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Synthesis Development, Spectroscopy Characterizations, and Molecular Docking Study of Some New Bis-1,3-Oxazepine and Bis-1,3-Benzoxazepine Derivatives

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ABSTRACT

Several novel Bis-Oxazepine and Bis-Benzoxazepine derivatives have been produced by condensation and cyclization processes over two effective practical stages. The first stage involved utilizing the Dean-Stark apparatus to create imine intermediates through the condensation reactions of 3-hydroxy benzaldehyde with various aromatic diamine substrates in the presence of glacial acetic acid as a catalyst. The second stage required treatment of bis-Schiff base intermediate with maleic- or phthalic anhydride in dry benzene to produce the desired Bis-Oxazepine and Bis-Benzoxazepine derivatives with 70-95% yields using microwave irradiation. The molecular docking of the produced chemicals was conducted against the progesterone receptor. The results indicate potential anticancer properties for three compounds, which show the most promising findings. These compounds obtained higher docking scores (ΔG–9.58, –9.28, and –9.11 kcal/mol), forming three hydrogen bonds with the target protein.

Keywords: 3-hydroxy benzaldehyde, Bis-Schiff bases, Dean-Stark apparatus, Microwave irradiation, Bis-Oxazepine, Bis-Benzoxazepine, Cyclization process.

INTRODUCTION

Heterocyclic compounds are essential organic molecules that are used in various applications.[1] Oxazepine is a seven-member heterocyclic molecule with one nitrogen atom, one oxygen atom, and five carbon atoms.[2] Meanwhile, benzoxazepine is a bicyclic heterocyclic molecule composed of a benzene ring fused with an Oxazepine ring. Oxazepine has three different isomers: (1,2), (1,3) and (1,4), depending on the position of the nitrogen atom. Atoms of oxygen and nitrogen are precisely positioned in the seven-ring, which is the basis for this numbering.[3] (Figure 1).

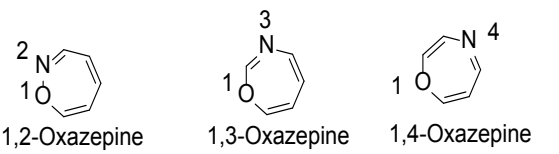
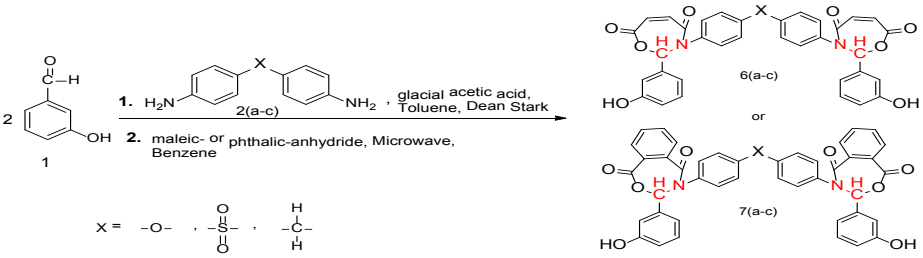


Fig. 1. Structure of various Oxazepine Derivatives

Various Bis-Oxazepine and Bis-Benzoxazepine compounds were synthesized

and assessed for different biological activities.[4] Some chemical derivatives have demonstrated strong biological activity, like anticonvulsant[5], antimicrobial[6], anticancer[7], antipsychotic agents[8], calcium antagonists, and neuroprotective.[9] Because of the significance of oxazepine and benzoxazepine, several synthetic procedures for their production have been developed.[10]

Due to the preparation and biological consequences of Bis-Oxazepine and Bis-Benzoxazepine compounds generating significant attention, our current study is the development, synthesis, and characterization of new Bis-oxazepine and Bis-benzoxazepine derived from Schiff bases[11–13], using two critical approaches: condensation[13-15] and cyclization reaction processes[17] (Scheme 1).

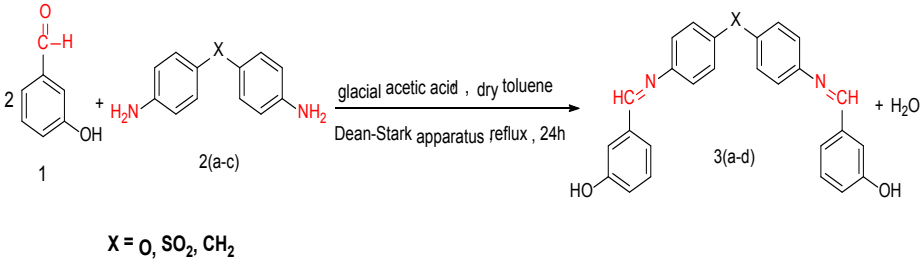


Scheme 1. Synthetic Route of Bis-oxazepine and Bis-benzaoxazepine Derivatives from 3-hydroxybenzaldehyde

