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Thiol derivatives of arylnaphthylmethane as novel anti-osteoporotic agents

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Abstract (Mercaptophenyl)naphthylmethane derivatives were synthesized as novel estrogen receptor binding ligands. [4-(Methylsulfonyl)phenyl](naphth-1-yl)ketone shows a very promising activity towards osteoporosis.

Keywords Osteoporosis; (Mercaptophenyl)naphthylmethane; Sulfide; Thiophenol; Sulfones.

Introduction

Type II osteoporosis is a common disease associated with old age. In females, it has been linked to post-menopausal decrease of estrogen level [1]. In an approach towards development of anti-osteoporotic agents, a large number of non-steroidal estrogens/anti-estrogens have been studied for estrogen replacement therapy. This study has led to the development of Selective Estrogen Receptor Modulators (SERMs) [2]. Their effectiveness towards treatment of bone formation/maintenance lies in their selective estrogenic action on bone with overall estrogen antagonistic activity in other tissues such as uterus and breast.

Our efforts towards the development of SERMs for fertility regulation had led to the introduction of Centchroman (**A**), as the first non-steroidal oral contraceptive. This compound also possessed potent anti-osteoporotic as well as antiinflammatory activities. It has been observed in our laboratory that compounds showing antiinflammatory property might also show contraceptive activity and *vice versa*. However, the two activities do not run parallel [3–7].

On the other hand prostaglandins and several Cyclo-Oxygenase (COX) inhibitors, such as indomethacin, having antiinflammatory property, have been found to inhibit osteoclastic bone resorption induced by certain cytokines and growth factors *in vitro* activity [8]. The sulfur containing SERM Raloxifene (**B**) with structural similarity to Centchroman is the only drug for osteoporosis.

Based on the above observations, it was considered worthwhile to design compounds having similarity to Raloxifene, the potent SERM, with substituents responsible for COX inhibitory activity as present in the potent COX-2 inhibitors [9–11] such as Rofecoxib (**C**), for enhanced anti-bone resorption activity.

Results and discussion

Chemistry

In the present study molecular modification of some of the reported antiimplantation agents, such as dia-

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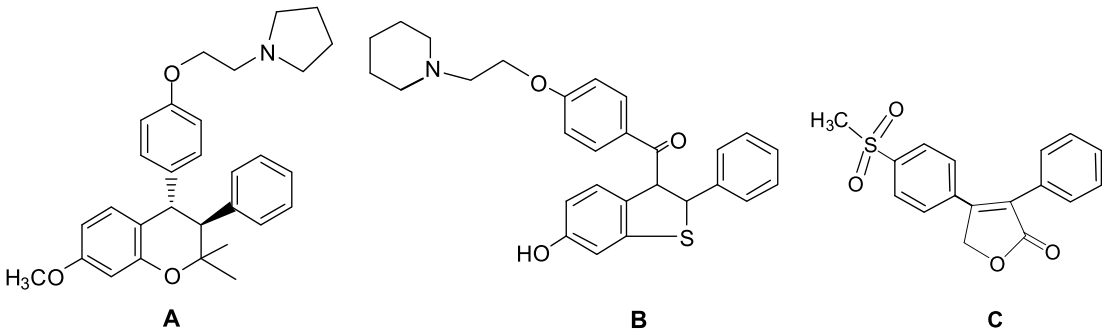
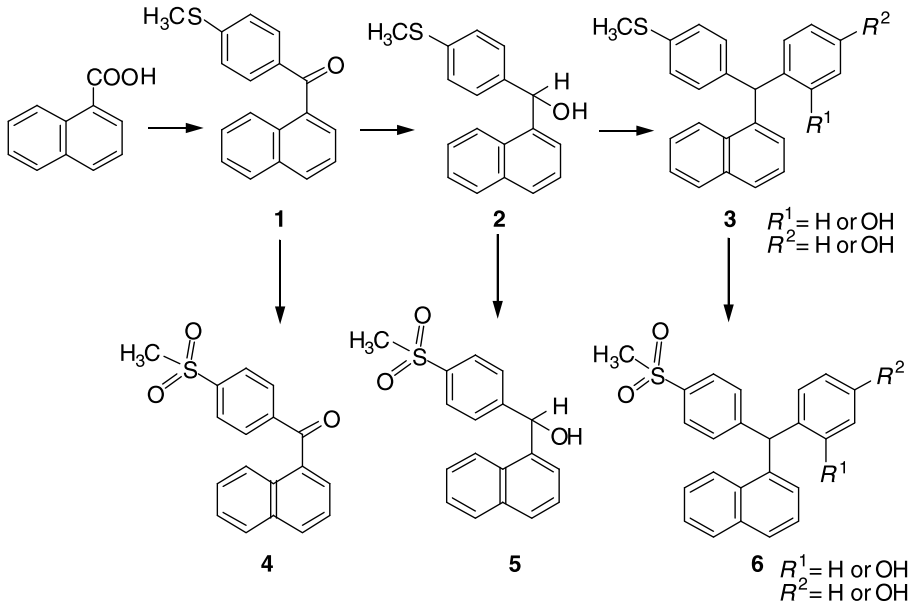
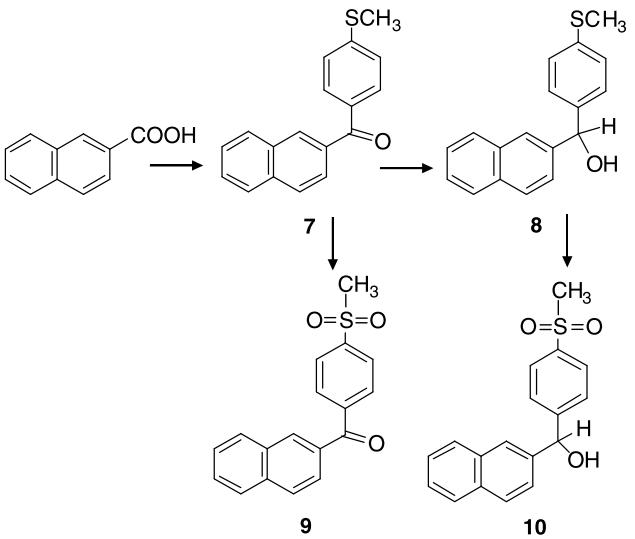
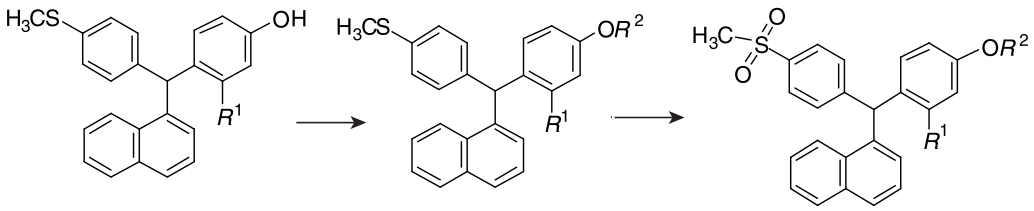




