ArCH_2-). Refluxing **145** with oxalic acid in methanol gave the oxalate of **145**. The NMR spectrum displayed proton peaks at δ 3.76 (s, 3H, -OCH_3) and at 4.04 (m, 4H, -OCH_2- & ArCH$_2$-).

The aldehyde **143** on treatment with hydroxylamine hydrochloride in the presence

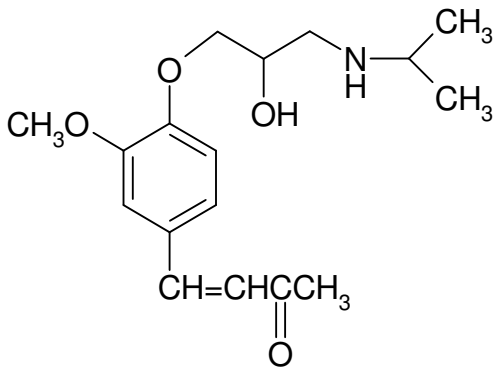


(146)

of sodium acetate trihydrate in ethanol gave the 4-(2-hydroxy-3-isopropylaminopropoxy)-3-methoxybenzaldehyde oxime (**146**), which was oily in nature. In ^{1}H NMR spectrum

there appeared a one proton singlet at δ 8.0 (ArC*H*=NOH) and at 1.13 (d, 6H, -CH(CH_3)$_2$). The oxime **146** was converted to its oxalate by usual procedure. The oxalate displayed proton NMR signals at δ 3.73 (s, 3H, -OCH_3) and at 4.01 ppm (m, 2H, -OCH_2-), in addition to other peaks.

Reaction of the aldehyde **143** with acetone in the presence of potassium hydroxide in methanol gave 4-[4-(2-hydroxy-3-isopropylaminopropoxy)-3-methoxyphenyl]but-3-en-2-one (**147**), which was purified by column chromatography using neutral alumina as the stationary phase and chloroform-methanol mixture (99:1) as eluent. Infrared spectrum of **147** showed a C=O stretching vibration at 1660 cm^{-1} and in ^{1}H NMR spectrum it revealed



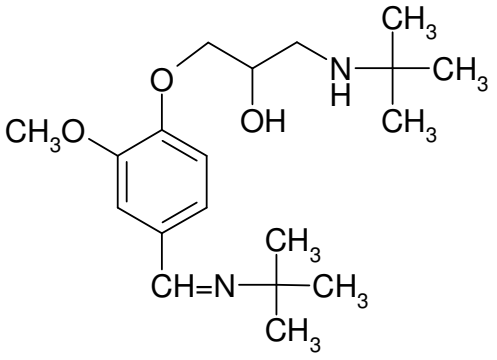
(147)

a singlet at δ 2.37 (3H, -COCH_3), a doublet at 6.59 (1H, ArCH=C*H*-) and another doublet at 7.44 ppm (1H, ArC*H*=CH-). The oxime **147** was converted to its oxalate, which showed all the essential proton signals in NMR spectrum.

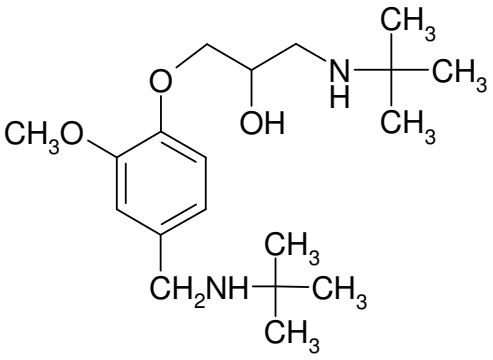
(ii) Compounds with *tert*-butylamino substituent in the oxypropanol side chain

The epoxy compound **140** was refluxed with excess of *tert*-butylamine in methanol to obtain 1-(*tert*-butylamino)-3-(4-*tert*-butyliminomethyl-2-methoxyphenoxy)propan-2-ol (**148**), which could not be crystallized. ^{1}H NMR spectrum

displayed two singlets at δ 1.2 and at 1.3 for two *tert*-butyl groups. Also, there appeared a one proton singlet at δ 8.2 (ArC*H*=N-). Sodium borohydride reduction of the



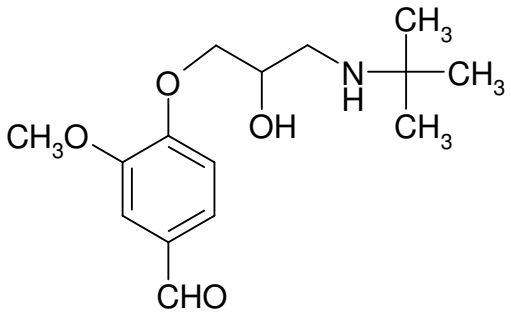
(148)



(149)

imine **148** gave 1-(*tert*-butylamino)-3-(4-*tert*-butylaminomethyl-2-methoxyphenoxy)-propan-2-ol (**149**). Proton NMR signals of **149** showed the presence of two *tert*-butyl groups at δ 1.10 (s, 9H) and 1.18 (s, 9H). A two proton singlet at δ 3.64 (ArCH_2-) was also observed. The compound **149** was converted to its oxalate by treatment with oxalic acid in refluxing methanol. The structure of oxalate of **149** was confirmed by IR and NMR datas.

The imine **148** was also hydrolyzed by refluxing in acetic acid (5%) to give the 4-(3-*tert*-butylamino-2-hydroxypropoxy)-3-methoxybenzaldehyde (**150**), which was oily in

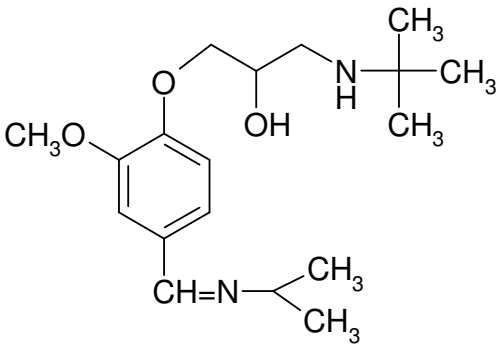


(150)

nature. Presence of formyl group in the compound was confirmed by signals at δ 9.84 (s, 1H, ArC*H*O) in ^{1}H NMR spectra. The compound **150** was converted to its oxalate by

usual procedure. IR spectrum showed characteristic carbonyl stretching vibration at 1685 cm^{-1}. Proton NMR showed signals at δ 1.32 (s, 9H) for *tert*-butyl group, 3.63 (s, 3H) for methoxy group and at 9.64 (s, 1H) for formyl group.

Treatment of **150** with isopropylamine gave 1-(*tert*-butylamino)-3-(4-isopropyliminomethyl-2-methoxyphenoxy)propan-2-ol (**151**). Reduction of **151** with sodium borohydride at low temperature gave 1-(*tert*-butylamino)-3-(4-isopropylaminomethyl-2-methoxyphenoxy)propan-2-ol (**152**), which was oily in nature. Proton magnetic resonance signals showed the presence of one isopropyl group and one



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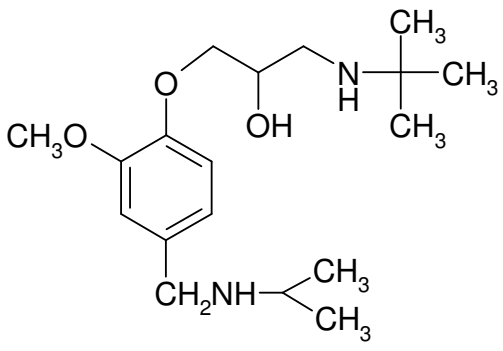
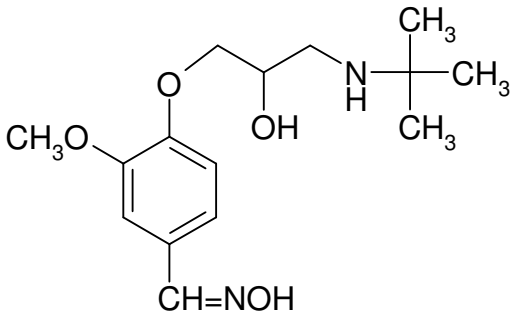


(152)

tert-butyl group in both **151** and **152**. Further compound **151** exhibited a one proton singlet at δ 8.2 (ArCH=N-), while **152** showed a two proton singlet at 3.72 ppm (ArCH_2-). The compound **152** was converted to its oxalate by the usual procedure. In ^{1}H NMR, signals appeared at δ 3.85 (s, 3H, -OCH_3) and at 4.13 ppm (m, 4H, -OCH_2- & ArCH_2-).

Reaction of the aldehyde **150** with hydroxylamine hydrochloride in the presence of sodium acetate trihydrate gave 4-(3-*tert*-butylamino-2-hydroxypropoxy)-3-methoxybenzaldehyde oxime (**153**), which displayed proton signals in NMR spectrum for *tert*-butyl group at δ 1.16 (s, 9H) and also a one proton singlet appeared at 8.00 ppm (ArC*H*=NOH). Refluxing **153** with oxalic acid in methanol gave the oxalate.

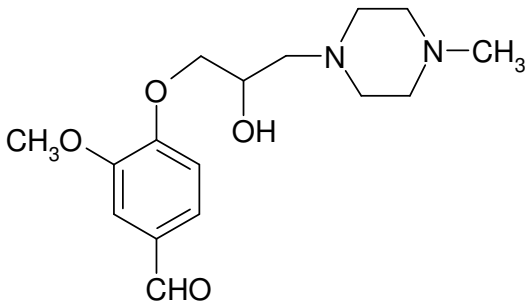
^{1}H NMR spectrum signals appeared at δ 3.68 (s, 3H, -OCH_3) and at δ 3.96 (m, 2H, -OCH_2-) for the oxalate.