RESULTS AND DISCUSSION

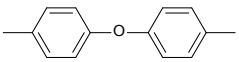
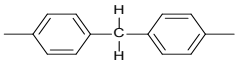
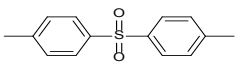
Chemistry

This research presents a novel approach for synthesizing bis-oxazepine and Bis-benzoxazepine compounds from bis-Schiff base over two practical processes. First step involved the treatment of 3-hydroxybenzaldehyde with various aromatic diamines 2(a-c) with a few drops of glacial acetic acid. under refluxing with toluene as a solvent and using Dean-Stark apparatus[18–20]. This step demonstrated a successful technique and supplied pure desired products 3(a-c) (73-88%) followed by a purification process through recrystallization from ethanol (Scheme 2 & Table 1). IR spectra of Schiff bases compounds 3(a-c) Medium bands appeared at 1627-1625 cm^{-1} attributed to the vibration of stretching of the imine group (C=N). The absorption bands were observed within the A spectrum of (1599-1593), (3047-3036), (2920-2910) cm^{-1} about the motion of stretching aromatic. (C=N), aromatic(C=N), and aliphatic(C-H) bonds, constantly Fig. 2. The ^{1}HNMR spectra of Schiff bases intermediate 3(a-c) detected new peaks with chemical imine signal positions at (8.57–8.51) ppm, which were compatible with the (CH=N) functional group. The appearance of additional signals for protons in the aromatic region, resulting in chemical shift at (8.01-6.92) ppm due to the aromatic structure of these compounds, Figure 3,4.



Scheme 2. Synthesis of Bis-Schiff Bases from 3-hydroxybenzaldehyde

Table 1: The physical properties of Bis-Schiff base products 3(a-c)

Products No	-X-	M.wt(gm/mol)	m.p.(°C)	Color	R_f	Yield%
3a		408	165 dec	Pale yellow	0.5	85
3b		406	197-199	White	0.6	88
3c		456	200-202	Pink	0.27	73

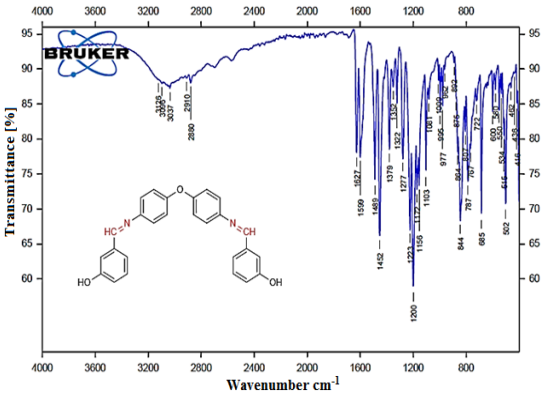


Fig. 2. FT-IR spectrum for Schiff base compound (3a)

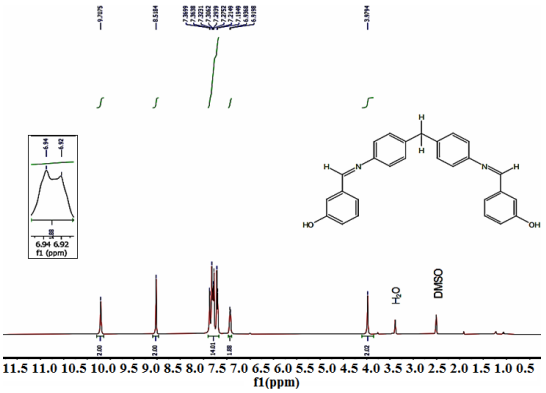


Fig. 3. ^{1}H-NMR (400 MHz, DMSO) Spectrum for Compound (3b)

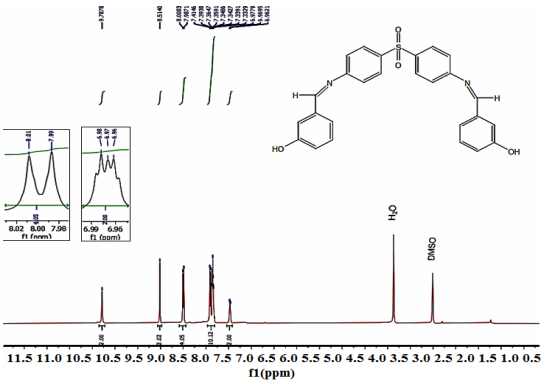
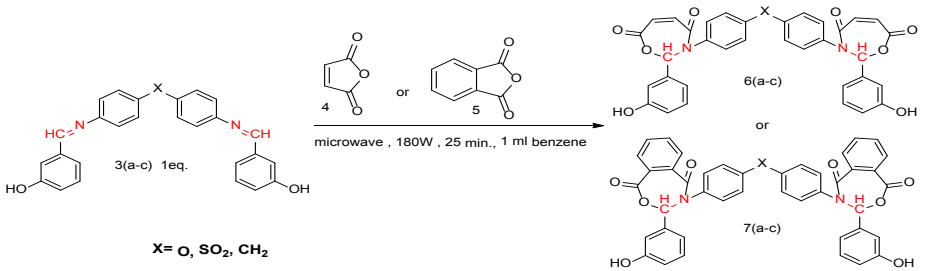