Scheme 1



Scheme 2



11–23 **24–31**

Scheme 3

ryl naphthyl methane derivatives, was carried out. Molecular residues such as methyl sulfone and methyl sulfide groups, responsible for antiinflammatory activity [12–15] were introduced at an appropriate positions.

Thus, synthesis of methylthio substituted arylnaphthylmethane derivatives, has been carried out by *Friedel Crafts* reaction using thioanisol or thiophenol with 1-naphthoic acid (Scheme 1) or 2-naphthoic acid (Scheme 2). The methylsulfone group was generated by oxidation of the S-methyl group. In the first step a *Friedel Crafts* reaction on naphthoic acid using *PPA* generated the carbonyl group which was reduced by sodium borohydride to a secondary alcohol.

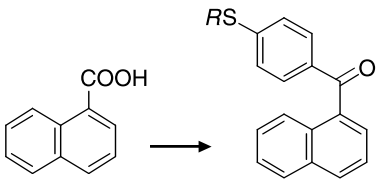
Friedel Crafts condensation of phenol/anisole with the carbinol in the presence of $SnCl_4$ and $AlCl_3$ led to the formation of substituted arylnaphthylmethane. Both *ortho* and *para* hydroxy/methoxy products were formed with the *para* isomer as major product.

In order to introduce an antiestrogenic subunit in the molecule, the phenolic diarylnaphthyl compounds were treated with appropriate tertiary amino alkyl halide in the presence of base. These tertiary amino alkoxy derivatives produced were finally converted into sulfones by treating it with H_2O_2 and acetic acid (Scheme 3). For introduction of a secondary amino alkoxy group as an antiestrogenic subunit, the phenolic compound was first reacted with epichlorohydrin at an elevated temperature in the presence of a base. 2,3-Epoxypropyloxy compounds thus formed were subsequently treated with different amines to give the desired secondary amino alkoxy derivatives (Scheme 3) (Table 1).

Since promising anti-osteoporotic activity was observed with (4-methylthiophenyl)(naphth-1-yl)ketone, its alkylated derivatives (Scheme 4) were prepared [16–17].

Table 1 Residues R^1 and R^2 in **11–31**

Compound nos.	R^1	R^2
11 and **24**	H	$(CH_2)_2N(CH_3)_2$
12 and **25**	H	$(CH_2)_2N(CH_2CH_3)_2$
13 and **26**	H	$(CH_2)_2N(CH_2)_4$
14 and **27**	H	$(CH_2)_2N(CH_2)_5$
15 and **28**	CH_3	$(CH_2)_2N(CH_3)_2$
16 and **29**	CH_3	$(CH_2)_2N(CH_2CH_3)_2$
17 and **30**	CH_3	$(CH_2)_2N(CH_2)_4$
18 and **31**	CH_3	$(CH_2)_2N(CH_2)_5$
19	H	CH_2–HC(O)
20	H	$CH_2CHOHCH_2N$ NH
21	H	$CH_2CHOHCH_2N(CH_2)_4$
22	H	$CH_2CHOHCH_2N(CH_2)_5$
23	H	$CH_2CHOHCH_2N(C_2H_5)_2$



Scheme 4

Compound no.	R
32	H
33	C_2H_5
34	$CH(CH_3)_2$
35	$(CH_2)_2N(CH_2)_5$

Biological activity

Inhibition in parathyroid hormone-induced resorption of ^{45}Ca from chick fetal bones in culture

Table 2 Biological activity of **1**, **2**, **4–6**, **10**, **13**, **14**, **19**, **20**, **23**, **33**

Compound no.	Concentration μM	T/C ratio
1	25	0.77
	50	0.66
	100	0.44
2	50	1.41
4	100	0.93
5	100	0.97
6	100	0.71
10	100	1.15
13	100	1.05
14	100	0.87
19	100	1.31
20	100	1.02
23	100	0.78
33	100	0.77

Conclusion

On the basis of biological activity data it has been observed that only compound **1** shows promising antiresorptive activity *in vitro* using chick foetal bone culture assay with T/C ratio of 0.4–0.8 at 25 μM to 100 μM concentrations in comparisons to Raloxifene having T/C of 0.6 [18]. It was devoid of any estrogenic or post-coital antifertility activities in rats.

Compound nos. **6**, **14**, **23**, and **33** also showed moderately antiresorptive activity. Thus, 4-(methylsulfonylphenyl)(naphth-1-yl)ketone will be a very useful antiresorptive agent in the treatment of postmenopausal osteoporosis.

Experimental

Chemicals were procured from Merck, Aldrich, and Fluka chemical companies. FT IR spectra (4000–200 cm^{-1}) were recorded on *Beckmann Perkin-Elmer* 881 and FT IR 8201 PC, Shimadzu spectrometers whereas ^1H NMR spectra were recorded on Bruker 400 FT NMR and Bruker advance DRX-300 NMR spectrometers. All spectra were obtained in $CDCl_3$ by using *TMS* as internal standard (chemical shift in δ/ppm). Microanalysis were done on Carlo erba model EA-11108 and Heraeus CHN rapid instrument and agreed favorably with calculated values.

