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ORIGINAL RESEARCH

Synthesis, anticancer evaluation, and molecular docking studies of benzoxazole linked combretastatin analogues

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Abstract

A novel series of benzoxazole linked combretastatin derivatives (**11a–11n**) have been synthesized and confirmed by ^{1}H NMR, ^{13}C NMR, and Mass spectral analysis. The synthesized compounds (**11a–11n**) were screened for anticancer activity against three human cancer cell lines, Breast (MCF-7), Lung (A549), and Melanoma (A375). Most of the compounds exhibit moderate to potent anticancer activity. Among the compounds, **11g**, **11h**, **11l**, **11m**, and **11n** showed more potent activity than the positive control Doxorubicin. In addition, compounds **11g**, **11l**, **11m**, and **11n** were carried out their molecular docking studies on EGFR receptor (PDB ID: 4hjo) and results indicated that **11g** and **11l** have strong binding interactions with the receptor. It was found that the binding energy calculations were in good agreement with the observed IC_{50} values.

Keywords Combretastatin A-4 · Benzoxazole · Anticancer activity · Docking

Introduction

Cancer is one of the most lethal and fast spreading disease. The treatment of cancer involves radiation, surgery, and chemotherapy. Chemotherapy is found to be the most effective treatment for various cancers. Numerous heterocyclic derivatives act as pharmacophore group in these chemotherapy drugs (Agarwal et al. 2016; Ahsan et al. 2015; Durgesh et al. 2018a, 2018b, 2018c; Hatti et al. 2015a, 2015b; Reddy et al. 2016a, 2016b; Sreenivasulu et al. 2017–2019; Subramanyam et al. 2018; Madhavi et al. 2016, 2017a, 2017b).

Combretastatin A-4 (**1a**, Fig. 1) was first isolated from the tree *Combretum caffrum* (Pettit et al. 1989, 1995). The naturally occurring combretastatin A-4 act as a tubulin inhibitor drug. It inhibits the tubulin polymerization by impeding directly with the tubulin system and the colchicines site (Lin et al. 1989; Li and Sham 2002). The structurally modified prodrug Combretastatin A-4 phosphate (CA4P) (**1b**, Fig. 1) was a powerful vascular targeting agent that preferentially inhibits the blood supply of immature tumors that leads to their death and is currently under multiple clinical trials (Galbraith et al. 2003; Patterson and Rustin 2007; Siemann et al. 2009; Lippert 2007). The various Combretastatin A-4 related drugs such as Tamoxifen (TMX), (**2a**, Fig. 1) is used to avert breast cancer and also studying therapeutic applications for other cancers (Tamoxifen citrate-NCI 2015). Clomifene (**2b**, Fig. 1) is used as anovulation or oligoovulation agent (American Society for Reproductive Medicine 2013).

Fused benzoxazole nucleous is an important heterocyclic compound in the field of medicinal chemistry. Benzoxazole ring used in the design of biologically active molecules with the broad range of therapeutic importance such as sleep disorders (Laibekman et al. 2003), antifungal (Schnurch et al. 2010), metabolic disorders (Clark et al. 2000), anticonvulsants (Singh et al. 2007), antitumor (Kumar et al. 2002; Murty et al. 2011), antineoplastic (O'Donnell et al. 2010), antiviral (Sato et al. 1997), and topoisomerase-I and II inhibitory (Oksuzoglu et al. 2008). The bis-benzoxazole derivative UK-1 (**3a**, Fig. 1) was isolated from Streptomyces sp. 517–02, which showed more potent growth inhibitory activity against the murine cancer cell line P388 (Ueki et al. 1993).