Fig. 4. ^{1}H-NMR(400 MHz, DMSO) Spectrum for Compound (3c)

While the Bis-1,3-Oxazepine 6(a-c) and Bis-1,3-Benzoxazepine 7(a-c) products were created at the last step by using microwave irradiation protocol, by reaction of Bis-imines 3(a-c) with maleic-or phthalic-anhydride and a small amount of drying benzene as a solvent after applying the purification method. This step (cyclization process) produced the expected products with acceptable yields 6(a-c) and 7 (a-c) (70-95%) (Scheme 3 and Table 2, 3). The ^{1}H-NMR analysis showed new and extra proton Signal peaks related to chemical shifts at (8.61-8.49) and (8.01-6.91) ppm which belong to the CH peak inside the Oxazepine and Benzoxazepine heterocyclic ring and aromatic ring region correspondingly Fig. 5. Moreover, In ^{13}C-NMR the appearance peaks of the new carbon signal with the corresponding chemical changes at (169.11-160.11) and (167.98-158.14) ppm for C=O of lactone and lactam respectively, as well as, the appearance of new signal with chemical changes at (114.65-114.64) ppm which belong to the CH in the 1,3-Oxazepine and 1,3-Benzoxazepine heterocyclic ring. Finally, the appearance of extra signal peaks with the chemical shifts at (160.63-115.11) ppm due to the aromatic region, Fig. 6, which sustained the structures of the desired products in 6(a-c) and 7(a-c), Scheme 3.



Scheme 3. Synthesis of New Bis 1,3-Oxazepine and Bis 1,3-Benzoxazepine from Schiff Bases

Table 2: The physical properties of the synthesized Bis 1,3-Oxazepine 6(a-c) and Bis1,3-Benzoxazepine 7(a-c) from 3-hydroxybenzaldehyde

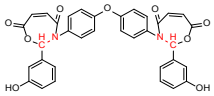
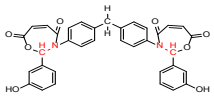
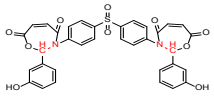
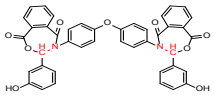
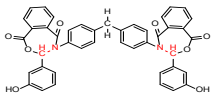
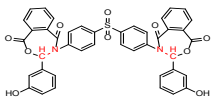
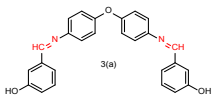
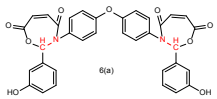
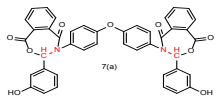
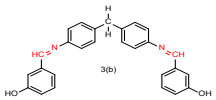
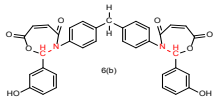
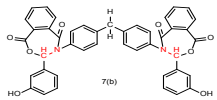
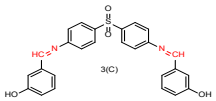
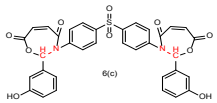
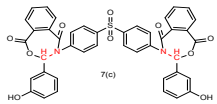
No	Products	M.wt.(g/mole)	m.p.	Color	R_f	Yields%
6(a)		604.12	196-198	cumin	0.47	70
6(b)		602.12	204-206	Yellow	0.58	86
6(c)		652.12	230-232	Off-white	0.55	95
7(a)		704.2	190-192	Deep yellow	0.41	75
7(b)		702.2	202-204	Yellow-green	0.6	83
7(c)		752.2	216-218	Pale-yellow	0.41	93

Table 3: The Bis 1,3-Oxazepine 6(a-c) and Bis 1,3-Benzoxazepine 7(a-c) derived from Bis-Schiff bases intermediates