(4-Methylthiophenyl)(naphth-1-yl)ketone (**1**, $C_{18}H_{14}OS$)
A mixture of 10 g 1-naphthoic acid (58.08 mmol), 8.19 cm^3 thioanisol (69.7 mmol), and 100 g polyphosphoric acid was heated for 10–12 h on a water bath at 80°C. The reaction mixture was poured onto ice-water and extracted with ethylacetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to give an oil, which was crystallized from methanol to give the desired compound. Yield 11.5 g (71.2%); mp 65°C; IR (KBr): $\bar{\nu} = 1647$ (C=O), 1585, 1550, 1506 (*Ar*H), 1025, 650 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.5$ (s, 3H, *Me*S), 7.23–7.25 (dd, 2H, *Ar*H), 7.27 (dd, 2H, *Ar*H), 7.47–8.01 (m, 7H, naphth) ppm; MS: $m/z = 278$.

(4-Methylthiophenyl)(naphth-1-yl)carbinol (**2**, $C_{18}H_{16}OS$)
(4-Methylthiophenyl)(naphth-1-yl)ketone (10 g, 35.9 mmol) was dissolved in 100 cm^3 methanol, then 4.5 g sodium borohydride (118.9 mmol) were added slowly and the reaction mixture was stirred for 5–6 h. Then methanol was distilled off and the reaction mixture was extracted with ethyl acetate. The organic layer extract was washed with water, dried over anhydrous sodium sulfate, and concentrated to give an oil, which was crystallized from benzene–*n*-hexane to give the desired compound. Yield 9.0 g (89.4%); mp 80°C; IR (KBr): $\bar{\nu} = 3400$ (OH), 2927 (CH), 1600, 1595, 1560 (*Ar*H), 1180, 1062, 669 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.45$ (s, 3H, *Me*S), 3.8 (s, 1H, OH), 6.5 (s, 1H, CH), 7.18–7.22 (dd, 2H, *Ar*H), 7.30–7.34 (dd, 2H, *Ar*H), 7.41–7.98 (m, 7H, naphth) ppm; MS: $m/z = 280$.

(4-Methylthiophenyl)(4-hydroxyphenyl)(naphth-1-yl)-methane (**3**, $C_{24}H_{20}OS$)
A mixture of 2.0 g (4-methylthiophenyl)(naphth-1-yl)carbinol (7.14 mmol) and 1.5 g phenol (15.9 mmol) was taken in a mixture of dry benzene and dry *n*-pentane (30 cm^3, 1:2) and was stirred. To this stirred solution, 0.6 g aluminium chloride (4.49 mmol) were added at 0–4°C under nitrogen atmosphere. After 15 min 10 cm^3 tin chloride (85.4 mmol) were added and stirring was continued for 4–6 h. The reaction mixture was poured onto ice–cold water and extracted with ethyl acetate. The organic extract was washed with water and dried over anhydrous sodium sulfate and concentrated to give an oil, which was purified by column chromatography on silica gel by using 5% ethyl acetate in *n*-hexane as eluent. Yield 1.7 g (66.9%); IR (Neat): $\bar{\nu} = 3149$ (OH), 2923 (CH), 1602, 1548, 1504, 1494 (*Ar*H), 1145, 669 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.18–8.03$ (m, 15H, *Ar*H), 4.93 (s, 1H, CHOH), 2.4 (s, 3H, *Me*S), 6.49 (s, 1H, CH) ppm; MS: $m/z = 356$.

(4-Methylsulfonylphenyl)(naphth-1-yl)ketone (**4**, $C_{18}H_{14}O_3S$)
A mixture of 1 g (4-methylthiophenyl)(naphth-1-yl)ketone (3.59 mmol) and 23 cm^3 hydrogen peroxide (30%, 223 mmol) in 5 cm^3 acetic acid was stirred for 14 h. The reaction mixture was poured onto water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated to give an oil, which was crystallized from methanol. Yield 0.7 g (62.8%); mp 150°C; IR (KBr): $\bar{\nu} = 1664$ (C=O), 1583, 1508, (*Ar*H), 1396, 1149, 678 (sulfone) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.06$ (s, 3H, *Me*SO_2), 7.2 (dd, 2H, *Ar*H), 7.4 (dd, 2H, *Ar*H), 7.5–8.1 (m, 7H, naphth) ppm; MS: $m/z = 310$.

(4-Methylsulfonylphenyl)(naphth-1-yl)carbinol (**5**, $C_{18}H_{16}O_3S$)
A mixture of 1 g (4-methylthiophenyl)(naphth-1-yl)carbinol (3.57 mmol) and 20 cm^3 hydrogen peroxide (30%, 194 mmol) in 5 cm^3 acetic acid was stirred for 15 h. Then solvent was distilled off and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to give an oil, which was crystallized from benzene–*n*-hexane to give the desired compound. Yield 0.6 g (53.9%); mp 160°C; IR (KBr): $\bar{\nu} = 3475$ (OH), 2927 (CH), 1598, 1514, 1481 (*Ar*H), 1311, 1149, 673 (sulfone) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.01$ (s, 3H, *Me*SO_2), 3.5 (s, 1H, OH), 6.47 (s, 1H, CH), 7.25 (dd, 2H, *Ar*H), 7.35 (dd, 2H, *Ar*H), 7.45–8.05 (m, 7H, naphth) ppm; MS: $m/z = 312$.

*(4-Methylsulfonylphenyl)(4-hydroxyphenyl)(naphth-1-yl)-methane (***6**, $C_{24}H_{20}O_3S$)
A mixture of 1.0 g (4-methylthiophenyl)(4-hydroxyphenyl) (naphth-1-yl)methane (2.80 mmol) and 25 cm^3 hydrogen peroxide (30%, 243 mmol) in 5 cm^3 acetic acid was stirred for 12 h. Solvent was distilled off and reaction mixture was extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate, and concentrated to give an oil, which was crystallized from benzene–*n*-hexane to give the desired compound. Yield 0.7 g (64.2%); mp 150–152°C; IR (KBr): $\bar{\nu} = 3394$ (OH), 2927 (CH), 1602, 1598, 1514, 1498 (*Ar*H), 1313, 1151, 1022, 669 (sulfone) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.06$ (s, 3H, *Me*SO_2), 4.93 (m, 1H, OH), 6.13 (s, 1H, CH), 6.8–7.8 (m, 15H, *Ar*H) ppm; MS: $m/z = 388$.