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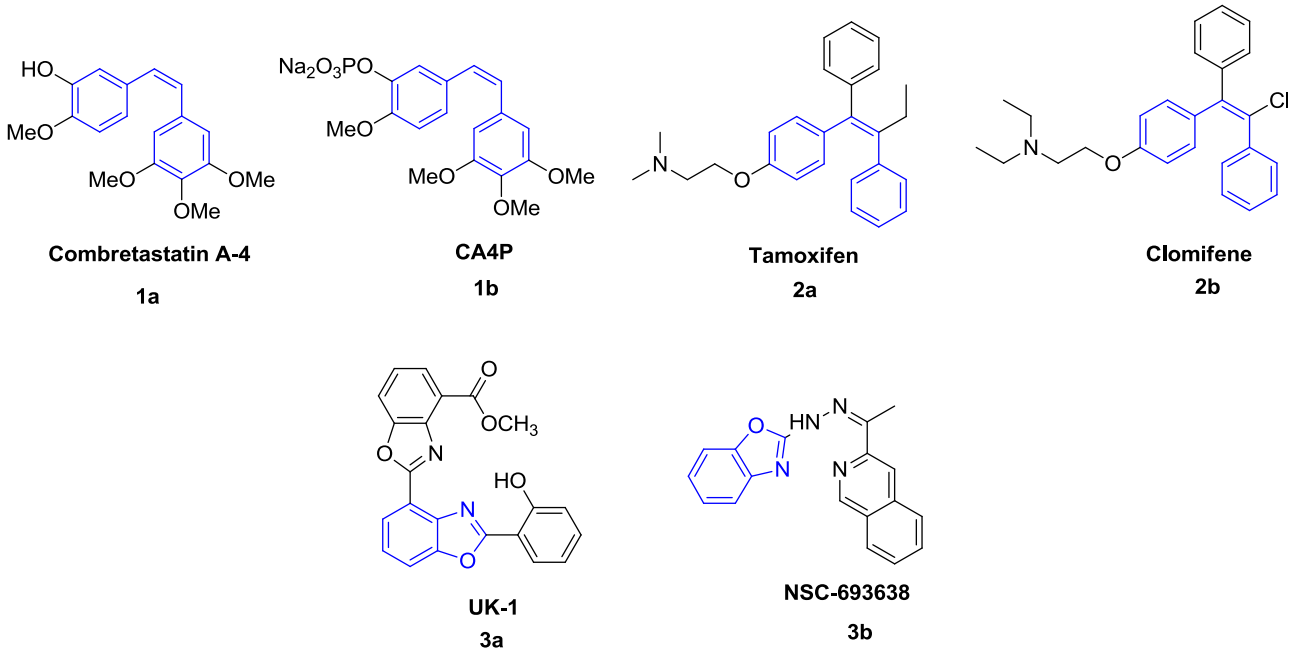


Fig. 1 Commercially available anticancer drug molecules

Based on the above literature survey, we have designed synthesized a new series of benzoxazole linked combretastatin derivatives (**11a**–**11n**) and evaluated against three cancer cell lines. In addition, molecular docking studies were correlated with protein target EGFR.

Results and discussion

Chemistry

The synthesis of benzoxazole linked combretastatin derivatives (**11a**–**n**) was shown in Scheme 1. Accordingly, 3,4,5-trimethoxybenzaldehyde **4** was treated with 5-bromo-1,2,3-trimethoxybenzene **5** in the presence of n-BuLi gave alcohol **6** in 76 yield. Next, the resulting Alcohol **6** was subjected to oxidation with pyridinium chlorochromate (PCC) afforded corresponding ketone **7**, which on Wittig reaction with (triphenylphosphoranylidene) acetaldehyde **8** in the presence of NaH yielded 3,3-bis(3,4,5-trimethoxyphenyl)acrylaldehyde **9** in **77** yield. Finally, compound **9** was condensed with substituted 2-aminophenols (**10a**–**n**) in ethanol, followed by the reaction with acetic acid and Pb $(OAc)_4$ to afford target benzoxazole derivatives (**11a**–**n**) in good yield.

