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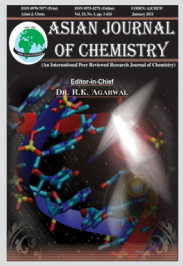

Synthesis, Characterisation and Cardiac Activity of Some Novel 2,3-Substituted-4-phenyl-1,3-oxazolidine Derivatives

VIJAYALAKSHMI GUDAPRTHI[1,*], K. BHARATHI [2] and G. OMPRAKASH[3]

[1]Raghu College of Pharmacy, Dakamarri, Visakhapatnam-531 162, India
[2]Institute of Pharmaceutical Technology, Sri Padmavathi Mahila University, Tirupati-517 502, India
[3]PharmaZell R & D (India) Private Limited, Modavalasa, Denkada Mandal, Vizianagaram (Dist.)-531 162, India

*Corresponding author: E-mail: vijayabn09@gmail.com; opgudaparthi@yahoo.com

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A series of 2,3-substituted-4-phenyl-1,3-oxazolidine derivatives were synthesized from DL-(±)-phenyl glycine. DL-(±)-Phenyl glycine was reduced to the corresponding alcohol, which was then condensed with different aldehydes to form Schiff bases, which are then reduced and further condensed with different substituted aldehydes to give the oxazolidine derivatives. The synthesized compounds are characterized by ^{1}H NMR, IR and mass spectral analysis. All the compounds were investigated for cardiac activity while all the compounds show significant activity.

Key Words: Oxazolidines, DL-(±)-Phenyl glycine, Schiff bases, Cardiac activity, Negative inotropic activity.

INTRODUCTION

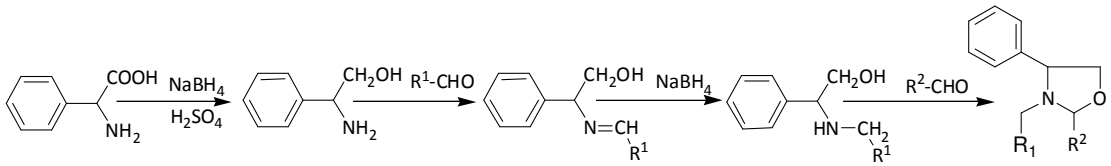
Oxazolidine derivatives are reported as antihypertensive[1], antiarrthymic[2] and calcium channel blockers[3]. Oxazolidines are usually prepared from β-amino alcohols and carbonyl compounds[4], by reaction of dimethylamino methanol with ethylene chlorohydrine[5] by reaction of aziridine with different aldehydes and ketones[6] prepared from norephedrine, a commercially available chiral molecule, by ketalization with aldehydes or ketones[7] from imines and epoxides catalyzed by samarium compounds[8], by using a nucleophillic displacement of epibromrhydrin with *p*-hydroxyl benzyl alcohol in presence of sodium hydroxide[9]. Many methods are available for the preparation of oxazolidine derivatives. Amino alcohols are very convenient reagents to prepare oxazolidine moiety. In the present study some novel oxazolidine derivatives are prepared from DL-(±)-phenyl glycine. DL-(±)-phenyl glycine was reduced to DL-(±)-phenyl glycinol by sodium borohydride[10,11] in the presence of catalytic amount of concentrated sulphuric acid. The resulting phenyl glycinol was condensed with different substituted aldehydes to form corresponding Schiff base intermediates, which on reduction with sodium borohydride and condensation with different substituted aldehydes gave the oxazolidine derivatives (**1-17**). All the synthesized compounds were investigated for cardiac activity by isolated frog heart preparation. While all the compounds show significant activity.

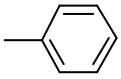
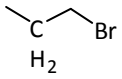
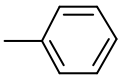
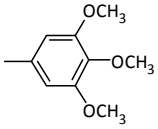
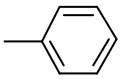
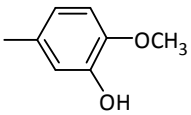
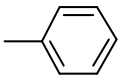
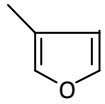
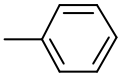
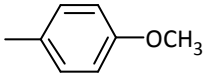
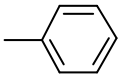
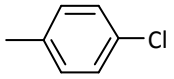
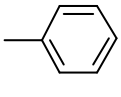
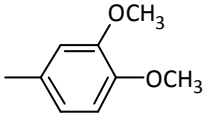
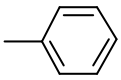
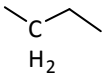
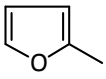
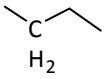
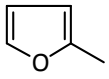
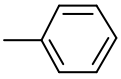
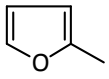
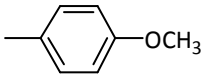
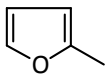
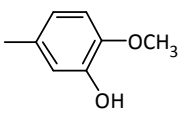
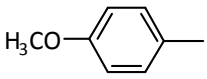
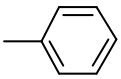
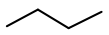
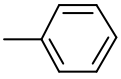
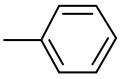
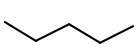
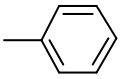
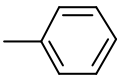
EXPERIMENTAL