(153)

(iii) Compounds with *N*-methylpiperazinyl substituent in the oxypropanol side chain

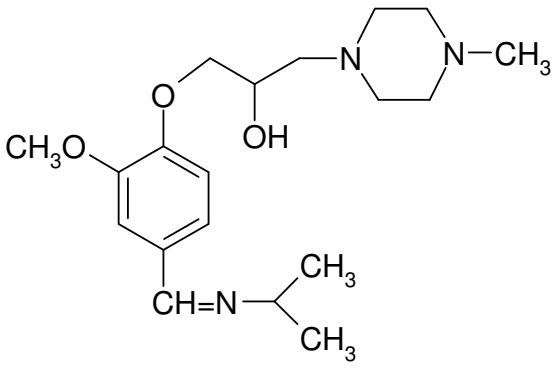
Further, reaction of the epoxy derivative **140** with *N*-methylpiperazine in refluxing methanol gave 4-[2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy]-3-methoxybenzaldehyde (**154**), which was purified by column chromatography using silica gel as stationary phase and chloroform as eluent. A three proton singlet at δ 2.30 (>NCH_3) and a one proton singlet at



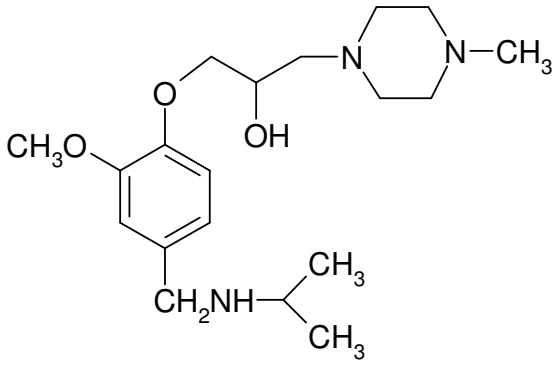
(154)

9.85 (ArC*H*O) were displayed for **154** in ^{1}H NMR spectrum. Refluxing of **154** with oxalic acid in methanol afforded the oxalate. In ^{1}H NMR spectrum, the oxalate exhibited signals at δ 3.87 (s, 3H, -OCH_3), at 7.09 (d, 1H), 7.44 (d, 1H) and 7.54 (dd, 1H) for aromatic protons.

Reaction of the aldehyde **154** with excess of isopropylamine in methanol gave 1-(4-isopropyliminomethyl-2-methoxyphenoxy)-3-(4-methylpiperazin-1-yl)propan-2-ol (**155**), which was reduced with sodium borohydride as usual at low temperature to give



(155)



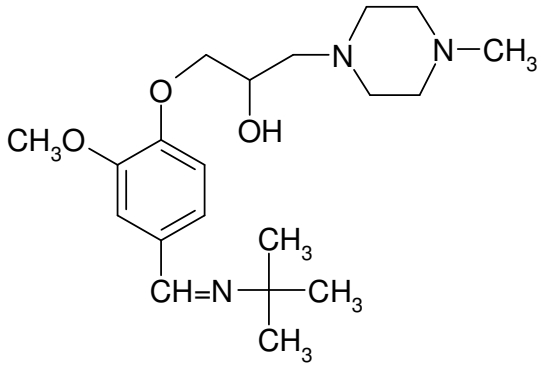
(156)

1-(4-isopropylaminomethyl-2-methoxyphenoxy)-3-(4-methylpiperazin-1-yl)propan-2-ol (**156**). The product **156** was oily in nature and was used for the preparation of oxalate. Structures of **155** and **156** were assigned on the basis of ^{1}H NMR spectrum. **155** Exhibited a doublet at δ 1.2 (6H, -CH(C*H*$_3$)$_2$) and a singlet at 2.2 ppm (3H, >NC*H*$_3$). Also there appeared a singlet at δ 8.3 (s, 1H, ArC*H*=N-), while **156** showed a singlet at δ 3.72 (2H, ArC*H*$_2$-) in addition to other proton peaks. Also, the absence of singlet at δ 8.3 for ArC*H*=N- confirmed the successful reduction of the imine **155** to **156**.

Conversion of **156** into oxalate was effected by normal procedure. The oxalate of **156** exhibited a singlet at δ 3.77 for methoxy group and a multiplet at 4.01 (4H) for -OC*H*$_2$- and ArC*H*$_2$- group in proton nuclear magnetic resonance spectrum. Other important signals of ^{1}H NMR are at δ 1.24 (d, 6H, -CH(C*H*$_3$)$_2$) and 2.94 (s, 3H, >NC*H*$_3$) showing the presence of both *N*-methylpiperazinyl and isopropyl groups.

Next, the aldehyde **154** was reacted with *tert*-butylamine by refluxing in methanol to give 1-(4-*tert*-butyliminomethyl-2-methoxyphenoxy)-3-(4-methylpiperazin-1-yl)propan-2-ol (**157**). ^{1}H NMR spectrum of **157** showed the presence of *tert*-butyl group by the appearance of a singlet at δ 1.3 (9H). Also, a one proton singlet appeared at δ 8.3 (ArC*H*=N-).

Reduction of the imine **157** with sodium borohydride in methanol at low temperature afforded 1-(4-*tert*-butylaminomethyl-2-methoxyphenoxy)-3-(4-methylpiperazin-1-yl)propan-2-ol (**158**), which could not be crystallized and used for the



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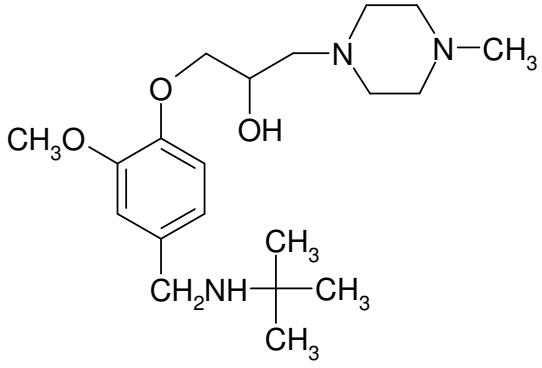
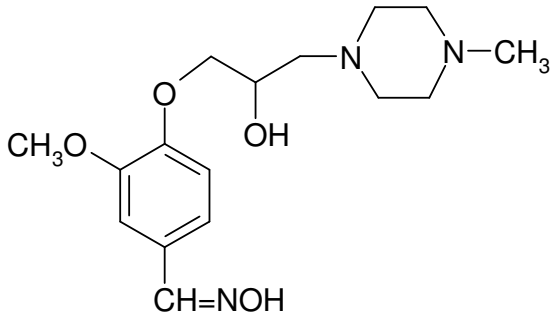


(158)

preparation of oxalate. ^{1}H NMR spectrum of **158** exhibited signals at δ 1.18 (s, 9H) for *tert*-butyl group, at 2.29 (s, 3H) for *N*-methyl group and at 3.66 ppm (s, 2H) for ArC*H*$_2$-group.

Refluxing **158** with oxalic acid afforded the oxalate, which exhibited a singlet at δ 3.8 (3H) for methoxy and at 6.96 (d, 3H) for aromatic protons in NMR spectrum. Other important signals appeared at δ 3.45 (d, 2H, -C*H*$_2$NH-) and at 4.06 ppm (s, 4H, -OC*H*$_2$- & ArC*H*$_2$-).

Finally, the aldehyde **154** was reacted with hydroxylamine hydrochloride in the presence of sodium acetate trihydrate in refluxing ethanol to give 4-[2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy]-3-methoxybenzaldehyde oxime (**159**), which was oily in



(159)

nature and was used for the oxalate preparation. Conversion of the aldehyde group of **154** to the aldoxime group in **159** was confirmed by the presence of a one proton singlet at δ 8.03 (ArC*H*=NOH) and the absence of aldehyde peak at δ 9.85 in NMR spectrum.

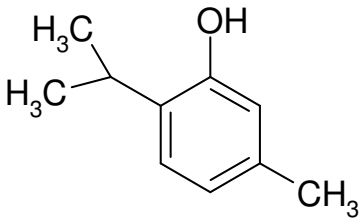
Conversion of **159** to its oxalate was effected by refluxing in methanol with oxalic acid. Proton NMR spectrum of the oxalate confirmed the presence of *N*-methyl group by the appearance of proton signal at δ 3.0 (s, 3H). Signals were also present at δ 3.87 (s, 3H) for methoxy group, 4.13 (m, 2H, -OCH_2-) and at 8.14 ppm (s, 1H, ArC*H*=NOH).

Structures of all the oxalates were further confirmed with help of IR spectroscopy and elemental analyses.