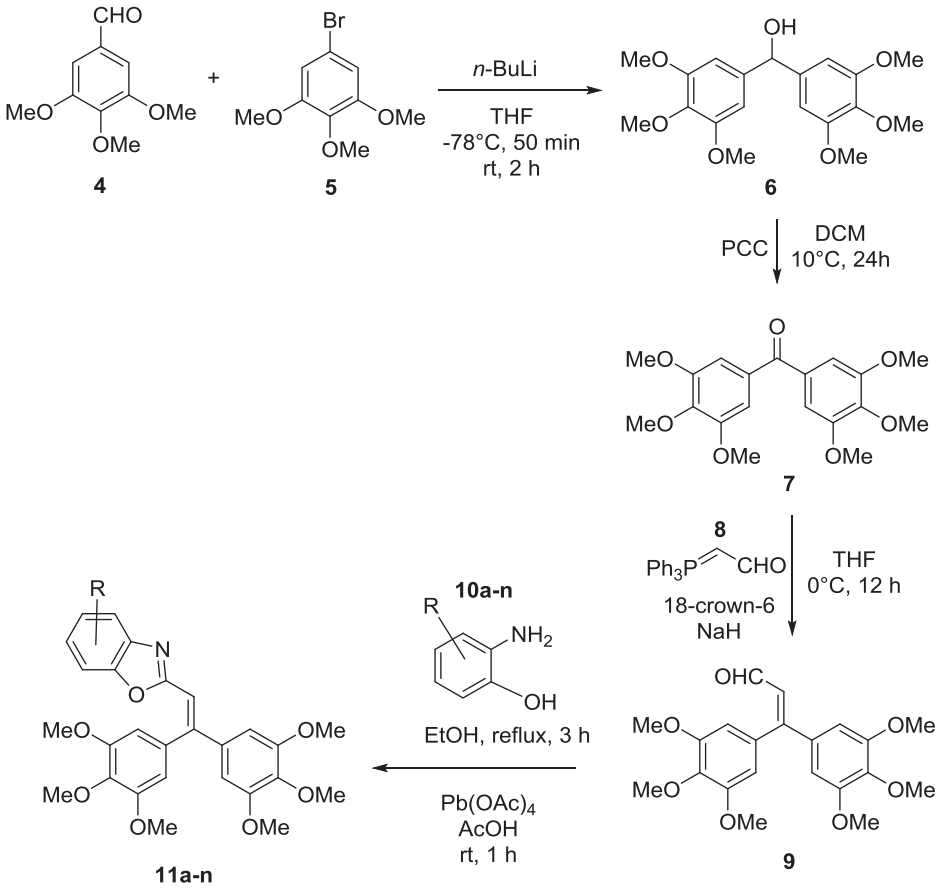
The structures of **11a**–**n** were confirmed by NMR and mass spectral analysis. ^{1}H NMR spectral data of **11g** exhibits five singlet peaks at δ 3.76 ppm (s, 3H), 3.82 (s, 6H), 3.85 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H) corresponds to seven methoxy protons and two singlet peaks at δ 6.54 ppm (s, 2H) and 6.63 (s, 2H) corresponds to two aromatic protons. One singlet appeared at δ 7.51 ppm (s, 1H) corresponds to olefinic proton. ^{13}C NMR exhibits four signals at δ 54.7, 56.4, 58.6, 62.7 ppm, corresponds to $-OCH_3$. Also, presence of two signals at δ 114.5 ppm and δ 120.6 ppm corresponds to Ar-C and = CH, respectively. The mass spectral analysis data of **11a**–**n** were also in good agreement with their molecular ion peak.

Biological evaluation

Anticancer activity

In continuation, the synthesized benzoxazole analogs (**11a**–**n**) were screened for anticancer activity by using MTT assay (Raju et al. 2016). The in vitro anticancer activity of **11a**–**n** were studied on breast (MCF-7), lung (A549), and melanoma (A375) cancer cell lines using doxorubicin as positive control. The results were showed in Table 1. From Table 1, all analogs showed a moderate to potent inhibition with IC_{50} values ranging between 0.11 ± 0.093 to 17.3 ± 1.33 μM, whereas, the standard doxorubicin shows 2.02 ± 0.11 to 5.51 ± 0.47. Among them, five analogs **11g**, **11h**, **11l**, **11m**, and **11n** showed potent inhibition than standard doxorubicin.

Further, these derivatives (**11a**–**n**) investigated structure-activity relationship (SAR) and indicated that compound **11n** having electron withdrawing group (5,7-dinitro benzoxazole) exhibits potent anticancer activity. Compound **11m** (5-chloro, 6-nitro benzoxazole) and **11l** (5-nitro



Scheme 1 Synnthesis of benzoxazole linked combretastatin derivatives

benzoxazole) exhibit next better anticancer activity. The halogen analogs **11k > 11j > 11i** shows less activity as compared with nitro analogs. In the electron donating series, the analogs with methoxy groups on benzoxazole (**11g** and **11h)** exhibit potent activity than methyl substituted benzoxazole (**11b–f**). In this study, analogs with strong donating groups (**11g** and **11h**) or strong withdrawing groups (**11l–11n)** on benzoxazole were found to be the most active compounds in the series.

Molecular docking studies

In order to understand the binding interaction of most active analogs, molecular docking studies were performed. Protein EGFR is found on the surface of some normal cells (including cancer cells) and involved in cell growth and cell division. Blocking of EGFR may control the growth of cancer cells and hence EGFR inhibitors are used in cancer treatment. Recent studies have shown that tyrosine kinase inhibitors (TKIs) involving mutations to the EGFR, are used for initial lung cancer therapy (Monic et al. 2013). Among the tested cancer cell lines (lung, breast and melanoma) lung cancer cells were inhibited better compared with breast and melanoma. Thus, we choose protein EGFR for screening of four compounds (**11g**, **11l**, **11m**, and **11n)** in molecular docking studies. The results indicates, **11l** binds strongly to EGFR receptor with minimum binding energy −9.33 Kcal/mol, while the binding energy of **11g**, **11m** and **11n** are −7.74, −6.89 and −7.40 Kcal/mol, respectively. The docking results were in good agreement with in vitro experimental IC_{50} values shown in Table 2.