Melting points were taken in open capillaries and are un corrected. IR spectra of the compounds were recorded on ABB bomer FTIR spectrometer MB 104 with KBr pellets. ^{1}H NMR spectra were recorded on 300 MHZ-Bruker DPX 200. Mass spectra were recorded on GCMS QP 5000 Shimadzu. Micro analysis for C, H and N were performed in Heraus rapid analyzer. The purity of compounds was checked by TLC on percolated SiO_2 gel (HF_{254}, 200 meshes) aluminium plates (E Merck) using chloroform, methanol (1:9:0) as mobile phase and visualized through UV-light. General synthetic scheme is shown in **Scheme-I**.

3-Benzyl-2-(2-bromoethyl)-4-phenyloxazolidine (1)

Step-1: Preparation of DL-(±)-phenyl glycinol: 12.07 g of sodium borohydride[10] (2.4 eq.) was added to a RB flask containing 200 mL of THF and added 20 g of DL-(±)-phenyl glycine (1.0 eq.) in one portion and flask was under argon atmosphere and cool the mass to 0 ºC in an ice bath. Add sulfuric acid 2 mL (0.1 volume) solution drop wise to the reaction mixture and stirred at reflux for 15 h reaction completion (about 12-14 h) and reaction was monitored by TLC (mobile phase for TLC 10 % methanol in chloroform). After completion of the reaction pH was adjusted up to 7.5 with sodium carbonate solution and diluted with 100 mL water. Separated organic layer and extracted the aqueous layer with 50 mL of ethyl acetate and combined organic layers washed with 2 × 50 mL



Compd.	R^1	R^2	Chemical name
1			3-Benzyl-2-(2-bromoethyl)-4-phenyloxazolidine
2			3-Benzyl-2-(3,4,5-trimethoxyphenyl)-4-phenyloxazolidine
3			5-(3-Benzyl-4-phenyloxazolidin-2-yl)-2-methoxyphenol
4			3-benzyl-2-(furan-2-yl)-4-phenyloxazolidine
5			3-Benzyl-2-(4-methoxyphenyl)-4-phenyloxazolidine
6			3-Benzyl-2-(4-chlorophenyl)-4-phenyloxazolidine
7			3-Benzyl-2-(3,4-dimethoxyphenyl)-4-phenyloxazolidine
8			3-Benzyl-4-phenyl-2-propyloxazolidine
9			3-((Furan-2-yl)-methyl)-4-phenyl-2-propyloxazolidine
10			3-((Furan-2-yl)-methyl)-2,4-diphenyloxazolidine
11			3-((Furan-2-yl)-methyl)-2-(4-methoxyphenyl)-4-phenyloxazolidine
12			5-(3-((Furan-2-yl)-methyl)-4-phenyl-oxazolidin-2-yl)-2-methoxyphenol
13			3-(4-Methoxyphenyl)-2,4-diphenyloxazolidine
14			3-Pentyl-2,4-diphenyloxazolidine
15			3-Benzyl-4-phenyl-2-((Z)-prop-1-enyl)-oxazolidine
16			3-Hexyl-2,4-diphenyloxazolidine
17			(Z)-3-benzyl-2-ethylidene-4-phenyloxazolidine

Scheme-I

of 10 % sodium bicarbonate solution followed by 2 × 50 mL of 10 % brine solution. Finally organic layer was dried over sodium sulphate and distilled under reduced pressure at below 45 ºC to afforded 11.0 g of DL-(±)-phenyl glycinol as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ : 2.0 (bs, 1H, O-H), 3.95 (d, 1H, -CH_2-), 3.89-4.0 (t, 1H, -CH-), 4.0-4.2 (d, 1H, -CH_2-), 7.08-7.20 (m, 5H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3526 (O-H), 3220 (-NH_2), 3032 (C-H in Ar-H), 2935 (C-H), 1610, 1583 and 1456 (C-C in Ar), 742 (C-H in Ar-H); EL-MS m/z (M^+): 137.23 (calcd. for $C_8H_{11}NO$: 137.18).