(4-Methylthiophenyl)(naphth-2-yl)ketone (**7**, $C_{18}H_{14}OS$)
A mixture of 6 g 2-naphthoic acid (34.84 mmol), 4.5 cm^3 thioanisol (38.33 mmol), and 60 g polyphosphoric acid was heated for 10–12 h on a water bath at 80°C. The reaction mixture was poured onto ice-water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated to give an oil, which was crystallized from methanol to give the desired compound. Yield 5 g (51.5%); mp 130°C; IR (KBr): $\bar{\nu} = 1684$ (C=O), 1610, 1466 (*Ar*H), 650 (C–S) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.55$ (s, 3H, *Me*S), 7.30–8.72 (m, 11H, *Ar*H) ppm; MS: $m/z = 278$.

(4-Methylthiophenyl)(naphth-2-yl)carbinol (**8**, $C_{18}H_{16}OS$)
(4-Methylthiophenyl)(naphth-2-yl)ketone (1 g, 3.59 mmol) was dissolved in 10 cm^3 methanol, then 0.5 g sodium borohydride (13.21 mmol) were added slowly and the reaction mixture was stirred for 5–6 h. Then methanol was distilled off and the reaction mixture was extracted with ethyl acetate. The organic layer extract was washed with water, dried over anhydrous sodium sulfate, and concentrated to give an oil, which was crystallized from benzene–*n*-hexane to give the desired compound. Yield 0.65 g (64.5%); mp 58°C; IR (KBr): $\bar{\nu} = 3306$ (OH), 2927 (CH), 1596, 1491 (*Ar*H), 1022, 627 (C–S) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.44$ (s, 3H, *Me*S), 3.9 (s, 1H, OH), 5.94 (s, 1H, CH), 7.19–7.86 (m, 11H, *Ar*H) ppm; MS: $m/z = 280$.

(4-Methylsulfonylphenyl)(naphth-2-yl)ketone (**9**, $C_{18}H_{14}O_3S$)
A mixture of 1 g (4-methylthiophenyl)(naphth-2-yl)ketone (3.59 mmol), 23 cm^3 hydrogen peroxide (30%, 223 mmol) in 5 cm^3 acetic acid was stirred for 14 h. The reaction mixture was poured onto water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated to give an oil, which was crystallized from methanol. Yield 0.5 g (44.8%); mp 160°C; IR (KBr): $\bar{\nu} = 1684$ (C=O), 1598, 1466 (*Ar*H), 1396, 1298, 1149 (sulfone) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.14$ (s, 3H, *Me*SO_2), 7.25–8.72 (m, 11H, *Ar*H) ppm; MS: $m/z = 310$.

(4-Methylsulfonylphenyl)(naphth-2-yl)carbinol (**10**, $C_{18}H_{16}O_3S$)
A mixture of 1 g (4-methylthiophenyl)(naphth-2-yl)carbinol (3.57 mmol) 20 cm^3 hydrogen peroxide (30%, 194 mmol) in 5 cm^3 acetic acid was stirred for 15 h. The solvent was distilled off and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated to give an oil, which was crystallized from benzene–*n*-hexane to give the desired compound. Yield 0.7 g (62.8%); mp 140°C; IR (KBr): $\bar{\nu} = 3413$ (OH), 1608, 1574, 1403 (*Ar*H), 1298, 1146 (sulfone) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.02$ (s, 3H, *Me*SO_2), 3.7 (s, 1H, OH), 6.08 (s, 1H, CH), 7.26–7.93 (m, 11H, *Ar*H) ppm; MS: $m/z = 312$.

*General experimental procedure for the synthesis of compounds **11–18***
A mixture of 1.0 mmol (4-methylthiophenyl)(4-hydroxyphenyl)(naphth-1-yl)-methane/(4-methylthiophenyl)(2-methyl-4-hydroxy phenyl)(naphth-1-yl)methane, 1.5 mmol tertiary alkylhalide, and 3.0 mmol anhydrous potassium carbonate in dry acetone was refluxed for 14–18 h. Potassium carbonate was filtered off. Acetone was distilled off. Reaction mixture was extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate, and concentrated to give an oil. The reaction mixture was passed through a basic alumina column using *n*-hexane–benzene as eluent. The oil thus obtained was treated with ethanolic HCl and crystallized with absolute alcohol and dry ether. It was filtered under anhydrous condition (hygroscopic) and dried in *Abderhalden* drying apparatus.

(4-Methylthiophenyl)(4-dimethylaminoethoxyphenyl)-(naphth-1-yl)methane hydrochloride (**11**, $C_{28}H_{29}NOS \cdot HCl$)
Yield 69.1%; mp 170°C; IR (KBr): $\bar{\nu} = 3759$ (amine), 2977 (CH), 1610, 1504 (*Ar*H), 1158, 1040, 667 (C–S) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.26$ (s, 6H, $N(CH_3)_2$), 2.42 (s, 3H, *Me*S), 2.74–2.80 (t, 2H, CH_2N), 4.03–4.08 (t, 2H, OCH_2), 6.1 (s, 1H, CH), 6.8–7.8 (m, 15H, *Ar*H) ppm; MS: $m/z = 427$ [$M^+ - 37$].

(4-Methylthiophenyl)(4-diethylaminoethoxyphenyl)(naphth-1-yl)methane hydrochloride (**12**, $C_{30}H_{33}NOS \cdot HCl$)
Yield 71.6%; mp 90°C; IR (KBr): $\bar{\nu} = 3352$ (amine), 2970 (CH), 1598, 1504, 1467 (*Ar*H), 1046, 667 (C–S) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 0.8$–0.9 (t, 6H, $2CH_3$), 2.46 (s, 3H, *Me*S),

3.46 (t, 2H, CH_2N), 3.86 (q, 4H, $2CH_2$ of N $(CH_2CH_3)_2$), 4.5 (t, 2H, OCH_2), 6.16 (s, 1H, CH), 6.79–7.9 (m, 15H, *Ar*H) ppm; MS: $m/z = 455$ $[M^+ - 37]$.

