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SYNTHESIS AND EVALUATION OF NOVEL CALCIUM CHANNEL BLOCKING AGENTS

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ABSTRACT

Benzothiopyran is a heterocyclic compound which contains sulphur as a heteroatom which is responsible for biological and pharmacological activity. Changing heterocyclic ring size will generate derivatives that are not only retained the calcium channel blocking activity but also resulted in several compounds that were more active than diltiazem. A receptor-binding model identifying the benzene ring as a lipophilic group that facilitates transport into the channel and the absolute stereochemistry for the selective binding. Benzothiopyran nucleus is similar to the benzothiazepine nucleuses which are used as calcium channel blockers. In these synthesis series, benzothiazepine nucleus containing nitrogen atom which is replace by bioisosterism of nitrogen.

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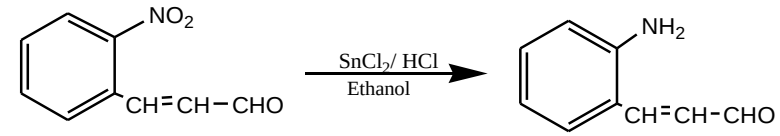
INTRODUCTION:

Calcium channel blocking agents (CCBs) inhibit the movement of calcium ions across the cell membrane by blocking the L-type (slow) calcium ion channel. This blockade reduces contraction of both smooth and cardiac muscle, and cells within the sinoatrial (SA) and atrioventricular (AV) nodes[1-3].

MATERIAL AND METHODS:

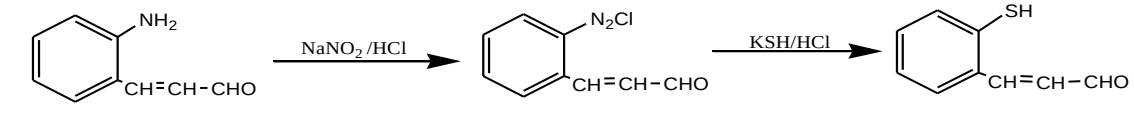
Synthesis of benzothiopyran derivatives The present work comprises synthesis of the benzothiopyran derivatives. The steps involved in the synthesis include the synthesis.

Step- I



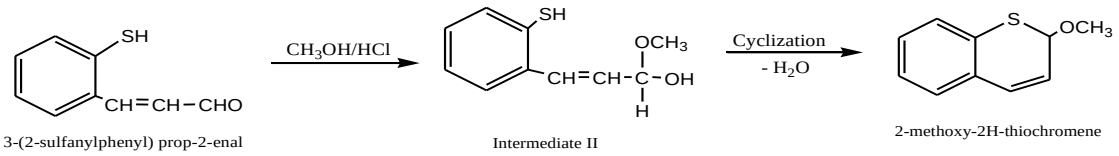
3-(2-nitrophenyl) prop-2-enal 3-(2-aminophenyl) prop-2-enal

Step-II



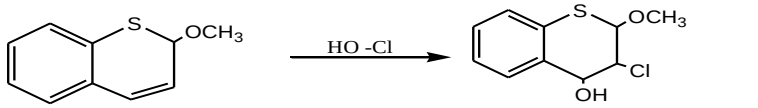
3-(2-aminophenyl) prop-2-enal Intermediate I 3-(2-sulfanylphenyl) prop-2-enal

Step-III



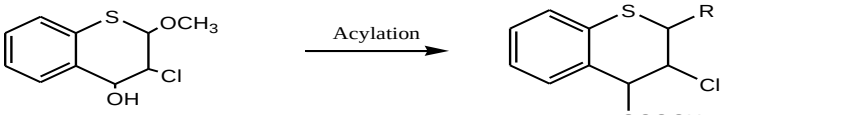
3-(2-sulfanylphenyl) prop-2-enal — Intermediate II — 2-methoxy-2H-thiochromene

Step-IV



2-methoxy-2H-thiochromene — 3-chloro-2-methoxy-3,4 dihydro-2H-1-benzothiopyran-4-ol