Entry	Bis-Schiff bases	Bis 1,3-Oxazepine	Bis 1,3-benzoxazepine
1			
2			
3			

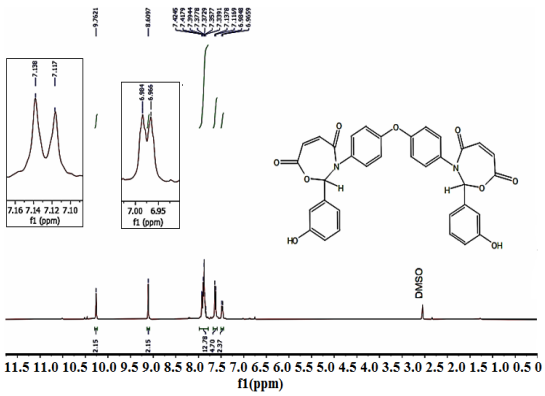


Fig. 5. ^{1}H-NMR (400 MHz, DMSO) Spectrum for Compound (6a)

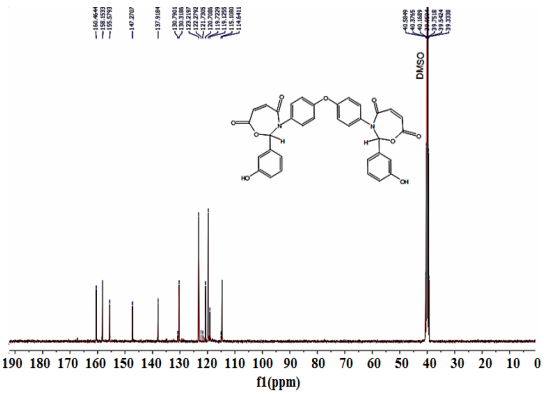


Fig. 6. ^{13}C-NMR (100.2 MHz, DMSO) Spectrum for Compound (6a)

Analysis and interpretation of molecular Docking

A comprehensive set of progesterone receptor (PDB ID: 4OAR) was subjected to docking, leading to the identification of three compounds.

Notably, the docking poses of these three hit compounds exhibited interactions remarkably similar to those of other anti-breast cancer compounds. Molecular docking analysis was conducted to assess the potential of these molecules in combating breast cancer.The docking process focused on a phytosterol isolated from Lagerstroemia speciosa seed ethanolic extract, aiming at the 4OAR binding pocket, a protein associated with breast cancer. All tested molecules exhibited binding scores greater than –9.11 when bound to 4OAR, with hydrophobic interactions observed with residues such as LEU718, CYS891, ASN719, ARG899, SER712, LEU887, MET759, and MET756. Notably, Diosgenin, a powerful anti-breast cancer chemical, and its derivatives reached an upper binding score of –9.58, forming hydrogen bonds with 4OAR at GLN725 and GLN916.

It is important to note which ligand-protein complexes display the lowest number of hydrophobic interactions when their binding scores are highest. These two- and three-dimensional ligand structures bind most strongly (7c) in complex with the protein presented in (Table 4).[21–23] The docking analysis reveals that all compounds in Fig. (7,8, and 9) bind to the amino acid active site in breast cancer.[24–26] Various types of bonds are involved, including van der Waals, carbon-hydrogen, π-alkyl, and most importantly, hydrogen bonds. Figure (7,8, and 9).

Table 4: Molecular Docking result data for Bis 1,3-Oxazepine and Bis-1,3-Benzoxazepine

Compound No	G[Kcal/mol]	Residue
7a	-9.28	LEU718, CYS891, ASN719, ARG899, SER712, LEU887, MET759, and MET756.
6b	-9.11	THR716, LEU715, LEU718, GLN725, MET759, LEU797 and ARG899
7c	-9.58	LEU718, CYS891, PHE895, GLN916, ALA915, VAL912, MET795, MET801 and GLN725