Step-2: Preparation of (E)-2-(2-phenylethylideneamino)-2-phenylethanol: 20.0 g of step-1 compound *i.e.*, DL-(±)-phenyl glycinol (1.0 eq.) and 18.4 g of benzadehyde (1.2 eq.) was dissolved in 200 mL of toluene (10.0 times w/v) and azeotropped with Dean-stark trap for 17 h. Then the reaction mass was cooled and washed with 10 % sodium bicarbonate solution separate and concentrated under reduced pressure to give 25 g of (E)-2-(2-phenylethylidene amino)-2-phenylethanol (Schiff base). ^{1}H NMR ($CDCl_3$) δ: 2.0 (bs, 1H, O-H), 2.6 (d, 2H, -CH_2-), 2.9 (t, 1H, -CH-), 3.7-4.0 (m, 2H, -CH_2-), 7.08 -7.25 (m, 10H, Ar-H), 7.5 (m, 1H, H-C=N). IR (KBr, ν_{max}, cm^{-1}): 3526 (O-H), 3032 (C-H in Ar-H), 2935 (C-H), 1612 (C=N), 1610, 1583 and 1456 (C-C in Ar), 742 (C-H in Ar-H); EL-MS m/z (M^+): 239.13 (calcd. for $C_{16}H_{17}NO$: 239.31). Elemental analysis for $C_{16}H_{17}NO$ (%): C-80.30, H-7.16, N-5.85; found: C-80.46, H-7.12, N-5.92.

Step-3: Preparation of 2-(phenethylamino)-2-phenylethanol: 10 g of step-2 compound *i.e.*, (E)-2-(2-phenylethylideneamino)-2-phenylethanol (1.0 eq.) was dissolved in 12 mL of methanol (10.0 times w/v), to this clear solution added slowly 1.9 g of sodium borohydride (1.2 eq.) powder at ambient temperatures. The reaction mixture was stirred at 35-45 °C till the reaction completion (about 2-4 h) and reaction was monitored by TLC (mobile phase for TLC 10 % methanol in chloroform). After completion of the reaction, solvent was removed by evaporation. The residue obtained was dissolved 60 mL of ethyl acetate (50.0 times w/v) and washed with 2 × 10.0 mL of 10 % sodium bicarbonate solution followed by 2 × 10.0 mL of 10 % brine solution. Finally organic layer was dried over sodium sulfate and distilled under reduced pressure at below 45 ºC to afforded 7.3 g of 2-(phenethylamino)-2-phenylethanol and the structure was confirmed by following

analysis. ^{1}H NMR ($CDCl_3$) δ: 2.0 (bs, 1H, O-H), 2.0 (bs, 1H, N-H), 2.6 (t, 2H, -CH_2-), 2.9 (t, 2H, -CH_2-), 3.7-4.1 (m, 2H, -CH_2-), 3.9 (m, 1H, -CH-), 7.05-7.21 (m, 10H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3528 (O-H), 3352 (N-H), 3030 (C-H in Ar-H), 2936 (C-H), 1602, 1582 (C-C in Ar), 745 (C-H in Ar-H); EL-MS m/z (M^+): 241.15 (calcd. for $C_{16}H_{19}NO$: 241.33). Elem. analysis for $C_{16}H_{19}NO$: C-79.63, H-7.94, N-5.80; found: C-79.82, H-7.85, N-5.92.

Step-4: Preparation of 3-benzyl-2-(2-bromoethyl)-4-phenyloxazolidine: 10 g of reduced Schiff base *i.e.*, 2-(phenethyl amino)-2-phenylethanol (1.0 eq.) was dissolved in 100 mL of toluene (10.0 times w/v) and stirred for 10 min, to this bromopropanaldehyde (1.2 eq.) was added and azeotropped with Dean-stark trap for 20 h to remove water from reaction mixture. Then the reaction mass was cooled and washed with 10 % sodium bicarbonate solution separate and concentrated under reduced pressure to give 12 g of crude. This crude was purified by column chromatography using 10 to 20 % ethyl acetate in pet ether afford 8 g of 3-benzyl-2-(2-bromoethyl)-4-phenyloxazolidine and the structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 2.0 (m, 2H, -CH_2-), 3.3 (m, 2H, -CH_2-), 3.6-4.0 (m, 5H, -CH_2-, -CH-), 4.2 (m, 1H, -CH-), 7.0-7.2 (m, 10H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3030 (C-H in Ar-H), 2929 (C-H), 1601, 1582 and 1456 (C-C in Ar), 1210 (C-N), 1066 (C-O), 739 (C-H in Ar-H); 554 (C-Br), EL-MS m/z (M^+): 345.07 (calcd. for $C_{18}H_{20}BrNO$: 346.26). Elemental analysis for $C_{18}H_{20}BrNO$: C-62.44, H-5.82, Br-23.08, N-4.05; found: C-62.52, H-5.91, Br-23.01, N-3.99.