THYMOL-DERIVED ARYLOXYPROPANOLAMINES

Recently, various aryloxypropanolamines were reported from naturally occurring substances.[370-373] We planned to synthesize a set of aryloxypropanolamine compounds using thymol (**160**) as the starting material. Thymol is obtained from *Thymus Vulgaris* L.,

Monarda punctata L. or *Carum copticum* Benth.& Hook. f., and is mainly used for its antiseptic action.[374] 2-Isopropyl-5-methylphenol (thymol, **160**) was condensed with epichlorohydrin in the presence of potassium carbonate to give 2,3-epoxypropoxy-1-(2-isopropyl-5-methyl)benzene (**161**)**,** which is oily in nature and used for the next step after column



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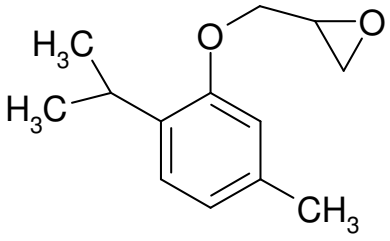
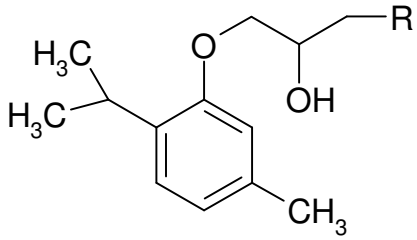


(161)

chromatography over silica gel. ^{1}H NMR spectrum showed a one proton double doublet (dd) at δ 2.75 and a one proton triplet at 2.87 for -CH_2 of oxirane ring. Also, a double signal was observed at δ 1.20 (6H) for -CH(CH_3)$_2$.

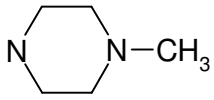
Reaction of **161** with isopropylamine, *tert*-butylamine and *N*-methylpiperazine gave **162**, **163** and **164**, respectively.

1-(Isopropylamino)-3-(2-isopropyl-5-methylphenoxy)propan-2-ol (**162**) in ^{1}H NMR



(162) R = NHCH(CH$_3$)$_2$

(163) R = NHC(CH$_3$)$_3$

(164) R = 

spectrum showed a six proton doublet at δ 1.09 for -NHCH(CH_3)$_2$ and another six proton doublet at 1.20 for ArCH(CH_3)$_2$. Other important peaks were observed at 2.30 (s, 3H,

ArCH_3) and 4.08 (bm, 1H, -C*H*(OH)-). While 1-(*tert*-butylamino)-3-(2-isopropyl-5-methylphenoxy)propan-2-ol (**163**) in ^{1}H NMR spectrum showed a nine proton singlet at δ 1.13 for -NHC(CH_3)$_3$ and a six proton doublet at 1.20 for ArCH(CH_3)$_2$. The aromatic protons gave signals in the range of 6.68 to 7.09 ppm. Proton signals of 1-(2-isopropyl-5-methylphenoxy)-3-(4-methylpiperazin-1-yl)propan-2-ol (**164**) appeared at δ 1.20 (d, 6H) for ArCH(CH_3)$_2$ and 3.98 (m, 2H) for -OCH_2- protons in ^{1}H NMR spectrum.

The compounds **162**, **163** and **164** were converted to their oxalates by treatment with oxalic acid in refluxing methanol. Structures of the oxalates were confirmed by ^{1}H NMR, IR spectroscopy and by elemental analyses.

The structure of the oxalate of **163** has been determined by x-ray crystallographic study by Professor Parthasarathi, Department of Physics, Bharathidasan University, Tirchirapalli, India.

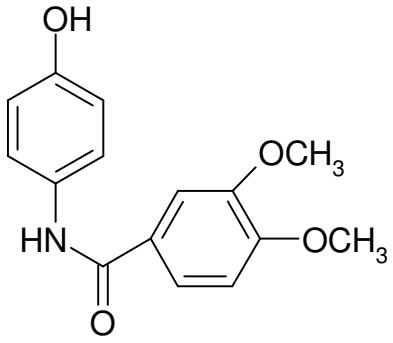
4-AMINOPHENOL-DERIVED ARYLOXYPROPANOLAMINES

A number of phenoxypropanolamines with *para*-amidic substituents are reported in literature to possess cardioselective β-adrenergic blocking action.[160, 166, 171] In an effort to obtain potent β-adrenergic blocking agents with cardioselective action, another series of compounds were synthesized starting from 4-aminophenol. The 4-amino functionality made it possible to prepare phenoxypropanolamines with *para*-amidic substituents. Two different series of compounds were prepared using 4-aminophenol as the starting material: (i) 3,4-dimethoxybenzamide series and (ii) 3,4,5-trimethoxybenzamide series.

(i) 3,4-dimethoxybenzamide series:

For this series of compounds, 4-aminophenol was condensed with 3,4-dimethoxybenzoyl chloride by refluxing in tetrahydrofuran to afford *N*-(4-hydroxyphenyl)-3,4-dimethoxybenzamide (**165**). Infrared spectrum showed a vibrational band at 1640 cm^{-1} for characteristic amide carbonyl stretching. Proton signals appeared at δ 3.93 (s, 6H) for two methoxy groups and at 9.12 (s, 1H) for –N*H*CO-, which was exchanged in D_2O.

The intermediate *N*-(2,3-epoxypropoxyphenyl)-3,4-dimethoxybenzamide (**166**), for



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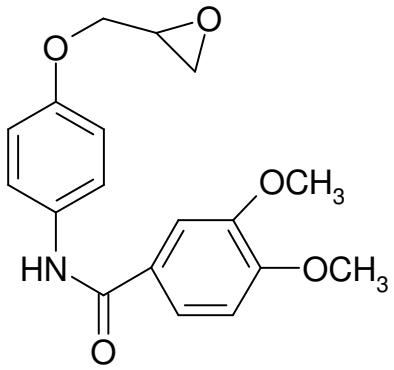
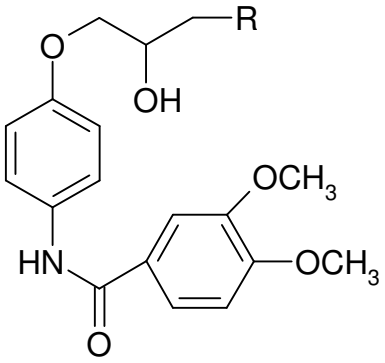


(166)

this series of compounds was prepared by the classical alkylation of **165** with epichlorohydrin in the presence of potassium carbonate. The intermediate oxirane **166** showed a characteristic stretching band at 1635 cm^{-1}, confirming the presence of amide functionality. Signals in proton NMR spectrum revealed a one proton multiplet for -C*H* of oxirane ring at δ 3.36 and a two proton multiplet for -CH_2 of oxirane ring at 2.77 (1H) and 2.92 (1H).

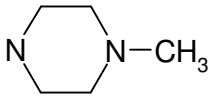
The epoxy derivative **166** was reacted with isopropylamine, *tert*-butylamine and *N*-methylpiperazine to give **167**, **168** and **169**, respectively.

The ^{1}H NMR spectrum of *N*-[4-(2-hydroxy-3-isopropylaminopropoxy)phenyl]-3,4-dimethoxybenzamide (**167**) exhibited a six proton doublet at δ 1.08 for two methyl groups of isopropyl moiety and the aromatic signals appeared at 6.91 (m, 3H) and 7.61 ppm (m, 4H). While, *N*-[4-(3-*tert*-butylamino-2-hydroxypropoxy)phenyl]-3,4-dimethoxybenzamide (**168**) displayed a singlet at δ 1.14 (9H, -C(C*H*$_3$)$_3$) and signals appeared at 2.69 (m, 1H) and 2.82 (m, 1H) for -C*H*$_2$NH-. In the NMR spectrum of *N*-{4-[2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy]phenyl}-3,4-dimethoxybenzamide (**169**)



(167) R = $NHCH(CH_3)_2$

(168) R = $NHC(CH_3)_3$

(169) R = 

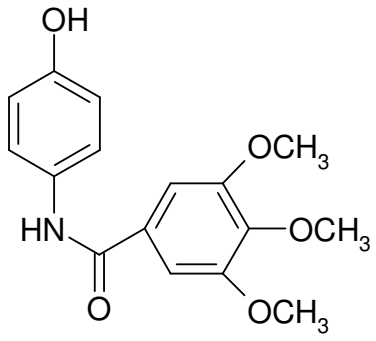
there appeared signals at δ 2.30 (s, 3H) for *N*-methyl group and a doublet at 3.98 ppm (2H, -OC*H*$_2$-). Proton signals for methoxy group were also present in all the three compounds.

The structures of **167**, **168** and **169** were further confirmed by infrared spectrum and with the help of elemental analyses. All the three compounds **167**, **168** and **169** were converted to their oxalates by refluxing with oxalic acid in methanol. The structures of the oxalates were confirmed on the basis of their NMR, IR spectral and elemental analyses datas.

(ii) 3,4,5-trimethoxybenzamide series:

Refluxed 4-aminophenol with 3,4,5-trimethoxybenzoyl chloride in tetrahydrofuran to afford *N*-(4-hydroxyphenyl)-3,4,5-trimethoxybenzamide (**170**). Presence of amide carbonyl group was confirmed by the appearance of vibrational band at 1655 cm^{-1} in infrared spectrum. Signals in the NMR spectrum were observed at δ 3.89 (s, 3H) and 3.93 ppm (s, 6H) for three methoxy groups and at 6.84 (d, 2H), 7.21 (s, 2H) and 7.49 ppm (d, 2H) for aromatic protons.