Figure 2 shows the best conformations of **11l** forming a cluster with EGFR receptor. Docking results reveal that protein EGFR receptor consisting of amino acids Met769,

Asp831, Phe832, Thr830, Lys721, and Thr830 are the most active sites and responsible for the interaction with the **11l**. In this cluster a strong hydrogen bond is observed with Lys721 with a distance of 2.848A°. In addition, some non-hydrogen bonding interactions were observed with Tyr867, Gly850, Lys851, Arg812, Ala852, and Pro853 amino acids. Similarly, **11g**–EGFR cluster (Fig. 3) shows three strong hydrogen bonds with Ala698 and Arg817 amino acids at a distance of 3.606A°, 2.230A° and 1.932A° respectively. Also, a hydrophobic interactions with amino acids Ala698, Arg817, Ser696 and Leu834 are observed. In conclusion, the experimental in vitro results strongly correlate with the molecular docking analysis.

Conclusions

A series of benzoxazole linked combretastatin derivatives (**11a–n**) have been synthesized and screened for anticancer activity. All compounds shows moderate to potent activity with IC_{50} values ranging between 0.11 ± 0.093 and 17.3 ± 1.33 μM. Among the synthesized compounds, compounds, **11g**, **11h**, **11l**, **11m**, and **11n** exhibit potent activity. Further, these compounds investigated molecular docking studies. Among them, **11g** and **11l** have strong binding interactions with the receptor.

Table 1 In vitro cytotoxic activity of compounds **11a–n** in (IC_{50} μM)

Compound	R	MCF-7	A549	A375
11a	H	2.78 ± 0.17	6.45 ± 0.51	–
11b	4-Me	3.99 ± 0.27	16.3 ± 1.17	11.30 ± 1.03
11c	5-Me	5.19 ± 0.41	–	–
11d	6-Me	4.79 ± 0.41	7.99 ± 0.61	–
11e	5,6-DiMe	13.90 ± 0.98	2.26 ± 0.17	6.39 ± 0.57
11f	7-Me	17.3 ± 1.33	–	–
11g	5-OMe	1.22 ± 0.11	0.78 ± 0.059	–
11h	6-OMe	2.11 ± 0.18	1.09 ± 0.091	3.40 ± 0.27
11i	5-Br	9.50 ± 0.84	–	13.6 ± 1.11
11j	6-Br	6.23 ± 0.47	12.45 ± 1.16	8.56 ± 0.69
11k	6-Cl	4.89 ± 0.34	7.09 ± 0.58	3.90 ± 0.25
11l	5-NO_2	1.70 ± 0.13	0.23 ± 0.016	5.89 ± 0.49
11m	5-Cl,6-NO_2	0.98 ± 0.078	0.11 ± 0.093	1.90 ± 0.14
11n	5,7-DiNO_2	0.56 ± 0.038	0.13 ± 0.095	0.18 ± 0.012
Doxorubicin		2.02 ± 0.11	2.18 ± 0.13	5.51 ± 0.47

The results were expressed as the (IC_{50} μM), values are mean ± SEM and "–" = Not active

Experimental section

General

All chemicals and reagents were purchased from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualization on TLC was achieved by UV light or iodine indicator. ^{1}H and ^{13}C NMR spectra were recorded on Bruker UXNMR/XWIN-NMR (400 MHz, 300 MHz) instrument. Chemical shifts (δ) were reported in ppm downfield from internal TMS standard. ESI mass spectra were recorded on Micro mass, Quattro LC using ESI + software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined with an electro thermal melting point apparatus, and were uncorrected.

Synthesis

Bis(3,4,5-trimethoxyphenyl)methanol (6)

To a stirred solution of 5-bromo-1,2,3-trimethoxybenzene **5** (80.9 mmol, 20.0 g, 1.0 eq) in anhydrous THF (75 mL) at −78 °C was added 1.6 M n-BuLi in hexane (88.9 mmol, 83 mL, 1.1 eq) dropwise. After 50 min, 3,4,5-trimethoxybenzaldehyde **4** (97.1 mmol, 19 g, 1.2 eq) in THF (25 mL) was added drop wise to the reaction mixture at same temperature and slowly warmed to room temperature then stirred for 2 h. After completion of the reaction, itwas quenched with saturated solution of NH_4Cl (16 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water (3 × 20 mL) and

Table 2 Binding energies, number of hydrogen bonds and residues involved in hydrogen bonding of compounds **(11g, 11l, 11m,** and **11n)** against **EGFR** (PDB ID: 4hjo)

S.No.	Compound	Binding Energy (kcal mol^{-1})	Number of hydrogen bonds	Residues involved in hydrogen bonding
1	**11g**	−7.77 (4)	3	Ala698, Arg817(2)
2	**11l**	−9.33 (5)	1	Lys721
3	**11m**	−6.89 (9)	2	Lys721, Ala835
4	**11n**	−7.40 (8)	5	Ser696, Lys721(2), Arg817, Arg779