Synthesis of other compounds from 2-17

3-Benzyl-2-(3,4,5-trimethoxyphenyl)-4-phenyloxazolidine (2): To get title compound, 3,4,5-trimethoxy benzaldehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 3 g of 3-benzyl-2-(3,4,5-trimethoxyphenyl)-4-phenyloxazolidine (**2**) was obtained as solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 3.6 (s, 2H, -CH_2-), 3.7 (s, 9H, -CH_3), 3.8 (m, 2H, -CH_2-), 4.2 (t, 1H, -CH-), 5.2 (s, 1H, -CH-), 6.2 (s, 2H, Ar-H), 7.0-7.2 (m, 10H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 2928 (C-H), 2812 (C-H in -OCH_3), 1211 (C-N), 3032 (C-H in Ar-H), 1611, 1586 and 1456 (C-C in Ar), 1069 (C-O), 741 (C-H in Ar-H), 888 (C-H in Ar-H); EL-MS m/z (M^+): 405.19 (calcd. for $C_{25}H_{27}NO_4$: 405.49). Elem. analysis for $C_{25}H_{27}NO_4$: C-74.05, H-6.71, N-3.45; found : C-74.16, H-6.82, N-3.54.

5-(3-Benzyl-4-phenyloxazolidin-2-yl)-2-methoxyphenol (3): To get title compound, 3-hydroxy-4-methoxybenzadehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 4 g of 5-(3-benzyl-4-phenyloxazolidin-2-yl)-2-methoxyphenol (**3**) was obtained as light yellow solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 3.6 (s, 2H, -CH_2-), 3.7 (s, 3H, -CH_3), 3.8 (m, 2H, -CH_2-), 4.2 (t, 1H, -CH-), 5.0 (bs, 1H, -OH), 5.2 (s, 1H, -CH-), 6.6 (s, 2H, Ar-H), 7.0 -7.2 (m, 11H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3623 (O-H), 3032 (C-H in Ar-H), 2938 (C-H), 2810 (C-H in -OCH_3), 1601, 1576 (C-C in Ar), 1215 (C-N), 1065 (C-O), 842 (C-H in Ar-H); 752 (C-H in Ar-H), EL-MS m/z (M^+): 361.17 (calcd. for $C_{23}H_{23}NO_3$: 361.43). Elem. analysis for $C_{23}H_{23}NO_3$: C-76.43, H-6.41, N-3.88; found: C-76.41, H-6.38, N-3.92.

3-Benzyl-2-(furan-2-yl)-4-phenyloxazolidine (4): To get title compound, furan-2-carboxaldehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 3.5 g of 3-benzyl-2-(furan-2-yl)-4-phenyloxazolidine (**4**) was obtained as solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 3.6 (s, 2H, -CH_2-), 3.8 (m, 2H, -CH_2-), 4.2 (t, 1H, -CH-), 5.5 (s, 1H, -CH-), 6.2 (s, 2H, Ar-H), 7.0-7.3 (m, 11H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3031 (C-H in Ar-H), 2938 (C-H), 1215 (C-N), 1576 and 1448 (C-C in Ar), 1062 (C-O), 742 (C-H in Ar-H); EL-MS m/z (M^+): 305.14 (calcd. for $C_{20}H_{19}NO_2$: 305.37). Elem. analysis for $C_{20}H_{19}NO_2$: C-78.66, H-6.27, N-4.59; found: C-78.59, H-6.28, N-4.52.