Alkylation of **170** with epichlorohydrin in the presence of potassium carbonate



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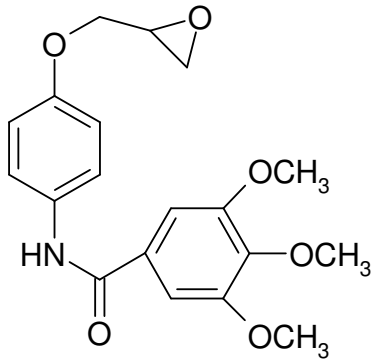
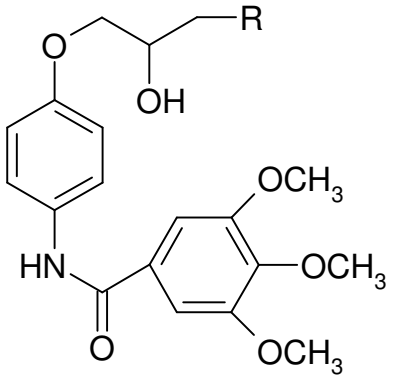


(171)

gave *N*-(2,3-epoxypropoxyphenyl)-3,4,5-trimethoxybenzamide (**171**). The epoxy compound in NMR spectrum exhibited signals at δ 2.78 (q, 1H), 2.93 (t, 1H) for -C*H*$_2$ of oxirane ring and a multiplet at 3.73 ppm (1H, -C*H* of oxirane ring). Other signals were also present for methoxy and aromatic protons.

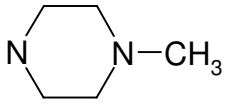
The epoxy compound **171** on treatment with isopropylamine, *tert*-butylamine and *N*-methylpiperazine by the standard procedures gave **172**, **173** and **174**, respectively. The compounds **173** and **174** were oily in nature and used for the preparation of oxalate as such.

Proton nuclear magnetic resonance of *N*-[4-(2-hydroxy-3-isopropylaminopropoxy)phenyl]-3,4,5-trimethoxybenzamide(**172**) gave signals at δ 1.10 (d, 6H, -CH(C*H*$_3$)$_2$) and 4.01 (m, 3H, -OC*H*$_2$C*H*<). It showed C=O stretching at 1640 cm^{-1} in infrared spectrum. Elemental analysis results were in order for **172**. Structure of *N*-[4-(3-*tert*-butylamino-2-hydroxypropoxy)phenyl]-3,4,5-trimethoxybenzamide (**173**) was assigned on the basis of ^{1}H NMR spectrum, which



(172) R = NHCH(CH$_3$)$_2$

(173) R = NHC(CH$_3$)$_3$

(174) R = 

displayed a nine proton singlet at δ 1.13 for three methyl groups of *tert*-butyl moiety, and a mutiplet at 3.96 ppm (3H, -OC*H*$_2$C*H*<). While proton signals were observed for *N*-{4-[2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy]phenyl}-3,4,5-trimethoxybenzamide (**174**) at δ 2.3 (s, 3H, -NC*H*$_3$) and a broad mutiplet at 2.6 (10H, -C*H*$_2$N(C*H*$_2$C*H*$_2$)$_2$N-). In addition all the three compounds showed proton signals for three methoxy groups.

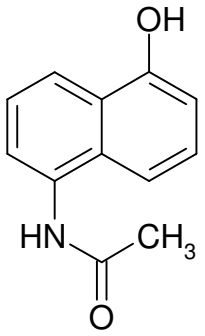
Conversion of **172**, **173** and **174** to their oxalates was effected as usual and their structures were confirmed on the basis of their infrared, NMR spectrum and elemental analyses.

5-AMINO-1-NAPHTHOL-DERIVED ARYLOXYPROPANOLAMINES

Next, a series of aryloxypropanolamines were synthesized with amide functionality using 5-amino-1-naphthol as the starting material. Amide functionality was introduced at the 5-position of the naphthyl ring to see the effect of amide substitution on the cardioselectivity or β_1/β_2-receptor selectivity. Two series of compounds (i) acetamide and (ii) 3,4-dimethoxybenzamide were synthesized using 5-amino-1-naphthol as the starting point, which are described below:

(i) acetamide series:

Acetylation of 5-amino-1-naphthol with acetic anhydride gave *N*-(5-hydroxynaphthalen-1-yl)acetamide (**175**). The vibrational bands characteristic for amide were present in the



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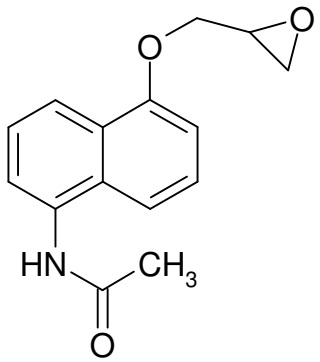
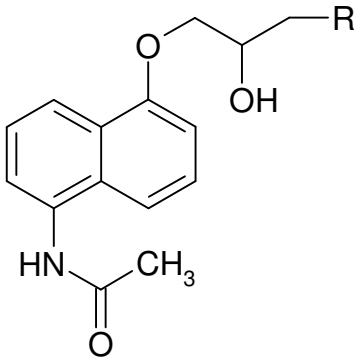


(176)

infrared spectrum at 1620 cm^{-1}. The NMR spectrum showed proton peaks at δ 2.28 (s, 3H, -NHCOCH_3) and the aromatic peaks appeared in the range of 6.91-8.12 ppm.

N-[5-(2,3-Epoxypropoxy)naphthalen-1-yl]acetamide (**176**) was prepared by reacting **175** with epichlorohydrin. The infrared spectrum showed vibrational band at 1650 cm^{-1} for the amide. In ^{1}H NMR spectrum, **176** exhibited signals at δ 2.86 (q, 1H), 2.96 (t, 1H) for -CH_2 of oxirane ring and a one proton multiplet at 3.5 ppm for -C*H* of oxirane ring.

The oxirane ring of **176** was opened by reaction with isopropylamine and *tert*-butylamine, which gave **177** and **178**, respectively. Presence of amide carbonyl group in both the compounds were confirmed by the appearance of bands at 1655 and 1660 cm^{-1} in



(177) R = $NHCH(CH_3)_2$

(178) R = $NHC(CH_3)_3$

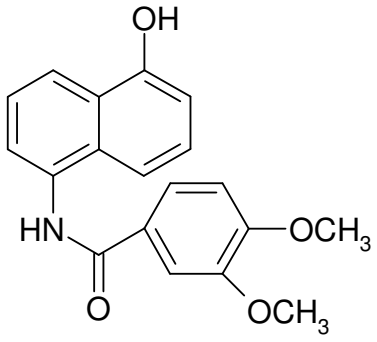
infrared spectrum. Proton signals were observed at δ 1.1 (d, 6H) for two methyl groups of isopropyl moiety for **177** and at 1.14 (s, 9H) for three methyl groups of *tert*-butyl group for **178** in ^1H NMR spectrum. Both the compounds displayed signals for aromatic protons between 6.8 and 8.4 ppm.

Both **177** and **178** were converted to their oxalates. The structure of oxalates were determined with the help of infrared, NMR spectral and elemental analyses datas.

(ii) 3,4-dimethoxybenzamide series:

Another series of compounds were also prepared using 5-amino-1-naphthol. *N*-(5-Hydroxynaphthalen-1-yl)-3,4-dimethoxybenzamide (**179**) was synthesized by refluxing 5-amino-1-naphthol with 3,4-dimethoxybenzoyl chloride in tetrahydrofuran. Proton signals of **179** appeared at δ 3.94 (s, 6H) for two methoxy group. Aromatic protons were present in the range of 6.91-8.17 ppm. The characteristic carbonyl stretching vibration of the amide appeared at 1635 cm^{-1} in IR spectrum.

Refluxing of **179** in epichlorohydrin gave *N*-[5-(2,3-epoxypropoxy)naphthalen-1-yl]-3,4-dimethoxybenzamide (**180**). Presence of oxirane ring in the compound was



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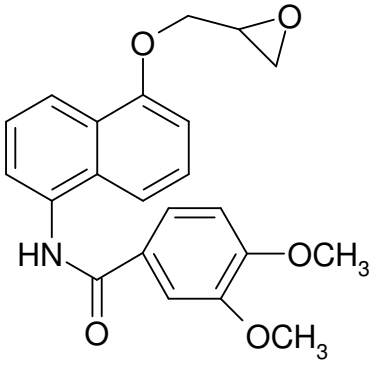
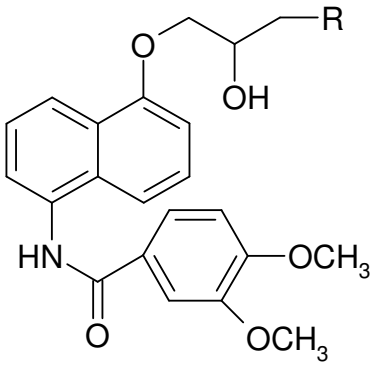


(180)

established by the signals at δ 2.87 (q, 1H) and 2.98 (q, 1H) for -C*H*$_2$ of oxirane. Aromatic proton signals were also present as expected.

Reaction of the epoxy derivative **180** with isopropylamine and *tert*-butylamine



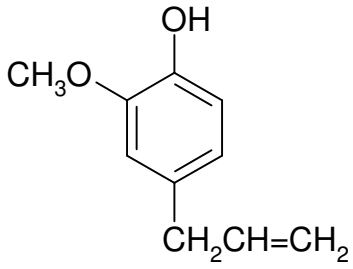
(181) R = $NHCH(CH_3)_2$

(182) R = $NHC(CH_3)_3$

gave **181** and **182**, respectively. Both the compounds in infrared spectrum displayed carbonyl stretching vibration characteristic of amide group. Isopropyl group of **181** gave a six proton doublet at δ 1.11 and *tert*-butyl group of **182** showed a nine proton singlet at 1.15 ppm in NMR spectrum. Also, proton signals were observed for two methoxy group in both the compounds. The elemental analyses were in accordance to the calculated value for both the compounds. Oxalates of both the compounds were also prepared.