Step-V



3-chloro-2-methoxy-3,4 dihydro-2H-1-benzothiopyran-4-ol — 3-chloro-2-methoxy-3,4 dihydrothiopyran-4yl acetate

RESULTS AND DISCUSSION:

Step	Melting point	TLC	^{1}HNMR	IR SPECTRA (KBr) cm^{-1}
STEP- I	232^{0}C	Methanol: Ethyl acetate (9:1) R_f for 3-(2-nitrophenyl) prop-2-enal =0.8 R_f for 3-(2-aminophenyl) prop-2-enal = 0.6	δ 3.03(s, 2H, NH_2), 6.66 (d, 1H, -CH=C-), 6.68 (dd, 1H,aromatic proton, ortho to amino group), 7.74 (td,1H, aromatic proton, para to amino group), 7.66 (dd, 1H, aromatic proton, meta to amino group), 7.80 (td,1H, aromatic proton, meta to amino group), 8.12(d, 1H,-C=CH-), 9.77 (s,1H, -CHO).	3228 (N-H Stretch of amine group), 3049.25 (C-H Stretch of aromatic ring),2975.96 (C-H Stretch of alkene)2736.80 (C-H Stretch of -CHO) 1680.56 (C=O Stretch of -CHO) 1625.81 (C=C Stretch of alkene), 1610.43 and1442.66(C=C Stretch of aromatic ring), 1569.95 cm^{-1} (N-H bending of amine group), 1172.64 (C-N Stretch of amine and aromatic carbon), 1037.63- 977.84 (C=C bending (oop) of alkene), 806.19 (N-H bending (oop) of amine group),738.69 (aromatic =C-H bending (oop) for ortho-substitution.
STEP-2	248^{0}C	Methanol: Ethyl acetate (9:1) R_f for 3-(2-aminophenyl) prop-2-enal (1) = 0.5 R_f for 3-(2-sulfanylphenyl) prop-2-enal (2) = 0.29	δ 3.47 (s, 1H, SH), 6.73 (td, 1H, J_o = 7.36 Hz,aromatic proton, meta to SH group), 7.65 (d, 1H, -C=CH-), 7.77 (dd, 1H,aromatic proton, meta to SH group), 7.81 (td, 1H,aromatic proton, para to SH group), 7.92 (dd,1H, aromatic proton, ortho to SH group), 8.02 (d, 1H, -CH=C-), 9.78 (s,1H, -CHO).	3045.11 (C-H Stretch of aromatic ring) , 2925.81 (C-H Stretch of alkene), 2735.13 (C-H Stretch of -CHO), 1681.81 (C=O Stretch of -CHO), 1618.17 (C=C Stretch of alkene), 1519.80 and 1456.16 (C=C Stretch of aromatic ring), 671.18 (C-S Stretch of mercapto and aromatic carbon), 1035.70- 964.34 (C=C bending (oop) of alkene), 746.40 (aromatic =C-H bending (oop) for ortho-substitution).