3-Benzyl-2-(4-methoxyphenyl)-4-phenyloxazolidine (5): To get title compound, 4-methoxy benzaldehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 4.1 g of 3-benzyl-2-(4-methoxyphenyl)-4-phenyloxazolidine (**5**) was obtained as solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 3.6 (s, 2H, -CH_2-), 3.7 (s, 3H, -CH_3), 3.8 (m, 2H, -CH_2-), 4.2 (t, 1H, -CH-), 5.2 (s, 1H, -CH-), 6.7 (s, 2H, Ar-H), 7.0 -7.2 (m, 12H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3031 (C-H in Ar-H), 2939 (C-H), 2810 (C-H in -OCH_3), 1601, 1576 (C-C in Ar), 1217 (C-N), 1069 (C-O), 826 (C-H in Ar-H); 762 (C-H in Ar-H), EL-MS m/z (M^+): 345.17 (calcd. for $C_{23}H_{23}NO_2$: 345.43). Elem. analysis for $C_{23}H_{23}NO_2$: C-79.97, H-6.71, N-4.05; found: C-80.02, H-6.68, N-4.10.

3-Benzyl-2-(4-chlorophenyl)-4-phenyloxazolidine (6): To get title compound, 4-chloro benzaldehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 3.70 g of 3-benzyl-2-(4-chlorophenyl)-4-phenyloxazolidine (**6**) was obtained as solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 3.6 (s, 2H, -CH_2-), 3.7 (s, 2H, -CH_2-), 4.2 (t, 1H, -CH-), 5.2 (s, 1H, -CH-), 7.0 -7.2 (m, 14H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3039 (C-H in Ar-H), 2949 (C-H), 1606, 1571 (C-C in Ar), 1210 (C-N), 1059 (C-O), 836 (C-H in Ar-H); 761 (C-H in Ar-H), 750 (C-Cl), EL-MS m/z (M^+): 349.12 (calcd. for $C_{22}H_{20}ClNO$: 349.85). Elem. analysis for $C_{22}H_{20}ClNO$: C-75.53, H-5.76, Cl-10.13, N-4.00; found: C-75.62, H-5.81, Cl-10.09, N-4.08.

3-Benzyl-2-(3,4-dimethoxyphenyl)-4-phenyloxazolidine (7): To get title compound, 3,4-dimethoxy benzaldehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 2.5 g of 3-benzyl-2-(3,4-dimethoxyphenyl)-4-phenyloxazolidine (**7**) was obtained as solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 3.6 (s, 2H, -CH_2-), 3.7 (s, 6H, -CH_3), 3.8 (m, 2H, -CH_2-), 4.2 (t, 1H, -CH-), 5.2 (s, 1H, -CH-), 6.6 (s, 2H, Ar-H), 7.0-7.2 (m, 11H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3031 (C-H in Ar-H), 2938 (C-H), 2802 (C-H in -OCH_3), 1611, 1586 and 1456 (C-C in Ar), 1201 (C-N), 858 (C-H in Ar-H); 751 (C-H in Ar-H), EL-MS m/z (M^+): 375.18 (calcd. for $C_{24}H_{25}NO_3$: 375.46). Elem. analysis for $C_{24}H_{25}NO_3$: C-76.77, H-6.71, N-3.73; found: C-76.78, H-6.72, N-3.70.

3-Benzyl-4-phenyl-2-propyloxazolidine (8): To get title compound, butanaldehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 2.0 g of 3-benzyl-4-phenyl-2-propyloxazolidine (**8**) was obtained as solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 1.0 (t, 3H, -CH_3), 1.3 (m, 2H, -CH_2-), 1.5 (t, 2H, -CH_2-), 3.6 (s, 2H, -CH_2-), 3.8 (m, 2H, -CH_2-), 3.9 (s, 1H, -CH-), 4.2 (t, 1H, -CH-), 7.0 -7.2 (m, 10H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3036 (C-H in Ar-H), 2927 (C-H), 1602, 1581 and 1451 (C-C in Ar), 1212 (C-N), 1062 C-O), 748 (C-H in Ar-H); EL-MS m/z (M^+): 281.18 (calcd. for $C_{19}H_{23}NO$: 281.39). Elem. analysis for $C_{19}H_{23}NO$: C-81.10, H-8.24, N-4.98; found: C-81.15, H-8.21, N-4.95.

3-((Furan-2-yl) methyl)-4-phenyl-2-propyloxazolidine (9): To get title compound, furan-2-carboxaldehyde was used in step-2 instead of benzaldehyde and butanaldehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 1.70 g of 3-((furan-2-yl)methyl)-4-phenyl-2-propyloxazolidine (**9**) was obtained as solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 1.0 (t, 3H, $-CH_3$), 1.3 (m, 2H, $-CH_2-$), 1.5 (t, 2H, $-CH_2-$), 3.4 (s, 2H, $-CH_2-$), 3.8 (m, 2H, $-CH_2-$), 3.9 (s, 1H, -CH-), 4.2 (t, 1H, -CH-), 6.0 - 6.2 (s, 2H, Ar-H), 7.0-7.4 (m, 6H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3028 (C-H in Ar-H), 2931 (C-H), 1609, 1579 and 1451 (C-C in Ar), 1226 (C-N), 1062 (C-O), 752 (C-H in Ar-H); EL-MS m/z (M^+): 271.16 (calcd. for $C_{17}H_{21}NO_2$: 271.35). Elem. analysis for $C_{17}H_{21}NO_2$: C-75.25, H-7.80, N-5.16; found: C-75.21, H-7.82, N-5.18.