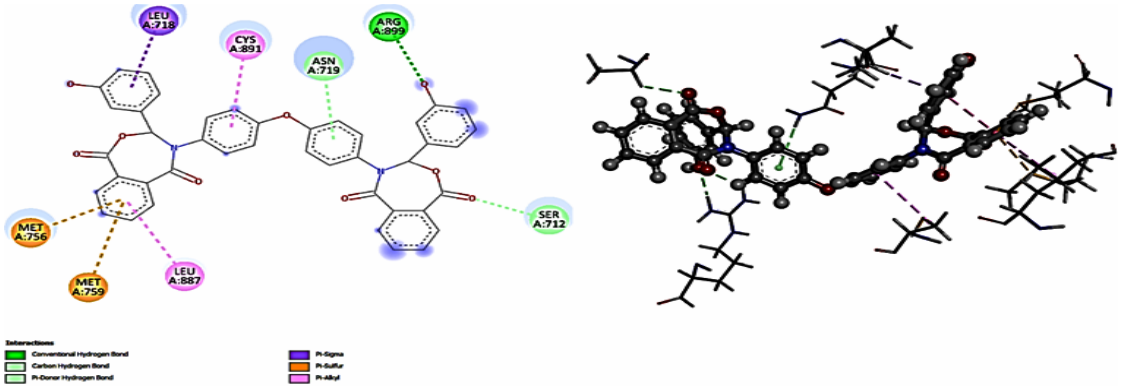


Fig. 7. Molecular docking of compound 7a with progesterone receptor in 2D and 3D

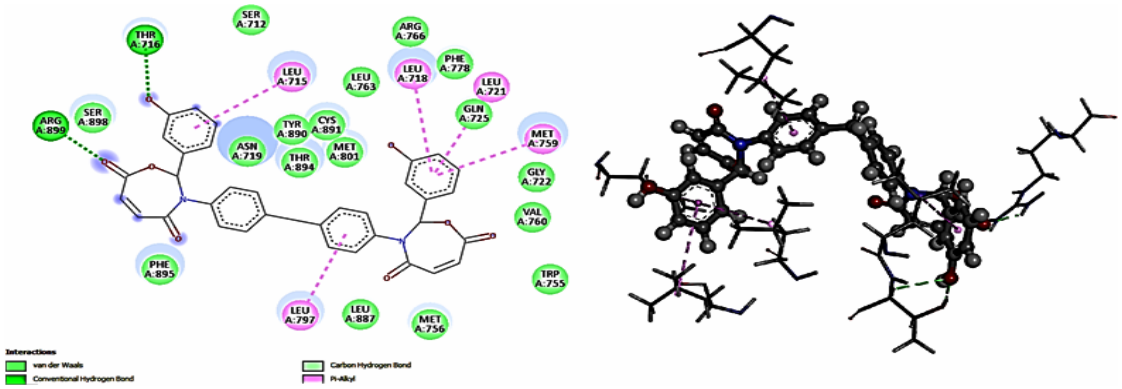


Fig. 8. Molecular docking of compound 6b with progesterone receptor in 2D and 3D

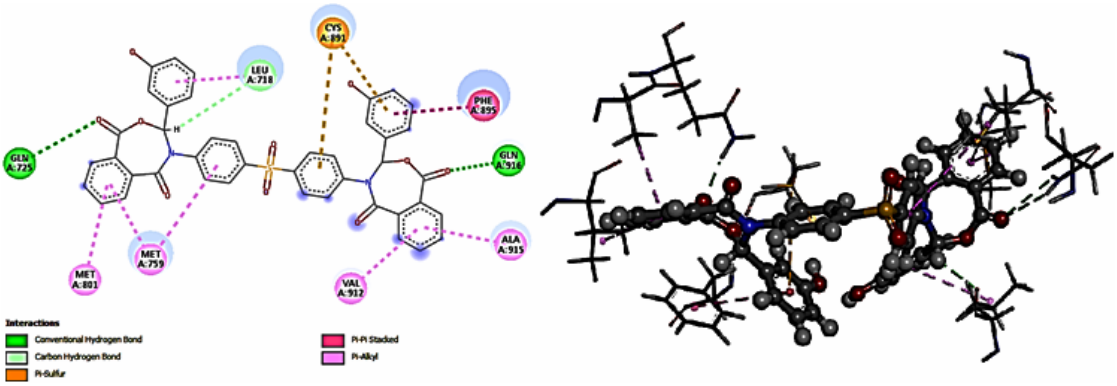


Fig. 9. Molecular docking of compound 7c with progesterone receptor in 2D and 3D

Experimental Materials and Methods

All reactions took place in anhydrous, dry conditions with the use of solvents. Commercial reagents weren't purified before usage. As an absolute solvent, ethanol was utilized. Electrothermal apparatus has been used for melting points determination, which may be uncorrected. Bruker DPX-300FT-NMR spectrometers have been used to generate ^{1}H- and ^{13}C-NMR spectra at 400 and 100.2 MHz. The Spectrum was recorded in $CDCl_3$. IR spectra were recorded using a 1710-FTIR Perkin-Elmer spectrometer. Merck Kiese gel 60 F254 Thin Layer Chromatography (TLC) on aluminum foil from Macherey-Nagel. UV light at 254 & 365 nanometers was used for detection.