(4-Methylthiophenyl)(4-pyrrolidinoethoxyphenyl)(naphth-1-yl)methane hydrochloride (**13**, $C_{30}H_{31}NOS \cdot HCl$)
Yield 75.2%; mp 140°C; IR (KBr): $\bar{\nu} = 3425$ (amine), 2968 (CH), 1610, 1504, 1463 (*Ar*H), 1053, 663 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.78$–1.83 (m, 4H, $2CH_2$ of pyrrolidine), 2.45 (s, 3H, *Me*S), 2.55–2.65 (m, 4H, $2NCH_2$), 2.88–2.9 (t, 2H, CH_2N), 4.06–4.1 (t, 2H, OCH_2), 6.16 (s, 1H, CH), 6.80–7.82 (m, 15H, *Ar*H) ppm; MS: $m/z = 453$ $[M^+ - 37]$.

(4-Methylthiophenyl)(4-piperidinoethoxyphenyl)(naphth-1-yl)methane hydrochloride (**14**, $C_{31}H_{33}NOS \cdot HCl$)
Yield 70.7%; mp 125°C; IR (KBr): $\bar{\nu} = 3436$ (amine), 2977 (CH), 1617, 1506 (*Ar*H), 1045, 667 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.57$–1.65 (m, 6H, $3CH_2$ of piperidine), 2.42 (s, 3H, *Me*S), 2.43–2.5 (m, 4H, $2NCH_2$), 2.72–2.78 (t, 2H, CH_2N), 4.04–4.10 (t, 2H, OCH_2), 6.79–8.07 (m, 15H, *Ar*H), 6.17 (s, 1H, CH) ppm; MS: $m/z = 467$ $[M^+ - 37]$.

(4-Methylthiophenyl)(2-methyl-4-dimethylaminoethoxyphenyl)(naphth-1-yl)methane (**15**, $C_{29}H_{31}NOS$)
Yield 68.8%; IR (Neat): $\bar{\nu} = 3400$ (amine), 2934 (CH), 1608, 1495 (*Ar*H), 1188, 1041, 622 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.25$ (s, 6H, $N(CH_3)_2$), 2.17 (s, 3H, *Me*), 2.5 (s, 3H, *Me*S), 2.67–2.73 (t, 2H, CH_2N), 3.99–4.04 (t, 2H, OCH_2), 6.17 (s, 1H, CH), 6.59–7.86 (m, 14H, *Ar*H) ppm; MS: $m/z = 441$.

(4-Methylthiophenyl)(2-methyl-4-diethylaminoethoxyphenyl)(naphth-1-yl)methane (**16**, $C_{31}H_{35}NOS$)
Yield 78.89%; IR (Neat): $\bar{\nu} = 3756$ (amine), 2969 (CH), 1607, 1495, 1450 (*Ar*H), 1046, 665 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.96$–1.05 (t, 6H, $2CH_2CH_3$), 2.17 (s, 3H, *Me*), 2.45 (s, 3H, *Me*S), 2.54–2.63 (q, 4H, $2CH_2CH_3$), 2.84 (t, 2H, CH_2N), 3.96–3.99 (t, 2H, OCH_2), 6.17 (s, 1H, CH), 6.59–7.82 (m, 14H, *Ar*H) ppm; MS: $m/z = 469$.

(4-Methylthiophenyl)(2-methyl-4-pyrrolidinylethoxyphenyl)-(naphth-1-yl)methane (**17**, $C_{31}H_{33}NOS$)
Yield 59.4%; IR (Neat): $\bar{\nu} = 3417$ (amine), 2928 (CH), 1601, 1491, 1454 (*Ar*H), 1192, 1089, 688 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.77$–1.79 (m, 4H, $2CH_2$ of pyrrolidine), 2.17 (s, 3H, *Me*), 2.45 (s, 3H, *Me*S), 2.46–2.63 (m, 4H, $2NCH_2$), 2.87 (t, 2H, CH_2N), 4.06 (t, 2H, OCH_2), 6.17 (s, 1H, CH), 6.59–7.87 (m, 14H, *Ar*H) ppm; MS: $m/z = 467$.

(4-Methylthiophenyl)(2-methyl-4-piperidinylethoxyphenyl)-(naphth-1-yl)methane hydrochloride (**18**, $C_{32}H_{35}NOS \cdot HCl$)
Yield 69.2%; mp 240–242°C; IR (KBr): $\bar{\nu} = 3404$ (amine), 2935 (CH), 1607, 1495, 1448 (*Ar*H), 1125, 1046, 664 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.25$–1.59 (m, 6H, $3CH_2$ of piperidine), 2.17 (s, 3H, *Me*), 2.45 (s, 3H, *Me*S), 2.48–2.53 (m, 4H, $2NCH_2$), 2.74 (t, 2H, CH_2N), 4.02–2.08 (t, 2H, OCH_2), 6.17 (s, 1H, CH), 6.57–7.86 (m, 14H, *Ar*H) ppm; MS: $m/z = 481$ $[M^+ - 37]$.

(4-Methylthiophenyl)[4-(2,3-epoxypropyloxy)phenyl]-(naphth-1-yl)methane (**19**, $C_{27}H_{24}O_2S$)
A mixture of 2 g (4-methylthiophenyl)(4-hydroxyphenyl)-(naphth-1-yl)methane (5.62 mmol), 6 g anhydrous potassium carbonate (43.4 mmol), and 20 cm^3 epichlorohydrin (255 mmol) was refluxed for 10 h at 120°C. The reaction mixture was filtered and solvent was distilled off. It was extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate, and concentrated to give an oil. This oil was purified by column chromatography on silica-gel using *n*-hexane–benzene as eluent to give the desired product. Yield 2.2 g; (95.05%), mp 160–162°C; IR (KBr): $\bar{\nu} = 2950$ (CH), 1610, 1514, 1483 (*Ar*H), 1373, 1022, 671 (C–S), 761 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.45$ (s, 3H, *Me*S), 2.75–2.87 (d, 2H, oxinane), 3.46–3.49 (m, 1H, oxinane), 4.12–4.19 (d, 2H, OCH_2), 6.16 (S, 1H, CH), 6.8–7.82 (m, 15H, *Ar*H) ppm; MS: $m/z = 412$.