3-((Furan-2-yl)methyl)-2,4-diphenyloxazolidine (10): To get title compound, furan-2-carboxaldehyde was used in step-2 instead of benzaldehyde and benzaldehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 1.0 g of 3-((furan-2-yl)methyl)-2,4-diphenyloxazolidine (**10**) was obtained as solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 3.4 (s, 2H, $-CH_2-$), 3.8 (m, 2H, $-CH_2-$), 4.2 (s, 1H, -CH-), 5.2 (s, 1H, -CH-), 6.0 - 6.2 (s, 2H, Ar-H), 7.0 -7.4 (m, 11H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3028 (C-H in Ar-H), 2931 (C-H), 1609, 1579 and 1452 (C-C in Ar), 1226 (C-N), 1062 (C-O), 752 (C-H in Ar-H); EL-MS m/z (M^+): 305.14 (calcd. for $C_{20}H_{19}NO_2$: 305.14). Elem. analysis for $C_{20}H_{19}NO_2$: C-78.66, H-6.27, N-4.59; found: C-78.64, H-6.25, N-4.63.

3-((Furan-2-yl)methyl)-2-(4-methoxyphenyl)-4-phenyloxazolidine (11): To get title compound, furan-2-carboxaldehyde was used in step-2 instead of benzaldehyde and 4-methoxy benzaldehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 1.6 g of 3-((furan-2-yl)methyl)-2-(4-methoxyphenyl)-4-phenyloxazolidine (**11**) was obtained as solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 3.4 (s, 2H, $-CH_2-$), 3.7 (s, 3H, $-CH_3$), 3.9 (m, 2H, $-CH_2-$), 4.2 (s, 1H, -CH-), 5.2 (s, 1H, -CH-), 6.0-6.2 (s, 2H, Ar-H), 6.70 (d, 3H, Ar-H), 7.0-7.4 (m, 7H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3035 (C-H in Ar-H), 2936 (C-H), 2812 (C-H in $-OCH_3$); 1604, 1580 and 1402 (C-C in Ar), 1225 (C-N), 842 (C-H in Ar-H), EL-MS m/z (M^+): 335.15 (calcd. for $C_{21}H_{21}NO_3$: 335.4). Elem. analysis for $C_{21}H_{21}NO_3$: C-75.20, H-6.31, N-4.18; found: C-75.25, H-6.28, N-4.19.

5-(3-((Furan-2-yl)methyl)-4-phenyloxazolidin-2-yl)-2-methoxyphenol (12): To get title compound, furan-2-carboxaldehyde was used in step-2 instead of benzaldehyde and 3-hydroxy-4-methoxy benzaldehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 4.0 g of 5-(3-((furan-2-yl)methyl)-4-phenyloxazolidin-2-yl)-2-methoxyphenol (**12**) was obtained as solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 3.4 (s, 2H, $-CH_2-$), 3.7 (s, 3H, $-CH_3$), 3.9 (m, 2H, $-CH_2-$), 4.2 (s, 1H, -CH-), 5.0 (s, 1H, -OH), 5.3 (s, 1H, -CH-), 6.0-6.2 (s, 2H, Ar-H), 6.6 (d, 3H, Ar-H), 7.0-7.4 (m, 6H, Ar-H) IR (KBr, ν_{max}, cm^{-1}): 3642 (O-H); 3035 (C-H in Ar-H), 2933 (C-H), 2810 (C-H in $-OCH_3$), 1604, 1584 and 1410 (C-C in Ar), 1221 (C-N), 763 (C-H in Ar-H), EL-MS m/z (M^+): 351.15 (calcd. for $C_{21}H_{21}NO_4$: 351.4). Elem. analysis for $C_{21}H_{21}NO_4$: C-71.78, H-6.02, N-3.99; found: C-71.79, H-6.08, N-3.91.