MISCELLANEOUS COMPOUNDS

Eugenol (4-allyl-2-methoxyphenol, **183**) a main component of clove oil or nutmeg oil has various effects including therapeutic effects in dentistry as local anaesthetic.[375] We prepared a series of eugenol-derived aryloxypropanolamine compounds, but while preparing the final manuscript of the thesis, there came to the author's notice a publication by Chen *et al*.[376] describing the development of eugenolol (**185**),



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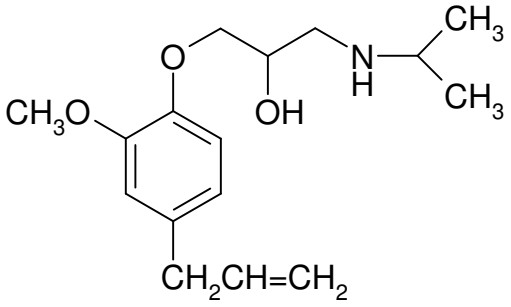
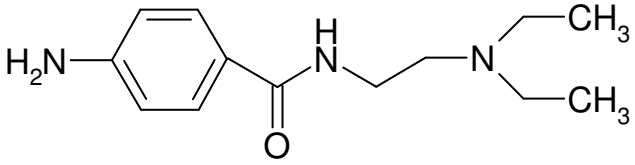


(184)

derived from eugenol (**183**). Therefore, the synthesis of this series of compounds is not presented in this investigation. During these investigations, we thought it to be worthwhile to insert -OCH_2- group between the aromatic moiety and the side chain *N*-(2-diethylaminoethyl)formamide present in procainamide (**185**), an antiarrhythmic agent,



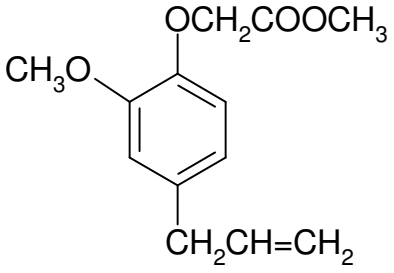
(**185**)

and then investigate these agents for antiarrhythmic and local anaesthetic activity.

Initially, eugenol (**183**) was condensed with methyl chloroacetate in the presence of potassium carbonate to give methyl 2-(2-isopropyl-5-methylphenoxy)acetate (**186**),

and was oily in nature. Its proton NMR, signals appeared at δ 3.78 (s, 3H, -$COOCH_3$) and 4.66 (s, 2H, -OCH_2-). Aromatic protons appeared at 6.76 ppm.

Next, this ester compound **186** was fused with 2-diethylaminoethylamine at 80°C gave *N*-(2-diethylaminoethyl)-2-(2-isopropyl-5-methylphenoxy)-acetamide (**187**). Proton



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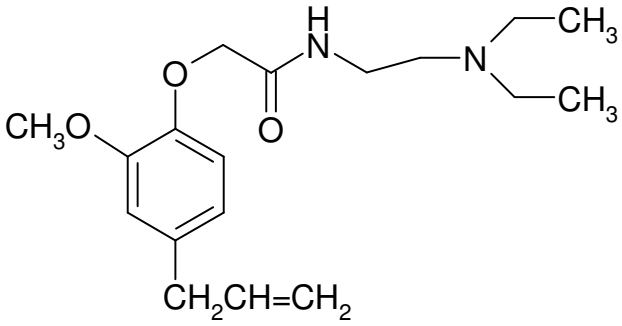
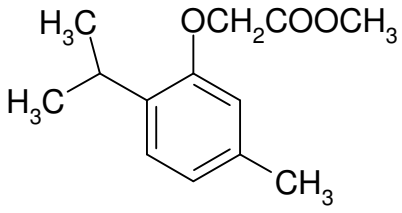


(187)

peaks were observed for **187** at δ 0.98 (t, 6H, -$N(CH_2CH_3)_2$) and at 3.86 (s, 3H, $ArOCH_3$). This was converted to oxalate by giving treatment with oxalic acid in methanol. IR, NMR spectral and elemental analyses datas further confirmed the structure.

Next, another naturally occurring substance thymol (2-isopropyl-5-methylphenol, **160**) was condensed with methyl chloroacetate in ethyl methyl ketone to give



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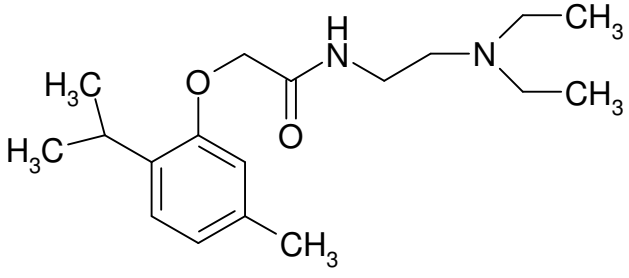
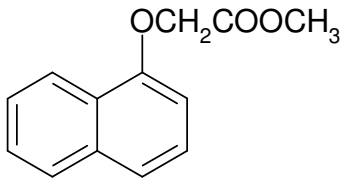


(189)

methyl 2-(2-isopropyl-5-methylphenoxy)acetate (**188**) which could not be crystallized and used as such for the next step. Signals appeared at δ 3.77 (s, 3H, -$COOCH_3$) and 1.22 (d, 2H, -$CH(CH_3)_2$). Compound **188** on fusion with 2-diethylaminoethylamine at

80°C gave *N*-(2-diethylaminoethyl)-2-(2-isopropyl-5-methylphenoxy)-acetamide (**189**). Proton peaks were observed for **189** at δ 0.98 (t, 6H, -N(CH_2CH_3)$_2$) and at 4.49 (s, 2H, -OCH_2-). Compound **189** was also converted to its oxalate by the normal procedure and its structure confirmed by NMR, IR spectral and elemental analyses.

Other compounds of this series were also synthesized using 1-naphthol, 2-naphthol and *N*-(5-hydroxynaphthalen-1-yloxy)acetamide (**175**). Condensation of 1-naphthol, 2-naphthol and *N*-(5-hydroxynaphthalen-1-yloxy)acetamide (**175**) with methyl chloroacetate



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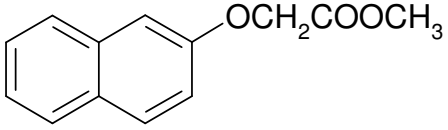

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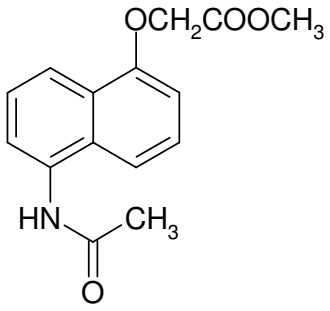
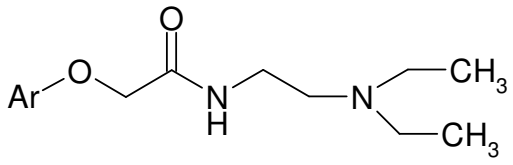


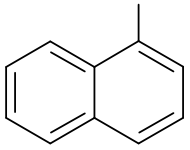
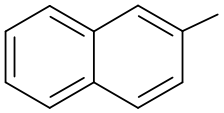
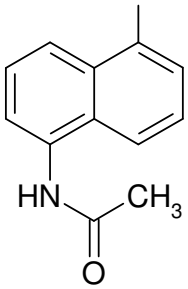
(192)

by refluxing in ethyl methyl ketone afforded **190**, **191**, and **192**, respectively. Methyl 2-(naphthalene-1-yloxy)acetate (**190**) was obtained as a viscous oily residue, which in ^{1}H NMR spectrum displayed a singlet at δ 3.82 (3H) for -COOCH_3 and a singlet at 4.82 (2H) for -OCH_2- group. Seven aromatic proton signals were also observed between 6.70 and 8.36 ppm. Infrared spectrum of methyl 2-(naphthalene-2-yloxy)acetate (**191**), showed vibrational band at 1760 cm^{-1}. Signals of NMR spectrum revealed the presence of acetate protons at δ 3.83 (s, 3H, -COOCH_3) and oxymethylene protons at 4.76 ppm (s, 2H, -OCH_2-). Elemental analyses were in order for the given structure. Characteristic IR vibrational bands appeared for methyl 2-(5-acetylaminonaphthalen-1-yloxy)acetate (**192**),

at 1740 and 1650 cm^{-1}, showing the presence of ester and amide C=O group in the compound. Elemental analyses were in order.

Fusion of **190**, **191**, and **192** with 2-diethylaminoethylamine at 80°C gave **193**, **194** and **195**, respectively. Compound **193** was oily in nature and used as such for the



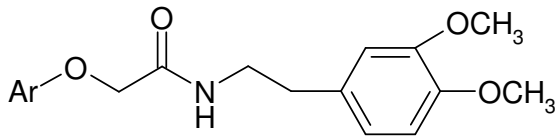
(193) Ar =  **(194)** Ar =  **(195)** Ar = 

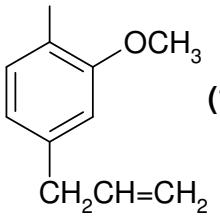
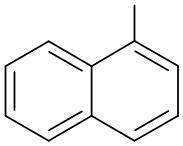
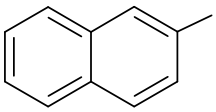
preparation of oxalates. ^{1}H NMR signals appeared at δ 0.95 (t, 6H, -N(CH_2CH_3)$_2$) for **193** and **194**, and at 0.98 ppm (t, 6H, -N(CH_2CH_3)$_2$) for **195**. The -CONH- group of **193**, **194** and **195** appeared at δ 7.61, 7.36 and 7.49 ppm, respectively. All these compounds showed other proton peaks as expected.