Synthesis

General procedure for synthesizing Bis-Schiff bases 3(a-c)

A solution of 3-hydroxybenzaldehyde 1(0.073 g, 0.6 mmol, 2 eq.) was added by dropping it to an aromatic diamine substitutes solution (2-4) (0.059 g, 0.3 mmol, 1 eq.) in dry toluene (60ml) with stirring using Dean-Stark apparatus at room temp. Subsequently, the mixture was refluxed overnight after being treated with a few drops of glacial acetic acid. It was used to monitor the progress of the reaction by TLC (PE: EtOAc 60:40). The crude products were obtained after evaporating the solvent under the vacuum followed by purification twice using ethanol, Hot filtration, and recrystallizing protocols using ethanol absolute were employed to generate the required Bis-Schiff base products 3(a-c) (Table 1).27–29

3,3'-((oxybis(4,1-phenylene))bis(azanylylidene)) bis(methanylylidene))diphenol 3(a)

Pale-yellow, yield (81%), R_f = 0.43, m.p. (165-166)°C. IR (cm^{-1}) = 3126 ($O\text{-}H_{broad}$), 3037 ($C\text{-}H_{ar}$), 2910 ($C\text{-}H_{aliph}$), 1627 (C=N), 1599-1552 ($C{=}C_{ar}$), 1200 ($C\text{-}O_{str}$), ^{1}HNMR (400 MHz, DMSO) (ppm) = 9.73(s, 2H, 2OH), 8.57 (s, 2H, 2(N=CH)), 7.39-7.30 (m, 10H, CH_{aro}), 7.08 (d, 4H, J = 8 Hz, CH_{aro}), 6.94 (d., 2H, J = 7.6 Hz, CH_{aro}).

3,3'((methylenebis(4,1phenylene))bis(azanyly -lidene))bis(methanylylidene))diphenol 3(b)

White, yield = (88%), R_f = 0.42, m.p. (197-199)°C. IR (cm^{-1}) = 3273 ($O\text{-}H_{broad}$), 3024 ($C\text{-}H_{ar}$), 2907 ($C\text{-}H_{aliph}$), 1624 (C=N), 1591-1576 ($C{=}C_{aro}$), ^{1}HNMR (400 MHz, DMSO) (ppm) = 9.71 (s, 2H, 2OH), 8.52 (s, 2H, 2(N=CH)), 7.37-7.20 (m, 14H, CH_{aro}), 6.93 (d, 2H, J = 6.8 Hz, CH_{aro}), 3.98 (s, 2H, CH_2).

3,3'-((sulfonylbis(4,1-phenylene))bis(azanyly -lidene))bis(methanylylidene))diphenol 3(c)

Pink, yield = (73%), R_f =0.27, m.p. (200-202)°C. IR. (cm^{-1}) = 3286 ($O\text{-}H_{broad}$), 3025 ($C\text{-}H_{ar}$), 2977 ($C\text{-}H_{aliph}$), 1626 (C=N), 1596-1578 (C=Car), ^{1}HNMR (400 MHz, DMSO) (ppm) = 9.79(s, 2H, 2OH), 8.51(s, 2H, 2(N=CH)), 7.99 (d, 4H, J = 8.4 Hz, CH_{aro}), 7.41-7.33 (m, 10H.CH_{aro}), 6.97 (t, 2H, J= 6.4Hz CHaro).

General procedure for preparation of Bis-Oxazepine 6(a-c) and Bis-Benzoxazepine 7(a-c).

In the crucible with dry benzene (1 mL), appropriate Schiff bases (0.123 mmole, 1eq.) 3(a-c), maleic- or phthalic anhydride (0.246 mmole, 2eq.) were dissolved. The solution was exposed to microwave irradiation at 180W for about 25 minute. The reaction process was monitored using TLC (PE: EtOAc 60:40). The crude products were obtained after evaporating the solvent below the vacuum, followed by purification twice using ethanol

absolute.to give the expected products 6(a-c) and 7(a-c). The physical properties of Bis-Oxazepine 6(a-c) and Bis-Benzoxazepine 7(a-c) are shown in (Table 2).[30–34]

3,3'-(oxy bis(4,1-phenylene)) bis(2-(3-hydroxyphenyl)-2,3-dihydro- 1,3-oxazepine-4,7-dione) (6a)

Cumin color, yield = (70%), R_f = 0.47, m.p. (196-198)°C. IR (cm^{-1}) = 3126 (O-H_{broad}), 3025 (C-H_{ar}), 2880 (C-H_{aliph}), 1711 (C=$O_{lactone}$), 1675 (C=O_{lactam}), 1598-1451 (C=C_{aro}), ^{1}HNMR (400 MHz, DMSO) (ppm) = 9.76(s, 2H, 2OH), 8.61 (s, 2H, 2 (N-CH)), 7.42-7.43 (m, 13H, CH), 7.13 (d, 5H. J = 8.4 Hz CHaro), 6.98-6.96 (d, 2H, J = 7.2,CHar). ^{13}C NMR (100.2, DMSO) = 160.46 (C=Olactone), 158.15 (C=O_{lactam}), 155.58(C_{ar}), 147.27(C_{aro}), 137.92(C_{aro}), 130.79(C_{aro}), 130.32(C_{aro}), 123.22 (2C_{aro}), 122.28(C_{aro}), 121.73(C_{aro}), 120.71(C_{aro}), 119.72(2C_{aro}), 119.13(C_{aro}), 115.11(C_{aro}), 114.64 ($C_{oxazepine\ ring}$).