3-(4-Methoxyphenyl)-2,4-diphenyloxazolidine (13): To get title compound, 4-methoxy benzaldehyde was used in step-2 instead of benzaldehyde and benzaldehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 1.2 g of 3-(4-methoxyphenyl)-2,4-diphenyloxazolidine (**13**) was obtained as solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 3.7 (s, 3H, $-CH_3$), 4.0 (m, 2H, $-CH_2-$), 4.2 (t, 1H, -CH-), 5.2 (s, 1H, -CH-), 6.4 (d, 2H, Ar-H), 6.6 (d, 2H, Ar-H), 7.0-7.2 (m, 10H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3030 (C-H in Ar-H), 2948 (C-H), 2812 (C-H in $-OCH_3$), 1601, 1582 and 1458 (C-C in Ar), 1204 (C-N), 848 (C-H in Ar-H); 731 (C-H in Ar-H), EL-MS m/z (M^+): 331.16 (calcd. for $C_{22}H_{21}NO_2$: 331.41). Elem. analysis for $C_{22}H_{21}NO_2$: C-79.73, H-6.39, N-4.23; found: C-79.79, H-6.29, N-4.26.

3-Pentyl-2,4-diphenyloxazolidine (14): To get title compound, pentanaldehyde was used in step-2 instead of benzaldehyde and benzaldehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 0.90 g of 3-pentyl-2,4-diphenyloxazolidine (**14**) was obtained as solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 0.96 (t, 3H, $-CH_3$), 1.2-1.4 (m, 6H, $-CH_2-$), 2.4 (t, 2H, $-CH_2-$), 3.7 (d, 2H, $-CH_2-$), 4.2 (t, 1H, -CH-), 5.2 (s, 1H, -CH-), 7.0 -7.2 (m, 10H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3038 (C-H in Ar-H), 2936 (C-H), 1583 and 1450 (C-C in Ar), 1203 (C-N), 734 (C-H in Ar-H); EL-MS m/z (M^+): 295.19 (calcd. for $C_{20}H_{25}NO$: 295.42). Elem. analysis for $C_{20}H_{25}NO$: C-81.31, H-8.53, N-4.74; found: C-81.29, H-8.49, N-4.77.

3-Benzyl-4-phenyl-2-((Z)-prop-1-enyl)oxazolidine (15): To get title compound, 2-butenaldehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 2.65 g of 3-benzyl-4-phenyl-2-((Z)-prop-1-enyl)-oxazolidine (**15**) was obtained as solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 1.7 (m, 3H, $-CH_3$), 3.6 (s, 2H, $-CH_2-$), 3.8 (m, 2H, $-CH_2-$), 4.2 (s, 1H, -CH-), 5.7 (m, 2H, -CH=CH-), 7.0-7.2 (m, 10H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3045 (CH=CH *cis*), 3030 (C-H in Ar-H), 2929 (C-H), 1602, 1581 and 1450 (C-C in Ar), 1222 (C-N), 1060 (C-O), 758 (C-H in Ar-H); EL-MS m/z (M^+): 279.16 (calcd. for $C_{19}H_{21}NO$: 279.38). Elem. analysis for $C_{19}H_{21}NO$: C-81.68, H-7.58, N-5.01; found: C-81.66, H-7.61, N-5.08.

3-Hexyl-2,4-diphenyloxazolidine (16): To get title compound, hexanaldehyde was used in step-2 instead of benzaldehyde and benzaldehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 1.1 g of 3-hexyl-2,4-diphenyloxazolidine (**16**) was obtained as solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 0.96 (t, 3H, $-CH_3$), 1.2-1.4 (m, 8H, $-CH_2-$), 2.4 (t, 2H, $-CH_2-$), 3.7 (d, 2H, $-CH_2-$), 4.2 (t, 1H, -CH-), 5.2 (s, 1H, -CH-), 7.0 -7.2 (m, 10H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3038 (C-H in Ar-H), 2946 (C-H), 1583 and 1450 (C-C in Ar), 1203 (C-N), 738 (C-H in Ar-H); EL-MS m/z (M^+): 309.21 (calcd. for $C_{21}H_{27}NO$: 309.45). Elem. analysis for $C_{21}H_{27}NO$: C-81.51, H-8.79, N-4.53; found: C-81.55, H-8.75, N-4.58.