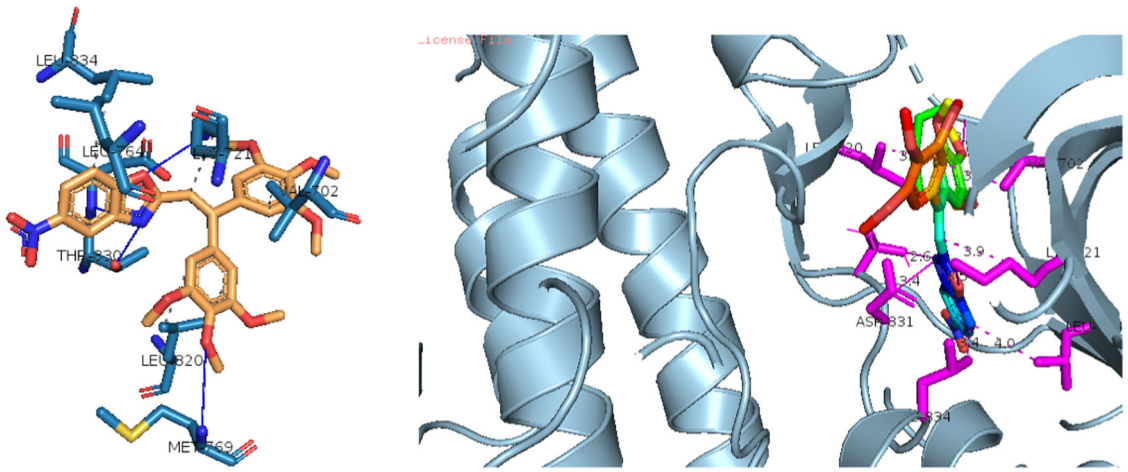


Fig. 2 Binding poses and interactions of compound **11l** to the binding sites of target protein EGFR (PDB ID: 4hjo)

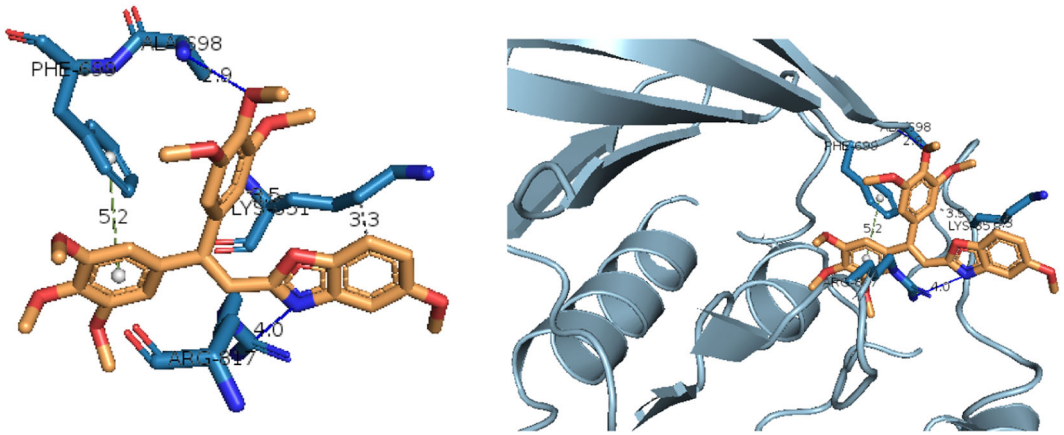


Fig. 3 Binding poses and interactions of compound **11g** to the binding sites of target protein EGFR (PDB ID: 4hjo)

brine (30 mL), dried over Na_2SO_4, filtered and distilled under reduced pressure to get crude residue which was purified by flash column chromatography (hexane/ethyl acetate = 5:1) on silica gel to afford the desired compound **6**, 22.3 g (76%). ^{1}HNMR (400 MHz, $CDCl_3$): δ 2.79 (brs, 1H), 3.82 (s, 6H), 3.91 (s, 12H), 5.66 (s, 1H), 6.58 (s, 4H); MS (ESI): 365 $[M+H]^+$. Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63; H, 6.64; Found: C, 62.68; H, 6.59.

Bis(3,4,5-trimethoxyphenyl)methanone (7)

PCC (76.2 mmol, 16.8 g, 1.46 eq) was added lot wise to ice cold stirred solution of compound **6** (52.1 mmol, 19 g, 1.0 eq) in CH_2Cl_2 (76 mL) and stirred for 24 h at 10 °C. After completion of the reaction, it was filtered and concentrated under reduced pressure to afford the desired compound **7** (17.9 g, 95%). It was directly used for the next reaction without further purification. ^{1}HNMR (400 MHz, $CDCl_3$): δ 3.82 (s, 6H), 3.91 (s, 12H), 6.67 (s, 4H); MS (ESI): 363 $[M+H]^+$. Anal. Calcd for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12; Found: C, 62.88; H, 6.09.