3,3'-(methylenebis(4,1-phenylene))bis(2-(3-hydroxyphenyl)-2,3-dihydro-1,3 oxazepine-4,7-dione) (6b)

Yellow, yield = 83%, R_f = 0.6, m.p.(204-206)°C. IR (cm^{-1}) = 3273 (O-H_{broad}), 3025 (C-H_{ar}), 2921 (C-H_{aliph}), 1703 (C=$O_{lactone}$),1667 (C=O_{lactam}), 1589-1452 (C=C_{aro}), ^{1}HNMR (400 MHz, DMSO) (ppm) = 9.70(s, 2H, 2OH), 8.52 (s, 2H, 2 (N-CH), 7.54 (d, 2H, J = 8.4Hz CH_{aro}), 7.37-7,17 (m, 16H, CH_{aro}), 6.925 (d, 2H, J = 6.4Hz CHaro). ^{13}C NMR (100.2, DMSO) = 160.63 (C=$O_{lactone}$), 158.14 (C=O_{lactam}), 149.85(C_{aro}), 139.71(C_{aro}), 137.93(C_{aro}), 130.31(C_{aro}), 129.94(2C_{aro}), 129.38 (C_{aro}), 128.69(C_{aro}), 125.80(C_{aro}), 121.63(2C_{aro}), 120.69(C_{aro}), 120.19(C_{aro}), 119.11(C_{aro}), 114.64 ($C_{oxazepine\ ring}$), 40.60($C_{methane}$).

3,3'-(sulfonylbis(4,1-phenylene))bis(2-(3-hydroxyphenyl)-2,3-dihydro-1,3-oxazepine-4,7-dione) (6C).

Off-white, yield = 95%, R_f = 0.55, m.p.(230-232)°C. IR (cm^{-1}) = 3388 (O-H_{broad}), 3049 (C-H_{aro}), 2958 (C-H_{aliph}), 1724 (C=$O_{lactone}$),1694 (C=O_{lactam}), 1597-1557 (C=C_{aro}), ^{1}HNMR (400 MHz, DMSO) (ppm) = 9.78(s, 2H, 2OH), 8.50. (s, 2H, 2(N-CH)), 7.99 (d, 2H, J = 8Hz CH_{aro}), 7.90-7.81 (m, 3H, CH_{aro}), 7.58-6.96 (m, 15H, CH_{aro}). ^{13}C NMR (100.2, DMSO) = 165.06 (C=$O_{lactone}$), 158.45 (C=O_{lactam}), 156.55(C_{aro}), 139.81(C_{aro}), 137.83(C_{aro}), 130.86(C_{aro}), 129.18 (2C_{aro}),126.13(C_{aro}), 125.79 (C_{aro}), 123.11 (2C_{aro}), 122.49(C_{aro}), 121.17(C_{aro}), 119.50(C_{aro}), 116.18(C_{aro}), 113.47(C-$N_{oxazepine\ ring}$).

4,4'-(oxybis (4,1-phenylene))bis(3-(3-hydroxyphenyl) -3,4-dihydrobenzo [e][1,3] oxazepine-1,5-dione) (7a)

Deep Yellow, yield = 75%, R_f =0.41, m.p. (190-192)°C. IR (cm^{-1}) = 3126 (O-H_{broad}), 3025 (C-H_{aro}), 2977 (C-H_{aliph}), 1716 (C=$O_{lactone}$), 1684 (C=O_{lactam}), 1597-1557 (C=C_{aro}). ^{1}H-NMR: d (ppm) = 9.69 (s,2H, 2OH), 8.57 (s, 2H, 2(N=CH)), 7.38-7.25 (m, 16H. CH_{aro}), 7.09 (d, 5H, J = 8.4Hz CH_{aro}), 6.95-6.92 (m, 2H, CH_{aro}). ^{13}C NMR (100.2, DMSO) = 160.46 (C=$O_{lactone}$), 158.15 (C=O_{lactam}) 155.58(C_{aro}), 147.28(C_{aro}), 137.93(C_{aro}), 130.31(C_{aro}), 129.38(C_{aro}), 128.68(C_{aro}), 125.79 (C_{aro}), 123.22 (2C_{aro}), 122.95(C_{aro}),122.27(C_{aro}), 121.30(C_{aro}), 120.70(C_{aro}), 119.72(2C_{aro}), 119.12(C_{aro}), 117.54(C_{aro}), 115.40(C_{aro}), 114.65(C-$N_{oxazepine\ ring}$).