(Z)-3-Benzyl-2-ethylidene-4-phenyloxazolidine (17): To get title compound, 2-propenaldehyde was used in step-4 instead of bromo propanaldehyde in the above general synthesis 0.75 g of (Z)-3-benzyl-2-ethylidene-4-phenyloxazolidine (**17**) was obtained as solid and structure was confirmed by following analysis. ^{1}H NMR ($CDCl_3$) δ: 1.7 (d, 3H, $=CH_3$), 3.2 (d, 1H, -CH=), 3.8 (s, 2H, $-CH_2-$), 4.2-4.5 (m, 3H, $-CH_2-$ and -CH-), 7.0-7.2 (m, 10H, Ar-H). IR (KBr, ν_{max}, cm^{-1}): 3044

(CH=CH *cis*), 3032 (C-H in Ar-H), 2943 (C-H), 1615, 1578 and 1452 (C-C in Ar), 1212 (C-N), 753 (C-H in Ar-H); EL-MS m/z (M^+): 265.15 (calcd. for $C_{18}H_{19}NO$: 265.35). Elem. analysis for $C_{18}H_{19}NO$: C-81.47, H-7.22, N-5.28; found: C-81.51, H-7.23, N-5.25.

Cardiac activity: The study was conducted on frogs (*Rana tigriva*) weighing between 200-260 g. The experimintal procedures were approved by insitutional animals ethical committee and the experiments were conducted in an institution approved by CPCSEA (commettee for the purpose of control and supervision of experiments on animals).

The frogs were pithed so as to destroy the central nervous system without causing any injury to their heart and associated blood vessels. The sternum was completely removed and the pericardium was cut open exposing the heart. The liver was pushed aside from the inferior vena Cava as far as hepatic veins. A small cut was made into the venous sinuses, symes canula was inserted towards the heart and isolated. A steady flow of perfusion (frog ringer)[12], was perfused through this canula. Through the opening of the canula, digoxin, standard drug compounds, standard could be injected by pushing a capillary tube attached to a syringe through an injection needle. A small hook was attached to the tip of beating heart which was tied with a thread. The other end of the thread was attached to the storling heart lever so that the movements of the beating heart could be recorded on a Kymographic paper. The force of contraction was recorded and the rate of contraction[13] was counted and tabulated.

Entire experimental study was carried out in the following stages: A stabilizing period of 15 min was allowed. After basal recording, the heart was perfused with Ringer solution. The heart was then perfused with calcium channel blocker (nifedipine) and its antagonizing effect on the digoxin induced positive inotropic effect was studied. The compounds (**1-17**) were then administered as usual.

Data analysis: The cardiac effects of digoxin, standard and compounds (**1-17**) were compared with that of basal values. The data was analysed by using one way analysis of varience (ANOVA) followed by Tukey best. A value $p < 0.05$ was considered and staistically significant. Control valve HR (heart rate): 43.6 ± 1.288 beats/min. FOC (force of contraction): 17.4 ± 1.0877 mm values are mean ± SEM.

RESULTS AND DISCUSSION

From the results obtained, the following was deduced. The mean basal value of amplitute of contraction was 17.40 ± 1.08 mm and heart rate was 43.60 ± 1.28 beats/min, respectively. Administration of synthesized compounds (**1-17**) showed a significant decrease in a dose of 500 µg/mL in the mean force of contraction of the heart and on the heart rate. The positive inotropic effect of digoxin (1.28×10^{-5} m) was antagonized by the calcium channel blocker indicating the involvement of Ca^{2+} channels in its mechanism of action. Similarly when synthesized compounds (**1-17**) at a dosage of 500 µg/mL were administered, positive inotopic effect of digoxin was antagonized by the compounds and also the heart rate was also reduced significantly by the synthesized compounds. Further among the synthesized compounds, compounds **11** and **12** shows negative inotropic and chromotropic effect more than that of standard. Compounds **9** and **10** show activity almost similar to that of standard. While all the synthesized compounds shows a significant activity.

When myocardium is excited, action potential is generated followed by contraction of myocardium. In the process one electrical and other mechanical event occurs coupled ® together and the coupling agent is calcium. Na^+K^+ ATPase inhibition by digoxin leads ultimately to increase intracellular Ca^{2+} concentration through Na^+/Ca^{2+} exchange and associated increase in slow inward Ca^{2+} current[14,15] as well as in transient Ca^{2+} current. This is a general mechanism that most cells use to amplify Ca^{2+} signals. In heart cells, this mechanism is operated between voltage- gated L-type calcium channels[16]. Nifedipine is an L-type calcium channel antagonized compounds. In the present investigation all the synthesized compounds antagonized the positive inotropic effect of digoxin and also show a significant decrease in heart rate and the activity is comparable with that of standard nifidipine that the compounds might have produced their action by involvement of calcium channels.

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