*General experimental procedure for the synthesis of compounds **20–23***
A mixture of 412 mg (4-methylthiophenyl)[4-(2,3-epoxypropyloxy)phenyl](naphth-1-yl)methane (1.0 mmol) and 1.5 mmol secondary amine in 15 cm^3 absolute alcohol was refluxed for 4–5 h. The alcohol was distilled off, and the reaction mixture was passed through a basic alumina column using *n*-hexane–benzene as eluent. The solvent was distilled off to give the product as oil. The oil thus obtained was treated with ethanolic HCl. The solvent was distilled off and the compound was crystallized from absolute alcohol and dry ether, filtered off under anhydrous condition (hygroscopic), and dried in *Abderhalden* drying apparatus.

(4-Methylthiophenyl)[4-(2-hydroxy-3-piperazinylpropyloxy)-phenyl](naphth-1-yl)methane hydrochloride
(**20**, $C_{31}H_{34}N_2O_2S \cdot HCl$)
Yield 80.7%; mp 95°C; IR (KBr): $\bar{\nu} = 3772$ (amine), 3425 (OH), 2927 (CH), 1602, 1569, 1510, 1481 (*Ar*H), 1388, 1097, 661 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.46$ (s, 3H, *Me*S), 2.78 (m, 8H, $4CH_2$ piperazine), 2.83 (d, 2H, CH_2N), 3.56 (s, 1H, NH), 3.86 (d, 2H, OCH_2), 4.03 (m, 1H, CHOH), 6.09 (s, 1H, CH), 6.73–7.86 (m, 15H, *Ar*H) ppm; MS: $m/z = 498$ $[M^+ - 37]$.

(4-Methylthiophenyl)[4-(2-hydroxy-3-n-pyrrolidinyl-propyloxy)phenyl](naphth-1-yl)methane (**21**, $C_{31}H_{33}NO_2S$)
Yield 59.7%; IR (Neat): $\bar{\nu} = 3363$ (OH), 3759 (amine), 2929 (CH), 1614, 1506 (*Ar*H), 1053, 667 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.06$–1.58 (m, 4H, $2CH_2$ of pyrrolidine), 2.35–2.4 (m, 4H, $2NCH_2$ of pyrrolidine), 2.45 (s, 3H, *Me*S), 2.86 (d, 2H, CH_2N), 3.94 (d, 2H, OCH_2), 4.0 (m, 1H, CHOH), 6.16 (s, 1H, CH), 6.45–7.83 (m, 15H, *Ar*H) ppm; MS: $m/z = 483$.

(4-Methylthiophenyl)[4-(2-hydroxy-3-piperidinylpropyloxy)-phenyl](naphth-1-yl)methane hydrochloride
(**22**, $C_{32}H_{35}NO_2S \cdot HCl$)
Yield 82.9%; mp 195°C; IR (KBr): $\bar{\nu} = 3749$ (amine), 3392 (OH), 2937(CH), 1606, 1510, 1390 (*Ar*H), 669 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.45$–1.65 (m, 6H, $3CH_2$ of piperidine

ring), 2.45 (s, 3H, *Me*S), 2.48–2.58 (m, 4H, $2NCH_2$), 2.8 (d, 2H, CH_2N), 3.92 (d, 2H, OCH_2), 4.1 (m, 1H, CHOH), 6.16 (s, 1H, CH), 6.8–7.8 (m, 15H, *Ar*H) ppm; MS: $m/z = 497$ [$M^+ - 37$].

(4-Methylthiophenyl)[4-(2-hydroxy-3-diethylamino-propyloxy)phenyl](naphth-1-yl)methane hydrochloride (**23**, $C_{31}H_{35}NO_2S \cdot HCl$)
Yield 71.9%; mp 95°C; IR (KBr): $\bar{\nu} = 3745$ (amine), 3389 (OH), 2940 (CH), 1608, 1510, 1460 (*Ar*H), 1045, 669 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.99$ (t, 6H, $2CH_3$), 2.45 (s, 3H, *Me*S), 2.52 (q, 4H, $2CH_2$), 2.55 (d, 2H, CH_2N), 3.94 (d, 2H, OCH_2), 4.0 (m, 1H, CHOH), 6.16 (s, 1H, CH), 6.8 (m, 15H, *Ar*H) ppm; MS: $m/z = 485$ [$M^+ - 37$].

*General experimental procedure for the synthesis of compounds **24–31***
A mixture of 1.0 mmol (4-methylthiophenyl)(4-alkoxyaminophenyl)(naphth-1-yl)methane and 2 cm^3 hydrogen peroxide (30%, 20.0 mmol) in acetic acid was stirred for 10–12 h. The solvent was distilled off. The reaction mixture was extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate, and concentrated to give an oil.

(4-Methylsulfonylphenyl)(4-dimethylaminoethoxyphenyl)-(naphth-1-yl)methane (**24**, $C_{28}H_{29}NO_3S$)
Yield 77.5%; IR (Neat): $\bar{\nu} = 3419$ (amine), 2970 (CH), 1600, 1504 (*Ar*H), 1373, 1155, 1028, 667 (sulfone) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.25$ (s, 6H, $N(CH_3)_2$), 3.06 (s, 3H, *Me*SO_2), 3.84 (t, 2H, CH_2N), 4.54 (t, 2H, OCH_2), 6.29 (s, 1H, CH), 6.82–7.89 (m, 15H, *Ar*H) ppm; MS: $m/z = 459$.

(4-Methylsulfonylphenyl)(4-diethylaminoethoxyphenyl)-(naphth-1-yl)methane (**25**, $C_{30}H_{33}NO_3S$)
Yield 50.5%; IR (Neat): $\bar{\nu} = 3402$ (amine), 2929 (CH), 1606, 1510 (*Ar*H), 1384, 1150, 1025, 670 (sulfone) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.88$–0.91 (t, 6H, $2CH_3$), 3.06 (s, 3H, *Me*SO_2), 3.46–3.53 (t, 2H, CH_2N), 3.82 (q, 4H, $2CH_2$), 4.54 (t, 2H, OCH_2), 6.29 (s, 1H, CH), 6.81–7.87 (m, 15H, *Ar*H) ppm; MS: $m/z = 487$.