3,3-Bis(3,4,5-trimethoxyphenyl)acrylaldehyde (9)

NaH (176.4 mmol, 42 g, 4.0 eq) was added to a stirred suspension of **7** (44.1 mmol, 16 g, 1.0 eq), (triphenylphosphoranylidene)acetaldehyde **8** (132.5 mmol, 40 g, 3.0 eq) and 18-crown-6 (4.41 mmol, 116 mg, 0.1 eq) in anhydrous THF at 0 °C and stirred at same temperature for 12 h. After completion of the reaction, reaction was quenched by slowly adding ice cold water followed by 10% HCl solution. After vigorous stirring for 60 min at room temperature, the mixture was extracted with ethyl acetate (2 × 100 mL), 10% HCl and water (50 mL). The combined organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure to get crude compound which was purified by flash chromatography (ethyl acetate:hexane, 2:8) to afford pure compound **9** (13.2 g, 77%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.82 (s, 6H), 3.85 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H), 6.51 (d, 1H, $J = 8.3$ Hz), 6.54 (s, 2H), 6.63 (s, 2H), 9.56 (d, 1H, $J = 7.80$ Hz); MS (ESI): 389 $[M+H]^+$. Anal. Calcd for $C_{21}H_{24}O_7$: C, 64.94; H, 6.23; Found: C, 64.91; H, 6.19.

2-(2,2-Bis(3,4,5-trimethoxyphenyl)vinyl)benzoxazole (11a)

Compound **9** (1.2 mmol, 500 mg, 1.0 eq) and 2-aminophenol **10a** (1.2 mmol, 130 mg, 1.0 eq) were taken in ethanol (30 mL) and refluxed for 3 h. After completion of the reaction, reaction mixture was cooled to room temperature, and ethanol was evaporated under reduced pressure. Lead tetra acetate (6 mmol, 266 mg, 5.0 eq) was added to the resulting Schiff base was dissolved in 12 mL of acetic acid and stirred at room temperature for 1 h. After 1 h, reaction mixture was diluted with 30 mL H_2O and extracted with ethyl acetate (2 × 50 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to get the crude product which was purified by column chromatography (ethyl acetate:hexane, 1:1) to afford pure **11a**, (431 mg, 70%). Mp: 228–230 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 6H), 3.85 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H), 6.54 (s, 2H), 6.63 (s, 2H), 7.37–3.39 (m, 2H), 7.44–7.48 (m, 2H), 7.51 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.4, 58.6, 60.4, 62.7, 111.4, 114.5, 119.5, 120.6, 124.6, 126.3, 138.5, 139.5, 140.5, 143.5, 150.7, 153.5, 157.6, 159.6; MS (ESI): 478 $[M+H]^+$. Anal. Calcd for $C_{27}H_{27}NO_7$: C, 67.91; H, 5.70; N, 2.93; Found: C, 67.88; H, 5.74; N, 2.95.

2-(2,2-Bis(3,4,5-trimethoxyphenyl)vinyl)-4-methylbenzoxazole (11b)

Compound **11b** was prepared by following the method described for **11a**, employing **9** (1.2 mmol, 500 mg, 1.0 eq) with 2-amino-3-methylphenol **10c** (1.2 mmol, 158 mg, 1.0 eq), $Pb(OAc)_4$ (6 mmol, 266 mg, 5.0 eq) and the crude product was purified by column chromatography (ethyl acetate:hexane, 1:1) to afford pure **11b**, (428 mg, 68%). Mp: 227–229 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (s, 3H), 3.84 (s, 6H), 3.90 (s, 6H), 3.92 (s, 3H), 3.93 (s, 3H), 6.55 (s, 2H), 6.63 (s, 2H), 7.09 (t, 1H), 7.42–7.50 (m, 2H), 7.57 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.4, 57.4, 61.6, 108.4, 114.5, 120.5, 121.4, 126.3, 127.5, 138.4, 138.8, 139.4, 140.5, 149.7, 153.4, 157.6, 160.5; MS (ESI): 492 $[M+H]^+$. Anal. Calcd for $C_{28}H_{29}NO_7$: C, 68.42; H, 5.95; N, 2.85; Found: C, 68.48; H, 5.94; N, 2.91.