Next, all the three compounds were converted to their oxalates by treating with oxalic acid. The oxalate structures were confirmed with the help of infrared and NMR spectral datas. Elemental analyses were found to be consistent with the calculated values.

As a further modification in this series homoveratrylamine (3,4-dimethoxyphenylethylamine) was used instead of 2-diethylaminoethylamine to prepare new compounds. Thus treatment of **186**, **190** and **191** with homoveratrylamine at room temperature gave **196**, **197** and **198**, respectively.

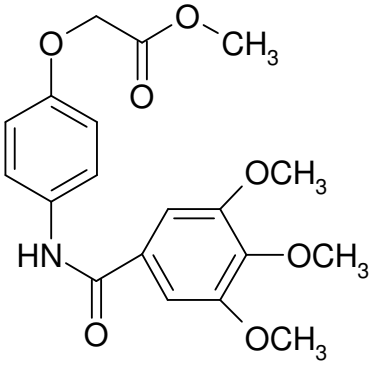
IR spectrum showed carbonyl stretching vibration at 1655, 1660 and 1655 cm^{-1} for **196, 197** and **198** showing the presence of amide functionality. Proton signals appeared at δ 3.77-3.85 (3s, 9H, 3 × -OC*H*$_3$), 3.80-3.81 (2s, 6H, 2 × -OC*H*$_3$) and 3.81-3.82 (2s, 6H, 2 × -OC*H*$_3$) in NMR spectrum of **196, 197** and **198**, respectively. Also -OC*H*$_2$- group



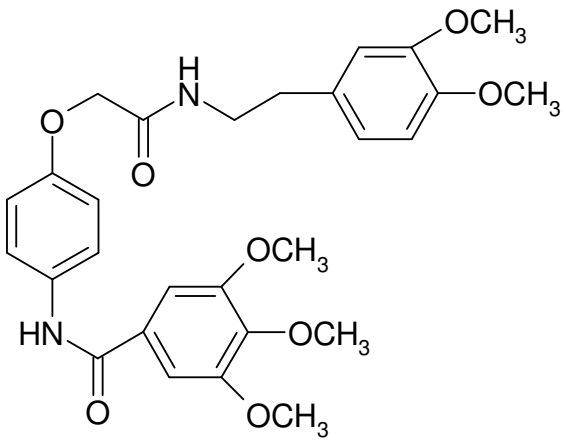
(196) Ar =  **(197)** Ar =  **(198)** Ar = 

gave a two proton singlet at δ 4.49, 4.66 and 4.59 ppm for **196, 197** and **198**, respectively. Other essential signals were also present.

Next, *N*-(4-hydroxyphenyl)-3,4,5-trimethoxybenzamide (**170**) was condensed



(199)



(200)

with methyl cloroacetate to give methyl 2-[4-(3,4,5-trimethoxybenzamido)phenoxy]acetate (**199**), which showed in infrared spectrum a carbonyl vibration at 1755, 1640 cm^{-1}. Proton

signals were present at δ 3.82 (s, 3H, -COOCH_3) and 3.90-3.92 (2s, 9H, 3 × -OCH_3) in NMR spectrum.

Reaction of **199** with homoveratrylamine gave *N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-[4-(3,4,5-trimethoxybenzamido)phenoxy]acetamide (**200**), which in IR spectrum showed only C=O stretching at 1645 cm^{-1} for the amide bond. NMR signals were observed for five methoxy groups between δ 3.82-3.90 ppm. The structure was further confirmed with the help of elemental analyses.

β-ADRENOCEPTOR BINDING ASSAY

All the aryloxypropanolamine compounds synthesized were tested for their β_1-adrenoceptor and β_2-adrenoceptor binding by Prof. Paola Massarelli and his colleagues at Dipartimento di Farmacologia, Siena, Italy. Synthesis and β-adrenoceptor binding affinities of all the aryloxypropanolamines synthesized have been accepted/communicated for publication.

The *in vitro* β_1- and β_2-adrenergic receptor binding affinities of the newly synthesized compounds were assessed in turkey erythrocyte membrane (β_1) and lung homogenate of rats (β_2). The oxalates of the compounds were subjected to binding studies. The binding affinities were compared with that of propranolol (**24**) and atenolol (**45**).

Table **2** shows the IC_{50}, Ki and % inhibition values of the compounds for binding to β_1-adrenoceptor. While, table **3** shows the IC_{50}, Ki and % inhibition values of the compounds for binding to β_2-adrenoceptor. Table **4** shows the selectivity of tested compounds on β-adrenoceptors.

Table 2. Inhibition of [^{3}H]DHA binding to β_1 adrenoceptor.

Compound[a]	Code	IC_{50} ± s.d. (M)[b]	Ki ± s.d. (M)[c]	% Inhibition (10^{-5} M)[d]
142	DPJ-634	Inactive	Inactive	13.43
143	DPJ-898	$1.94 \cdot 10^{-6} \pm 0.78$	$7.29 \cdot 10^{-7} \pm 0.29$	69.71
145	DPJ-906	Inactive	Inactive	21.18
146	DPJ-904	Inactive	Inactive	38.95
147	DPJ-913	Inactive	Inactive	48.74
149	DPJ-633	Inactive	Inactive	14.31
150	DPJ-811	$9.13 \cdot 10^{-7} \pm 0.47$	$3.43 \cdot 10^{-7} \pm 0.18$	79.41
152	DPJ-830	Inactive	Inactive	12.66
153	DPJ-834	$6.14 \cdot 10^{-6} \pm 1.89$	$2.31 \cdot 10^{-6} \pm 0.71$	59.64
154	DPJ-832	Inactive	Inactive	23.32
156	DPJ-859	Inactive	Inactive	26.99
158	DPJ-862	Inactive	Inactive	13.05
159	DPJ-933	Inactive	Inactive	11.67
162	DPJ-576	$3.72 \cdot 10^{-10} \pm 0.14$	$1.39 \cdot 10^{-10} \pm 0.05$	98.97
163	DPJ-577	$1.27 \cdot 10^{-9} \pm 50.25$	$4.77 \cdot 10^{-10} \pm 1.31$	100
164	DPJ-912	Inactive	Inactive	11.31
167	DPJ-888	$1.29 \cdot 10^{-6} \pm 0.60$	$4.85 \cdot 10^{-7} \pm 0.23$	58.94
168	DPJ-890	$4.32 \cdot 10^{-9} \pm 0.98$	$1.62 \cdot 10^{-9} \pm 0.37$	74.67
169	DPJ-893	Inactive	Inactive	6.08
172	DPJ-782	$1.46 \cdot 10^{-6} \pm 0.66$	$5.48 \cdot 10^{-7} \pm 0.25$	52.48
173	DPJ-784	Inactive	Inactive	42.20
174	DPJ-786	Inactive	Inactive	33.83
177	DPJ-953	$3.35 \cdot 10^{-7} \pm 1.31$	$1.25 \cdot 10^{-7} \pm 0.49$	63.58
178	DPJ-955	$2.30 \cdot 10^{-8} \pm 1.33$	$8.66 \cdot 10^{-9} \pm 2.50$	79.33
181	DPJ-983	(#)	(#)	(#)
182	DPJ-985	(#)	(#)	(#)

Compound[a]	IC_{50} ± s.d. (M)[b]	Ki ± s.d. (M)[c]	% Inhibition (10^{-5} M)[d]
Propranolol (**24**)	$4.26 \cdot 10^{-9} \pm 0.34$	$1.60 \cdot 10^{-9} \pm 0.13$	97.12
Atenolol (**45**)	$7.22 \cdot 10^{-8} \pm 1.38$	$2.70 \cdot 10^{-8} \pm 0.40$	73.06

(#) not tested because it is insoluble in water or in DMSO

[a] The oxalates were used for testing

[b] The concentration of the test compounds that inhibited [^{3}H]DHA binding by 50% (IC_{50})

[c] apparent inhibition constants (Ki)

[d] % Inhibition of [^{3}H]DHA binding to β_1 adrenoceptor at the highest used concentration (10^{-5} M).

Table 3. Inhibition of [^{3}H]DHA binding to β_2-adrenoceptor.