(4-Methylsulfonylphenyl)(4-pyrrolidinylethoxyphenyl)-(naphth-1-yl)methane (**26**, $C_{30}H_{31}NO_3S$)
Yield 42.0%; IR (Neat): $\bar{\nu} = 3735$ (amine), 2934 (CH), 1598, 1454 (*Ar*H), 1310, 1149, 1054, 667 (sulfone) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.78$–1.82 (m, 4H, $2CH_2$ of pyrrolidine), 2.56–2.7 (m, 4H, $2NCH_2$), 2.88 (t, 2H, CH_2N), 3.06 (s, 3H, *Me*SO_2), 4.1 (t, 2H, OCH_2), 6.1 (s, 1H, CH), 6.8–7.9 (m, 15H, *Ar*H) ppm; MS: $m/z = 485$.

(4-Methylsulfonylphenyl)(4-piperidinylethoxyphenyl)-(naphth-1-yl)methane (**27**, $C_{31}H_{33}NO_3S$)
Yield 46.8%; IR (Neat): $\bar{\nu} = 3430$ (OH), 3649 (amine), 2999 (CH), 1610, 1565 (*Ar*H), 1307, 1145, 667 (sulfone) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.52$–1.64 (m, 6H, $3CH_2$ of piperidine), 2.4–2.52 (m, 4H, $2NCH_2$), 2.8 (t, 2H, CH_2N), 3.06 (s, 3H, *Me*SO_2), 4.0–4.1 (t, 2H, OCH_2), 6.1 (s, 1H, CH), 6.81–8.07 (m, 15H, *Ar*H) ppm; MS: $m/z = 499$.

(4-Methylsulfonylphenyl)(2-methyl-4-dimethylaminoethoxyphenyl)(naphth-1-yl)methane (**28**, $C_{29}H_{31}NO_3S$)
Yield 74.6%; IR (Neat): $\bar{\nu} = 3398$ (amine), 2989 (CH), 1608, 1569 (*Ar*H), 1307, 1145, 668 (sulfone) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.25$ (s, 6H, $N(CH_3)_2$), 2.17 (s, 3H, CH_3), 3.06 (s, 3H, *Me*SO_2), 3.4 (t, 2H, CH_2N), 4.54 (t, 2H, OCH_2), 6.29 (s, 1H, CH), 6.81–7.87 (m, 14H, *Ar*H) ppm; MS: $m/z = 473$.

(4-Methylsulfonylphenyl)(2-methyl-4-diethylaminoethoxyphenyl)(naphth-1-yl)methane (**29**, $C_{31}H_{35}NO_3S$)
Yield 56.2%; IR (Neat): $\bar{\nu} = 3396$ (amine), 2985 (CH), 1600, 1568 (*Ar*H), 1307, 1148, 666 (sulfone) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.9$–1.07 (t, 6H, $2CH_2CH_3$), 2.17 (s, 3H, *Me*), 2.5–2.6 (q, 4H, $2CH_2CH_3$), 3.4 (t, 2H, CH_2N), 4.54 (t, 2H, OCH_2), 3.06 (s, 3H, *Me*SO_2), 6.29 (s, 1H, CH), 6.80–7.82 (m, 14H, *Ar*H) ppm; MS: $m/z = 501$.

(4-Methylsulfonylphenyl)(2-methyl-4-pyrrolidinylethoxyphenyl)(naphth-1-yl)methane (**30**, $C_{31}H_{33}NO_3S$)
Yield 51.5%; IR (Neat): $\bar{\nu} = 3754$ (amine), 2924 (CH), 1598, 1499, 1454, 1399 (*Ar*H), 1307, 1149, 668 (sulfone) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 6.60$–7.87 (m, 14H, *Ar*H), 3.07 (s, 3H, *Me*SO_2), 6.29 (s, 1H, CH), 2.18 (s, 3H, *Me*), 2.96 (t, 2H, CH_2N), 3.92 (t, 2H, OCH_2), 1.79–1.95 (m, 4H, $2CH_2$ of pyrrolidine), 2.46–2.69 (m, 4H, $2NCH_2$ of pyrrolidine) ppm; MS: $m/z = 499$.

(4-Methylsulfonylphenyl)(2-methyl-4-piperidinylethoxyphenyl)(naphth-1-yl)methane hydrochloride (**31**, $C_{32}H_{35}NO_3S \cdot HCl$)
Yield 56.3%; mp 170°C; IR (Neat): $\bar{\nu} = 3410$ (amine), 2999 (CH), 1608, 1566 (*Ar*H), 1307, 1147, 667 (sulfone) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.25$–1.6 (m, 6H, $3CH_2$ of piperidine), 2.17 (s, 3H, *Me*), 2.4–2.53 (m, 4H, $2NCH_2$), 3.06 (s, 3H, *Me*SO_2), 3.4 (t, 2H, CH_2N), 4.54 (t, 2H, OCH_2), 6.29 (s, 1H, CH), 6.60–7.8 (m, 14H, *Ar*H) ppm; MS: $m/z = 513$ [$M^+ - 37$].

(4-Mercaptophenyl)(naphth-1-yl)ketone (**32**, $C_{17}H_{12}OS$)
A mixture of 8 g 1-naphthoic acid (46.46 mmol), 8 cm^3 thiophenol (78.05 mmol), and 80 g polyphosphoric acid was heated for 10–12 h on a water bath at 80°C. The reaction mixture was poured onto ice-water and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated to give an oil, which was crystallized from methanol to give the desired compound. Yield 6.5 g (52.9%); mp 65°C; IR (KBr): $\bar{\nu} = 2360$ (SH), 1683 (C=O), 1592, 1507, 1475 (*Ar*H) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.3$ (s, 1H, SH), 7.18–8.48 (m, 11H, *Ar*H) ppm; MS: $m/z = 264$.