2-(2,2-Bis(3,4,5-trimethoxyphenyl)vinyl)-5-methylbenzoxazole (11c)

Compound **11c** was prepared by following the method described for **11a**, employing **9** (1.2 mmol, 500 mg, 1.0 eq) with 2-amino-4-methylphenol **10c** (1.2 mmol, 148 mg, 1.0 eq), $Pb(OAc)_4$ (6 mmol, 266 mg, 5.0 eq) and the crude product was purified by column chromatography (ethyl acetate:hexane, 1:1) to afford pure **11c**, (439 mg, 70%). Mp: 229–231 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.82 (s, 6H), 3.85 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H), 6.54 (s, 2H), 6.63 (s, 2H), 6.93 (d, 1H, $J = 7.23$ Hz), 7.52–7.56 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.7, 56.4, 58.6, 60.4, 62.7, 109.6, 114.6, 120.8, 122.4, 128.6, 132.5, 138.5, 139.5, 140.5, 141.4, 147.8, 153.4, 157.8, 160.5; MS (ESI): 492 $[M+H]^+$. Anal. Calcd for $C_{28}H_{29}NO_7$: C, 68.42; H, 5.95; N, 2.85; Found: C, 68.45; H, 5.96; N, 2.81.

2-(2,2-Bis(3,4,5-trimethoxyphenyl)vinyl)-6-methylbenzoxazole (11d)

Compound **11d** was prepared by following the method described for **11a**, employing **9** (1.2 mmol, 500 mg, 1.0 eq) with 2-amino-5-methylphenol **10d** (1.2 mmol, 158 mg, 1.0 eq), $Pb(OAc)_4$ (6 mmol, 266 mg, 5.0 eq) and the crude product was purified by column chromatography (ethyl acetate:hexane, 1:1) to afford pure **11d**, (442 mg, 70%). Mp: 232–234 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 3H), 3.84 (s, 6H), 3.90 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H), 6.54 (s, 2H), 6.62 (s, 2H), 7.38–7.45 (m, 2H), 7.49 (d, 1H, $J =$ 8.17 Hz), 7.56 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.5, 57.5, 61.8, 111.5, 114.6, 120.5, 121.5, 125.7, 134.3, 138.4, 139.2, 140.5, 141.4, 149.6, 153.4, 157.5, 160.6; MS (ESI): 492 $[M+H]^+$. Anal. Calcd for $C_{28}H_{29}NO_7$: C, 68.42; H, 5.95; N, 2.85; Found: C, 68.44; H, 5.93; N, 2.88.

2-(2,2-Bis(3,4,5-trimethoxyphenyl)vinyl)-5,6-dimethylbenzoxazole (11e)

Compound **11e** was prepared by following the method described for **11a**, employing **9** (1.2 mmol, 500 mg, 1.0 eq) with 2-amino-4,5-dimethylphenol **10e** (1.2 mmol, 164 mg, 1.0 eq), $Pb(OAc)_4$ (6 mmol, 266 mg, 5.0 eq) and the crude product was purified by column chromatography (ethyl acetate:hexane, 1:1) to afford pure **11e**, (434 mg, 67%). Mp: 238–240 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3H), 2.47 (s, 3H), 3.84 (s, 6H), 3.90 (s, 6H), 3.92 (s, 3H), 3.94 (s, 3H), 6.54 (s, 2H), 6.62 (s, 2H), 7.37 (s, 1H), 7.48 (s, 1H), 7.56 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.5, 123.7, 57.5, 61.7, 110.6, 114.5, 120.6, 125.4, 134.5, 138.5, 139.4, 140.3, 140.6, 143.3, 146.5, 153.5, 157.6, 60.6; MS (ESI): 506 $[M+H]^+$. Anal. Calcd for $C_{29}H_{31}NO_7$: C, 68.90; H, 6.18; N, 2.77; Found: C, 68.88; H, 6.21; N, 2.81.

2-(2,2-Bis(3,4,5-trimethoxyphenyl)vinyl)-7-methylbenzoxazole (11f)

Compound **11f** was prepared by following the method described for **11a**, employing **9** (1.2 mmol, 500 mg, 1.0 eq) with 2-amino-6-methylphenol **10f** (1.2 mmol, 158 mg, 1.0 eq), $Pb(OAc)_4$ (266 mg, 6 mmol) and the crude product was purified by column chromatography (ethyl acetate:hexane, 1:1) to afford pure **11f**, (423 mg, 67%). Mp: 230–232 °C,

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 3H), 3.85 (s, 6H), 3.91 (s, 6H), 3.92 (s, 3H), 3.94 (s, 3H), 6.53 (s, 2H), 6.63 (s, 2H), 7.10 (d, 1H, $J = 8.14$ Hz), 7.19 (d, 1H, $J = 8.14$ Hz), 7.38 (t, 1H), 7.56 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.4, 57.4, 61.5, 114.6, 119.5, 120.5, 123.5, 125.5, 127.6, 138.4, 139.5, 140.5, 140.8, 148.5, 153.5, 157.8, 160.6; MS (ESI): 492 $[M+H]^+$. Anal. Calcd for $C_{28}H_{29}NO_7$: C, 68.42; H, 5.95; N, 2.85; Found: C, 68.45; H, 5.97; N, 2.81.