Compound[a]	Code	IC_{50} ± s.d. (M)[b]	Ki ± s.d. (M)[c]	% Inhibition (10^{-5} M)[d]
142	DPJ-634	Inactive	Inactive	21.64
143	DPJ-898	$6.85 \cdot 10^{-7} \pm 1.14$	$2.57 \cdot 10^{-7} \pm 0.43$	69.36
145	DPJ-906	$3.58 \cdot 10^{-6} \pm 0.85$	$1.34 \cdot 10^{-6} \pm 0.32$	58.86
146	DPJ-904	Inactive	Inactive	23.10
147	DPJ-913	$9.02 \cdot 10^{-6} \pm 3.69$	$3.39 \cdot 10^{-6} \pm 1.27$	56.57
149	DPJ-633	Inactive	Inactive	15.40
150	DPJ-811	$1.11 \cdot 10^{-6} \pm 0.23$	$4.15 \cdot 10^{-7} \pm 0.11$	87.90
152	DPJ-830	Inactive	Inactive	22.85
153	DPJ-834	Inactive	Inactive	46.62
154	DPJ-832	Inactive	Inactive	0.00
156	DPJ-859	Inactive	Inactive	0.00
158	DPJ-862	Inactive	Inactive	0.00
159	DPJ-933	Inactive	Inactive	0.00
162	DPJ-576	$3.24 \cdot 10^{-9} \pm 0.40$	$1.21 \cdot 10^{-9} \pm 0.45$	98.33
163	DPJ-577	$7.08 \cdot 10^{-10} \pm 3.03$	$2.66 \cdot 10^{-10} \pm 1.14$	94.58
164	DPJ-912	$2.75 \cdot 10^{-9} \pm 0.33$	$1.03 \cdot 10^{-9} \pm 0.13$	86.57
167	DPJ-888	$4.59 \cdot 10^{-5} \pm 2.62$	$1.72 \cdot 10^{-5} \pm 0.98$	30.89
168	DPJ-890	Inactive	Inactive	46.79

Compound[a]	Code	IC_{50} ± s.d. (M)[b]	Ki ± s.d. (M)[c]	% Inhibition (10^{-5} M)[d]
169	DPJ-893	Inactive	Inactive	0.00
172	DPJ-782	$3.43 \cdot 10^{-5} \pm 2.87$	$1.28 \cdot 10^{-5} \pm 1.08$	43.00
173	DPJ-784	$4.32 \cdot 10^{-6} \pm 2.30$	$2.66 \cdot 10^{-6} \pm 1.05$	54.56
174	DPJ-786	Inactive	Inactive	0.00
177	DPJ-953	Inactive	Inactive	42.97
178	DPJ-955	$4.58 \cdot 10^{-7} \pm 1.20$	$1.72 \cdot 10^{-7} \pm 0.65$	72.16
181	DPJ-983	(#)	(#)	(#)
182	DPJ-985	(#)	(#)	(#)
Propranolol (**24**)		$6.65 \cdot 10^{-9} \pm 0.45$	$2.50 \cdot 10^{-9} \pm 0.18$	99.80
Atenolol (**45**)		Inactive	Inactive	34.34

(#) not tested because it is insoluble in water or in DMSO

[a] The oxalates were used for testing

[b] The concentration of the test compounds that inhibited [^{3}H]DHA binding by 50% (IC_{50})

[c] apparent inhibition constants (Ki)

[d] % Inhibition of [^{3}H]DHA binding to β_2 adrenoceptor at the highest used concentration (10^{-5} M).

Many of the tested compounds showed β-adrenoceptor binding affinity. Only thymol-derived aryloxypropanolamines **162** and **163** showed binding affinity comparable with that of propranolol (**24**), suggesting that both the compounds may possess non-selective β-adrenergic blocking activity. Both the compounds were tested for β-adrenergic blocking activity in animal models.

Vanillin-derived aryloxypropanolamines showed lesser binding affinity to β-adrenoceptor in comparison to propranolol (**24**). Only two of the compounds **143** and **150** with a formyl group at the *para*-position showed appreciable amount of binding affinity without selectivity. While some of the compounds synthesized from 4-aminophenol (**168**) and 5-amino-1-naphthol (**178**) showed good β-adrenoceptor binding affinity with

Table 4. Selectivity of tested compounds on β adrenoceptors.

Compound	Code	% Inhibition [10^{-5} M] β_1	% Inhibition [10^{-5} M] β_2	Selectivity ratio β_1/β_2 [a]
142	DPJ-634	13.43	21.64	0.62
143	DPJ-898	69.71	69.36	1.01
145	DPJ-906	21.18	58.86	0.36
146	DPJ-904	38.95	23.10	1.69
147	DPJ-913	48.74	56.57	0.86
149	DPJ-633	14.31	15.40	0.93
150	DPJ-811	79.41	87.90	0.90
152	DPJ-830	12.66	22.85	0.55
153	DPJ-834	59.64	46.62	1.28
154	DPJ-832	23.32	0.00	-
156	DPJ-859	26.99	0.00	-
158	DPJ-862	13.05	0.00	-
159	DPJ-933	11.67	0.00	-
162	DPJ-576	98.97	98.33	1.01
163	DPJ-577	100	94.58	1.06
164	DPJ-912	11.31	86.57	0.13
167	DPJ-888	58.94	30.89	1.91
168	DPJ-890	74.67	46.79	1.60
169	DPJ-893	6.08	0.00	-
172	DPJ-782	52.48	43.00	1.22
173	DPJ-784	42.20	54.56	0.77
174	DPJ-786	33.83	0.00	-
177	DPJ-953	63.58	42.97	1.48
178	DPJ-955	79.33	72.16	1.10
Propranolol (**24**)		97.12	99.80	0.97
Atenolol (**45**)		73.06	34.34	2.13

a- selectivity ratio expressed as (% inhibition at β_1 / % inhibition at β_2)

168 showing cardioselectivity or β_1-adrenoceptor selectivity. Atenolol (**45**) a well established cardioselective β-adrenergic blocking agent showed better β_1-adrenoceptor selectivity in the binding studies than **168**. It was found that use of *N*-methylpiperazine as the amino substituent generally led to loss of activity (**154**, **169**, **174**). While *tert*-butyl substituted compounds (**150**, **168**, **178**) were generally more potent than the isopropyl substituted compounds (**143**, **167**, **177**), these results are in line with the previous reports that substitution with *tert*-butyl group showed better β-adrenergic receptor blocking activity than isopropyl group substituted compounds.[172, 377] Atenolol (**45**) a cardioselective beta blocker in binding study showed lesser binding affinity compared to propranolol (**24**). But atenolol showed a β_1-receptor selectivity ratio of approximately two while propranolol was non-selective. All the tested compounds showed lesser selectivity ratio than atenolol.

β-ADRENOCEPTOR BLOCKING ACTIVITY

The β-adrenergic blocking activity of oxalates of **162** (DPJ-576) and **163** (DPJ-577) were determined by Prof. Bodhankar at Department of Pharmacology, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Pune, India. Synthesis, β-adrenergic blocking activity and β_1-, β_2-adrenoceptor binding affinity of thymol-derived aryloxypropanolamines have been communicated for publication.

Pharmacological evaluation of oxalates of **162** and **163** were carried out using isolated frog heart, mouse E.C.G and isolated rat uterus models. In isolated frog heart experiments **162** (5 μg/ml and 10 μg/ml) and **163** (2.5, 3.5 and 5 μg/ml) blocked positive chronotropic and positive inotropic effect produced by adrenaline (0.2, 0.4 and 0.8 μg) (Table **5**).

Table 5. Effect of adrenaline (0.4 μg) alone and in presence of **162** (DPJ-576) and **163** (DPJ-577) on heart rate and amplitude of isolated frog heart

Compound	Dose (μg/ml)	Heart rate (beats / min)		Amplitude (mm)	
		Adr.	Comp.+ Adr.	Adr.	Comp.+ Adr
162[a] (DPJ-576)	3.5	37.33 ± 9.80	35.67 ± 10.2	11.67 ± 0.47	6.67 ± 1.69*
	5.0	41.50 ± 8.12	34.87 ± 6.93*	12.43 ± 6.12	7.75 ± 4.05*
	10	46.50 ± 3.57	26.25 ± 8.52*	7.87 ± 2.55	3.25 ± 0.43*
163[a] (DPJ-577)	2.5	40.14 ± 4.35	29.14 ± 7.86*	19.42 ± 7.70	13.28± 6.02*
	3.5	38.11 ± 7.57	25.55 ± 9.20*	15.77 ± 5.69	9.61 ± 2.90*
	5	40.87 ± 7.70	29.50 ± 8.51*	18.75 ± 7.29	8.93 ± 3.12*

*$p<0.05$ level significance applying paired Student's t – test; [a] oxalates used for testing

Comp.- compound; Adr.- adrenaline

Pretreatment of **162** (100 μg/kg, i.v.) and **163** (50 μg/kg, i.v.) antagonized isoprenaline (2 μg/kg, i.v.) induced tachycardia, similar to that of atenolol (20 μg/kg, i.v.) pretreatment in mouse ECG experiments as measured by heart rate (Table **6**), indicating blockade of β_1-adrenergic receptors. Out of the two compounds the *tert*-butyl derivative **163** was more active as a β_1-adrenergic blocker than the isopropyl derivative **162**.

Table 6. Effect of isoprenaline (**6**), atenolol (**45**), **162**[a] (DPJ-576) and **163**[a] (DPJ-577) on mouse ECG parameters

Sr. No.	Drug Treatment and Dose		Heart Rate
	1	2	
1	Isoprenaline (2 µg/kg)	-	617.458±39.685
2	Atenolol (20 µg/kg)	-	321.56*± 24.99
3	Atenolol (20 µg/kg)	Isoprenaline (2 µg/kg)	327*± 20.4
4	**162** (DPJ-576) (100 µg/kg)	-	337.4*± 65.002
5	**162** (DPJ-576) (100 µg/kg)	Isoprenaline (2 µg/kg)	414.7*± 20.76
6	**163** (DPJ-577) (50 µg/kg)	-	371.6*± 36.73
7	**163** (DPJ-577) (50 µg/kg)	Isoprenaline (2 µg/kg)	375.25*±10.493

*$p<0.05$ level significance applying paired Student's t – test.

[a] oxalate used for testing

Pretreatment of **162** and **163** blocked isoprenaline and adrenaline induced relaxation of isolated rat uterus (unprimed) (Table **7** & **8**). This experiment shows that both **162** and **163** to possess β_2-adrenergic blocking activity, with **163** being a better β_2-adrenergic blocker. These findings along with the β-adrenoceptor binding results suggest that both **162** and **163** compounds to possess non-selective β-adrenergic blocking activity.