*General experimental procedure for the synthesis of (4-alkyl substituted thiophenyl)(naphth-1-yl)ketones **33–34***
A mixture of 212 mg (4-mercaptophenyl)(naphth-1-yl)ketone (0.76 mmol) and 8.0 mmol haloalkane in 5 cm^3 10% NaOH was stirred for 12–14 h. The reaction mixture was extracted

with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated to give the desired compound as oil.

(4-Ethylthiophenyl)(naphth-1-yl)ketone (**33**, $C_{19}H_{16}OS$)
Yield 67.8%; IR (Neat): $\bar{\nu} = 1677$ (C=O), 1595, 1415 (*Ar*H), 773, 665 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.25$ (t, 3H, CH_2CH_3), 3.3 (q, 2H, CH_2CH_3), 7.25–9.10 (m, 11H, *Ar*H) ppm; MS: $m/z = 292$.

(4-Isopropylthiophenyl)(naphth-1-yl)ketone (**34**, $C_{20}H_{18}OS$)
Yield 60.4%; IR (Neat): $\bar{\nu} = 1668$ (C=O), 1582, 1441, (*Ar*H), 668, 759 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.25$ (d, 6H, $CH(CH_3)_2$), 3.5 (m, 1H, $CH(CH_3)_2$), 7.26–9.10 (m, 11H, *Ar*H) ppm; MS: $m/z = 306$.

(4-Piperidinylethylthiophenyl)(naphth-1-yl)ketone
(**35**, $C_{24}H_{25}NOS$)
A mixture of 212 mg (4-mercaptophenyl)(naphth-1-yl)ketone (0.76 mmol), 253 mg 1-(2-chloroethyl)piperidine hydrochloride (1.38 mmol), and 553 mg anhydrous potassium carbonate (4.0 mmol) in 15 cm^3 dry acetone was refluxed for 15–18 h. Potassium carbonate was filtered off and acetone was distilled off. The reaction mixture was extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate, and concentrated to give an oil. This was passed through a basic alumina column using *n*-hexane–benzene as eluent to yield the desired product as oil. Yield 44.2%; IR (Neat): $\bar{\nu} = 3429$ (amine), 1704 (C=O), 1610, 1509 (*Ar*H), 757, 661 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.18$–1.32 (m, 6H, $3CH_2$ of piperidine), 2.17 (m, 4H, $2NCH_2$), 4.28–4.33 (t, 2H, CH_2N), 4.53–4.59 (t, 2H, SCH_2), 7.27–8.94 (m, 11H, *Ar*H) ppm; MS: $m/z = 375$.

Animals and chemicals
Fertilized chicken eggs purchased from Government Poultry Farm, Lucknow on the day of ovulation (day 1) were incubated at 37°C in humidified air. Each egg was observed for embryonic growth on egg kindler and manually rotated at least once every 24 h. BGJ_b bone culture medium, parathyroid hormone (PTH, aa 1–34, and molecular weight 4117.7), bovine serum albumin (fraction V), *HEPES*, streptomycin, penicillin, *DMSO*, *PPO*, *POPOP*, and methoxyethanol were purchased from Sigma Chemical Company, USA. Toluene was purchased from Qualigen Fine Chemicals, Mumbai, $^{45}CaCl_2$ (specific activity: 0.185–1.85 g Bq/mg Ca) from Amersham Pharmacia Biotech, England and kits for biochemical markers of bone turnover from Boehringer Mannheim, Germany. All other chemicals were of analytical grade.

Experimental design

Antiresorptive activity in vitro
The antiresorbing activity of test agents was assessed as detailed earlier [18]. Briefly, femur bones isolated from chick embryos on day 11 post-ovulation were cleared of adhering connective tissue by carefully rotating each bone on dry *Whatman* (I) filter paper under a stereomicroscope. Each femur was placed in a drop of phosphate buffered saline (PBS) before culturing in 300 mm^3 of BGJ_b medium (*pH* 7.3) supplemented with penicillin (0.075 mg/mm), streptomycin (0.05 mg/mm), *HEPES* (2.382 mg/mm), and bovine serum albumin (1 mg/mm) in sterile 48-/96-well plates at 37°C under an atmosphere of 5% CO_2 in air for 24 h. Bones were transferred to BGJ_b culture medium containing $^{45}CaCl_2$ (0.5 μCi/300 mm^3 medium) and incubated for 3 h at 37°C under 5% CO_2 in air. Bones were then washed three times with BGJ_b medium for 3 h at 37°C under 5% CO_2 in air. Labeled bones were transferred to BGJ_b medium containing PTH (0.4 μM) and chase cultured for 96 h in presence or absence of test agents or vehicle (ethanol/*DMSO*; final concentration 0.1%) in 300 mm^3 of BGJ_b medium. Contralateral femur of each fetus served as corresponding control. Culture medium with respective treatment in each well was changed after 48 h. On termination of culture, bones were transferred to 0.1 *N* HCl for 24 h. Radioactivity due to ^{45}Ca in spent medium collected at 48 and 96 h of culture and HCl extract was quantified by Liquid Scintillation Spectrophotometer (LKB Wallac 1282 Gamma Counter, Finland) in 10 cm^3 of scintillation fluid (*PPO*: 2.00 g, *POPOP*: 0.05 g, toluene: 500 cm^3, methoxyethanol: 500 cm^3). One set of bones was heat killed by keeping in PBS in sterile tubes in boiling water for 15 min and cultured in parallel to assess viability of bones in culture system. Bone resorbing activity was expressed as percentage of ^{45}Ca released into culture medium and the effect of test agents as percent of corresponding contralateral control or T/C (Treatment/Control) ratio as shown below. T/C ratio close to unity shows lack of antiresorbing activity of the test agent.

$$^{45}\text{Ca resorption}(\%) = \frac{^{45}\text{Ca released into the medium}}{(^{45}\text{Ca released into the medium} + {}^{45}\text{Ca remaining inthe bone (HCl extract)})} \times 100$$

$$\text{T/C ratio} = \frac{^{45}\text{Ca resorption in presence of PTH + test agent}}{^{45}\text{Ca resorption in presence of PTH + vehicle}}$$

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