STEP -3	250-252°C	Solvent System = Ethyl acetate : Methanol (8 : 2) R_f Value for Intermediate 3-(2-sulfanylphenyl)prop-2-enal = 0.43 R_f Value for Intermediate 2-methoxy-2H-thiochromene = 0.54	δ 3.54 (s,3H, O-CH_3), 5.71 (d, 1H, -S-CH-),6.72(dd, 1H, -S-CH-CH-), 7.65(d,1H,-S-CH-CH=CH-), 7.79(td, 1H, aromatic proton), 7.81(dd,1H,aromatic proton), 8.06 (td, 1H, aromatic proton), 8.10(dd,1H, J_o = 7.54,aromatic proton).	3047.48 (C-H Stretch of aromatic ring) , 2862.96 (C-H Stretch of alkane), 1595.46 and 1416.10 (C=C Stretch of aromatic ring), 1440.51 and 1375.08 (C-H bending of alkane), 1224.71 and 1043.70(C-O-C Stretch of methoxy),1124.12 (C-O Stretch of methoxy),740.61 (aromatic =C-H bending (oop) for ortho-substitution),785.25 (C-S Stretch of mercapto and aromatic carbon)
STEP- 4	180-185 °C	Solvent System = Methanol : Chloroform (4 : 6) R_f Value for 2-methoxy-2H-thiochromene = 0.56 R_f Value for 3-chloro-2-methoxy-3,4 dihydro-2H-1-benzothiopyran-4-ol= 0.32	δ 2.19 (s,1H, -OH), 3.29(s, 3H, -O-CH_3), 4.49(d,1H, -S-CH-CH-CH-), 4.56 (d, -S-CH-),6.88 (td, 1H, aromatic proton), 7.01 (dd, 1H,aromatic proton), 7.11 (td, 1H, aromatic proton), 7.48 (dd, 1H, J_o = 6.76 Hz, aromatic proton).	3343.34(O-H Stretch of hydroxyl group), 2994.28 (C-H Stretch of aromatic ring) , 2856.38 (C-H Stretch of alkane), 1591.16 and 1512.08 (C=C Stretch of aromatic ring), 1452.30 and 1392.51 (C-H bending of alkane), 1150.24 (C-O Stretch of alcohol),1260.29 and 1047.31(C-O-C Stretch of methoxy),1101.28 (C-O Stretch of methoxy), 1O47.81 (C-Cl Stretch of Ar-chloride), 757.83 (aromatic =C-H bending (oop) for ortho-substitution),669.61 (C-S Stretch of mercapto and aromatic carbon).
STEP- 5	180-185 °C	Solvent System = Methanol : Chloroform (4 : 6) R_f Value for 3-chloro-2-methoxy-3,4 dihydro-2H-1-benzothiopyran-4-ol = 0.62 R_f Value for 3-chloro-2-methoxy-3,4 dihydrothiopyran-4yl acetate = 0.46	δ 2.12(s,3H, -C-(=O) CH_3), 3.63(s, 3H, -O-CH_3), 5.51(d,1H, -S-CH-CH-CH-), 5.98(d ,-S-CH-), s6.97(dd, 1H, aromatic proton), 7.36(dd,1H,aromatic proton), 7.56 (dd, 1H, aromatic proton), 7.59 (d,1H, aromatic proton).	1762.82 (C=O Stretch of ester group), 3082.28 (C-H Stretch of aromatic ring) , 2864.09 (C-H Stretch of alkane), 1627.81 and 1535.23 (C=C Stretch of aromatic ring), 1448.44 and 1388.65 (C-H bending of alkane), 1147.07 (C-O Stretch of alcohol),1147.07 and 1022.31(C-O-C Stretch of methoxy),1147.81 (C-O Stretch of methoxy), 1O74.81 (C-Cl Stretch of Ar-chloride), 761.83 (aromatic =C-H bending (oop) for ortho-substitution),667.32 (C-S Stretch of mercapto and aromatic carbon).

Pharmacological Evaluation

The pharmacological approach for evaluation of calcium channel blocking activity of compounds 5A, 5B derivation guinea-pig ileum by concentration response curve.

Table 2: Effect of Compounds (5A-2) in the Concentration Response Curves

Dose	Concentration (Mm)	Mean± S.E.M. (Compound 5a-2)
KCl	80	1.53
I	60	1.93
II	80	1.43
III	100	2.08
amlodipine	10	2.15

CONCLUSION:

The main objective of present study was synthesis of novel benzothiopyran derivatives for treatment of cardiovascular disease. In the current research work, substituted 3-chloro-3,4-dihydrothiochromen-4-one and 3-chloro-3,4-dihydro-2H-thiochromen-4yl acetate derivatives (5A-5B) were synthesized, with elaborate characterization by spectral data. Synthesize compounds were obtained in satisfactory yield and were characterized by TLC, FT-IR, ^{1}HNMR. In pharmacological evaluation, synthesize compounds 5A-1, 5A-2, 5B-1, 5B-2 gave *in-vitro* Calcium channel antagonist activity. On the basis of above study it is suggest that substituted 3-chloro-3,4-dihydrothiochromen-4-one and 3-chloro-3,4-dihydro-2H-thiochromen-4yl acetate derivatives having significant calcium channel antagonistic action agents, KCl induce contraction.

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