Table 7. Effect of adrenaline, isoprenaline alone and in presence of **162** (DPJ 576) on isolated rat uterus (unprimed).

Sr. No.	Drug Treatment and Dose		Height (mm)
	1	**2**	
1	Normal	-	22.00 ± 1.732
2	Adrenaline (0.02 μg/ml)	-	0.00 ± 0.00*
3	**162**[a] (DPJ-576) (5 μg/ml)	Adrenaline (0.02 μg/ml)	21.33 ± 1.155
4	**162**[a] (DPJ-576) (5 μg/ml)	Adrenaline (0.2 μg/ml)	20.33 ± 1.528
5	Normal	-	12.67 ± 6.506
6	Isoprenaline (0.02 μg/ml)	-	0.00 ± 0.00*
7	**162**[a] (DPJ-576) (5 μg/ml)	Isoprenaline (0.02 μg/ml)	12.00 ± 5.292
8	**162**[a] (DPJ-576) (5 μg/ml)	Isoprenaline (0.2 μg/ml)	14.33 ± 4.163

*$p<0.05$ level significance applying paired Student's t – test.
[a] Oxalate used for testing

LOCAL ANAESTHETIC ACTIVITY

The acetamide derivatives (**187**, **189**, **193**, **194** and **195**) synthesized by the introduction of oxymethylene group between the aromatic nucleus and the side chain present in procainamide (**185**) were prepared with the aim of developing new antiarrhythmic / local anaesthetic agents. One of the compound **193** (DPJ-574) was tested for local anaesthetic activity by Prof. Bodhankar, Department of Pharmacology, Poona

College of Pharmacy, Bharati Vidyapeeth Deemed University, Pune, India. Synthesis and local anaesthetic activity of **193** (DPJ-574) is accepted for publication.

Table 8. Effect of adrenaline, isoprenaline alone and in presence of **163** (DPJ 577) on isolated rat uterus (unprimed).

Sr. No.	Drug Treatment and Dose		Height (mm)
	1	2	
1	Normal	-	23.00 ± 11.53
2	Adrenaline (0.02 µg/ml)	-	4.00 ± 6.93*
3	**163**[a] (DPJ-577) (2.5 µg/ml)	Adrenaline (0.02 µg/ml)	24.33 ± 11.24
4	**163**[a] (DPJ-577) (2.5 µg/ml)	Adrenaline (0.2 µg/ml)	24.00 ± 10.82
5	Normal	-	22.33 ± 6.0807
6	Isoprenaline (0.02 µg/ml)	-	3.67 ± 3.52*
7	**163**[a] (DPJ-577) (2.5 µg/ml)	Isoprenaline (0.02 µg/ml)	23.33 ± 5.36
8	**163**[a] (DPJ-577) (2.5 µg/ml)	Isoprenaline (0.2 µg/ml)	22.67 ± 5.58

* $p<0.05$ level significance applying paired Student's t – test.
[a] Oxalate used for testing

The local anaesthetic activity of **193** (oxalate of **193** used for testing) was evaluated by infiltration anaesthesia, sciatic nerve block and corneal anaesthesia models. The onset and duration of local anaesthetic activity of the compound **193** in infiltration anaesthesia, sciatic nerve block and corneal anaesthesia models at different

concentrations (1%, 2% & 4%) are shown in table **9**. While the onset and duration of local anaesthetic activity of the compound **193** (2%), lidocaine (2%) and procaine (2%) in infiltration anaesthesia, sciatic nerve block and corneal anaesthesia models are shown in table **10**.

Table 9. Local anaesthetic activity of **193**[a] (DPJ-574).

Model	Onset of action[b]			Duration of action[b]		
	1%	**2%**	**4%**	**1%**	**2%**	**4%**
Infiltration anaesthesia	10	8.3±2.6	7.5±2.7	21.7±2.6	30±3.2	55.9±3.8
Sciatic nerve block	2.7±0.2	2.2±0.4	1.5±0.5	27.3±3.3	49.5±2.3	86±5.5
Corneal anaesthesia	8.3±2.6	5	5	20±3.2	30.8±2.0	34.1±2.0

[a] Oxalate used for testing

[b] Time in minutes ± standard deviation

Table 10. Comparison of local anaesthetic activity of **193** (2%) with lidocaine (2%) and procaine (2%)

Model	Onset of action[a]			Duration of action[a]		
	193[b] (2%) (DPJ-574)	**lidocaine (2%)**	**procaine (2%)**	**193[b] (2%) (DPJ-574)**	**lidocaine**	**procaine**
Infiltration anaesthesia	8.3±2.6	9.2±2.0	5	30±3.2	30.8±2.0	30±3.2
Sciatic nerve block	2.2±0.4*	1.3±0.5	12.8±2.5	49.5±2.3*	53±4.5	25.5±2.3
Corneal anaesthesia	5	5	5	30.8±2.0*	30	21.7±2.6

[a] Time in minutes ± standard deviation

[b] Oxalate used for testing

* P<0.001 compared to procaine treated group (student's t-test, n=6)

Compound **193** (1%, 2% & 4%) produced concentration dependent local anaesthetic response in infiltration, sciatic nerve block and corneal anaesthesia. As the concentration of **193** is increased, the time of onset of action decreased and the duration of local anaesthetic action increased. The onset of local anaesthetic action of **193** (2%) was not significantly different from that of Lidocaine (2%) and procaine (2%), except in the case of sciatic nerve block, where procaine (2%) had longer time for onset of action compared to **193**.

Thus the compound **193** was found to have potency, onset and duration of action comparable to that of lidocaine. Further studies are underway to determine the antiarrhythmic potential of this compound.

PARTITION COEFFICIENT

Partition coefficient of vanillin-derived (**142**, **143**, **145**, **146**, **147**, **149**, **150**, **152**, **153**, **154**, **156**, **158** and **159**); thymol-derived (**162**, **163** and **164**); 4-aminophenol-derived (**167, 168**, **169**, **172**, **173** and **174**); and 5-amino-1-naphthol-derived (**177**, **178**, **181** and **182**) aryloxypropanolamines were determined by shake flask method using standard procedure reported in literature.[378-380] A small quantity of the compound was allowed to partition between 1-octanol and 7.4 pH phosphate buffer. Partition coefficient is calculated from the logarithm of concentration of drug in 1-octanol layer / concentration of drug in the buffer layer. The amount of drug that had partitioned into the two layers is determined by UV spectroscopy by measuring the absorbance. The λ^{max} at which the absorbance is to be measured was first determined by potting the UV absorbance spectrum of the compound. The compound was dissolved in 1-octanol and then allowed to partition with buffer in a

Table 11. Partition coefficient (log P) in 1-octanol/7.4 pH buffer of vanillin-, thymol-, 4-aminophenol- and 5-amino-1-naphthol-derived aryloxypropanolamines

Compound	Code[a]	λ^{max} (nm)	log P
142	DPJ-634	278	-0.02
143	DPJ-898	307	0.24
145	DPJ-906	280	-0.10
146	DPJ-904	280	-0.30
147	DPJ-913	332	-0.21
149	DPJ-633	271	0.42
150	DPJ-811	307	0.20
152	DPJ-830	280	0.02
153	DPJ-834	271	-0.10
154	DPJ-832	307	-0.11
156	DPJ-859	278	-0.89
158	DPJ-862	277	-0.95
159	DPJ-933	271	-0.2
162	DPJ-576	280	1.35
163	DPJ-577	280	1.40
164	DPJ-912	280	1.30
167	DPJ-888	285	0.10
168	DPJ-890	290	0.40
169	DPJ-893	291	0.73
172	DPJ-782	281	0.32
173	DPJ-784	282	0.44
174	DPJ-786	282	0.75
177	DPJ-953	301	-0.14
178	DPJ-955	301	-0.08
181	DPJ-983	299	0.42
182	DPJ-985	299	0.49
Propranolol (**24**)		288	1.28

[a] code is given for the oxalate

thermostatic water bath for two hours. Separated the octanol layer, centrifuged at 3000 rpm for10 min., then 1-octanol layer was diluted with methanol so as to get absorbance in the range of 1.0. The absorbance of 1-octanol before partitioning and after partitioning with buffer was determined. From the absorbance of the compound in 1-octanol before and after partitioning, partition coefficient (log P) of the compound was calculated using the following formula:

$$\log P = \log \frac{\text{concentration of compound in 1-octanol layer}}{\text{concentration of compound in aqueous layer}}$$

$$= \log \frac{\text{absorbance of 1-octanol layer after partitioning}}{\text{(absorbance of 1-octanol layer before partitioning} - \text{absorbance of 1-octanol layer after partitioning)}}$$

Table **11** shows the experimentally determined log P values (partition coefficient) of the synthesized aryloxypropanolamines. The log P value of propranolol (**24**) was also determined for comparison purpose. Experimentally determined log P value of propranolol was consistent with the literature value of 1.24.[379]

The log P values of the compounds were correlated with β_1- and β_2-adrenoceptor binding results (both with Ki values and % inhibition) using multiple linear regression analysis software developed in house by Mr. Bhupinder Singh, Reader in Pharmaceutics, UIPS, Panjab University, Chandigarh. No significant correlation could be established between the lipophilicity parameter (log P) and the β-receptor binding results for the synthesized compounds. Absence of correlation shows that the lipophilicity parameter is not involved in the determination of β-receptor binding character of this set of aryloxypropanolamines.