4,4'-(methylenebis(4,1-phenylene))bis(3-(3-hydroxyphenyl)-3,4-dihydrobenzo[e] [1,3] oxazepine-1,5-dione) (7b)

Yellow-green, yield = 83%, R_f = 0.6, m.p. (202-204)°C. IR (cm^{-1}) 3273 (O-H_{broad}), 3025 (C-Har), 2977 (C-H_{aliph}), 1714 (C=$O_{lactone}$), 1667 (C=O_{lactam}), 1597-1557 (C=C_{ar}).^{1}H-NMR: d (ppm)= 9.71 (s, 2H, 2OH), 8.52 (s, 2H, 2(N-CH)), 7.36-7.18 (m, 21H, CH_{aro}), 6.92 (d, 3H, J = 6.4Hz, CH_{aro}), 3.98 (s, 2H, CH_2). ^{13}C NMR (100.2, DMSO) = 169.11 (C=Olactone), 167.98 (C=O_{lactam}), 160.63(C_{aro}), 158.15(C_{aro}), 149.85(C_{aro}), 139.71(C_{aro}), 137.93(C_{aro}), 135.16(C_{aro}), 130.31 (C_{aro}), 129.94 (C_{aro}), 129.38(C_{aro}),128.69(C_{aro}), 125.80(C_{aro}),122.28(C_{aro}), 121.62(C_{aro}), 120.70(C_{aro}), 120.10(C_{aro}), 119.11(C_{aro}), 114.64(C-$N_{oxazepine\ ring}$), 40.59 (CH_2).

4,4'-(sulfonyl bis (4,1-phenylene)) bis(3-(3-hydroxyphenyl)-3,4 dihydrobenzo[e][1,3] oxazepine-1,5-dione) (7C)

Pale-Yellow, yield. = 93%, R_f = 0.41, m.p. (216-218)°C. IR (cm^{-1}) = 3374 (O-H_{broad}), 3025 (C-H_{ar}), 2958 (C-H_{aliph}), 1690 (C=$O_{lactone}$),1686 (C=O_{lactam}), 1597-1557 (C=C_{aro}). ^{1}HNMR: d ppm. = 9.76 (s, 2H, 2OH), 8.50. (s, 2H, 2(N-CH)), 7.84 (d, 3H, J = 8 Hz, CH_{aro}), 7.56 (d, 3H, J = 8, CH_{aro}), 7.45-7.33 (m,17H, CH_{aro}). ^{13}C NMR (100.2, DMSO) = 165.06 (C=$O_{lactone}$), 158.45 (C=Olactam),158.19(C_{aro}), 147.28(C_{aro}), 138.47(C_{aro}), 137.22(C_{aro}), 130.80(C_{aro}), 129.18(C_{aro}), 129.14(2C_{aro}), 128.33(C_{aro}), 126.13(C_{aro}), 125.79 (C_{aro}), 123.11 (2C_{aro}),122.46(C_{aro}), 121.17(C_{aro}), 120.49(C_{aro}), 119.12(C_{aro}), 115.06(C_{aro}), 114.43(C-$N_{oxazepine\ ring}$)

Molecular Docking

All stationary points involved in the studied reactions were optimized with DFT method using the B3LYP functional in conjunction with 6-31G(d) basis set35 The calculations were done using Gaussian 16 software.[36,37] Molecular docking of the synthesized compounds against progesterone receptor (PDB ID: 4OAR) was executed utilizing Auto Dock Vina.[38] The geometry of the X-ray crystal of the progesterone receptor for docking purposes, it was obtained as a PDB file through the Protein Data Bank.[39] Thereafter, to eliminate water molecules and initial inhibitors from the structure of the protein of interest. Following the elimination of all the molecules of water, polar hydrogen molecules were included, and charges were allocated utilizing the Kollman unified atom library via Auto Dock Vina Tools (ADT; version 1.5.4).[40] The poses of the docked protein-ligand complexes in 2D and 3D have been observed using the Discovery Studio Client visualization software.[41]

CONCLUSION

In conclusion, we have disclosed an effective approach to the synthesis of Bis-Oxazepine and Bis-Benzoxazepine derivatives. This process started by synthesizing different derivatives of Bis-Schiff bases through the reaction of 3-hydroxybenzaldehyde with several aromatic diamine substrates over the condensation process and using the Dean-Stark apparatus. Secondly, the cyclization of Bis-Schiff bases with maleic- and phthalic anhydride afforded the desired oxazepine and benzoxazepine products using microwave irradiation, which gives high yields, short time, safety, and without using high amounts of solvent. The synthesized compounds were exposed to molecular docking against the progesterone receptor. The three final compounds 6b, 7a, and 7c indicate potential anticancer properties with higher docking scores (ΔG–9.58, –9.28, and –9.11 kcal/mol), forming three hydrogen bonds with the target protein.

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Conflict of interest

The authors declare that we have no conflict of interest.

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