2-(2,2-Bis(3,4,5-trimethoxyphenyl)vinyl)-5-methoxybenzoxazole (11g)

Compound **11g** was prepared by following the method described for **11a**, employing **9** (1.2 mmol, 500 mg, 1.0 eq) with 2-amino-4-methoxyphenol **10g** (1.2 mmol, 167 mg, 1.0 eq), $Pb(OAc)_4$ (6 mmol, 266 mg, 5.0 eq) and the crude product was purified by column chromatography (ethyl acetate:hexane, 1:1) to afford pure **11g**, (436 mg, 67%). Mp: 244–246 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 3H), 3.82 (s, 6H), 3.85 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H), 6.54 (s, 2H), 6.63 (s, 2H), 6.76 (s, 1H), 7.09 (d, 1H, $J = 7.24$ Hz), 7.32 (d, 1H, $J = 7.24$ Hz), 7.51 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.7, 56.4, 58.6, 60.4, 62.7, 104.6, 106.5, 109.7, 114.5, 120.6, 138.4, 139.6, 140.5, 144.5, 146.4, 153.4, 155.3, 157.3, 159.7; MS (ESI): 508 $[M+H]^+$. Anal. Calcd for $C_{28}H_{29}NO_8$: C, 66.26; H, 5.76; N, 2.76; Found: C, 66.38; H, 5.74; N, 2.69.

2-(2,2-Bis(3,4,5-trimethoxyphenyl)vinyl)-6-methoxybenzoxazole (11h)

Compound **11h** was prepared by following the method described for **11a**, employing **9** (1.2 mmol, 500 mg, 1.0 eq) with 2-amino-5-methoxyphenol hydrogen chloride **10h** (1.2 mmol, 211 mg, 1.0 eq), $Pb(OAc)_4$ (6 mmol, 266 mg, 5.0 eq) and the crude product was purified by column chromatography (ethyl acetate:hexane, 1:1) to afford pure **11h** (440 mg, 67%). Mp: 243–245 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 3H), 3.82 (s, 6H), 3.85 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H), 6.54 (s, 2H), 6.63 (s, 2H), 6.78 (s, 1H), 7.10 (d, 1H, $J = 7.24$ Hz), 7.31 (d, 1H, $J = 7.24$ Hz), 7.51 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.7, 56.4, 58.6, 60.4, 62.7, 96.6, 112.4, 114.5, 120.5, 121.6, 136.5, 138.6, 139.6, 140.6, 153.4, 153.8, 157.8, 158.6, 160.4; MS (ESI): 508 $[MH]^+$. Anal. Calcd for $C_{28}H_{29}NO_8$: C, 66.26; H, 5.76; N, 2.76; Found: C, 66.18; H, 5.84; N, 2.74.

2-(2,2-Bis(3,4,5-trimethoxyphenyl)vinyl)-5-bromobenzoxazole (11i)

Compound **11i** was prepared by following the method described for **11a**, employing **9** (1.2 mmol, 500 mg, 1.0 eq) with 2-amino-4-bromophenol **10i**, (1.2 mmol, 226 mg, 1.0 eq), $Pb(OAc)_4$ (6 mmol, 266 mg, 5.0 eq) and the crude product was purified by column chromatography (ethyl acetate:hexane, 1:1) to afford pure **11i**, (456 mg, 64%). Mp: 252–254 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 6H), 3.85 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H), 6.54 (s, 2H), 6.63 (s, 2H), 7.32 (d, 1H, $J = 7.29$ Hz), 7.39 (d, 1H, $J = 7.29$ Hz), 7.52 (s, 1H), 7.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.4, 58.6, 60.4, 62.7, 110.6, 113.4, 114.8, 120.6, 128.5, 129.6, 138.4, 139.7, 140.7, 143.4, 146.5, 146.7, 153.4, 157.4, 160.7; MS (ESI): 557 $[M+H]^+$. Anal. Calcd for $C_{27}H_{26}BrNO_7$: C, 58.28; H, 4.71; N, 2.52; Found: C, 58.28; H, 4.69; N, 2.61.

2-(2,2-Bis(3,4,5-trimethoxyphenyl)vinyl)-6-bromobenzoxazole (11j)

Compound **11j** was prepared by following the method described for the preparation of the **11a**, employing **9** (1.2 mmol, 500 mg, 1.0 eq) with 2-amino-5-bromophenol **10j** (1.2 mmol, 226 mg, 1.0 eq), $Pb(OAc)_4$ (6 mmol, 266 mg, 5.0 eq) and the crude product was purified by column chromatography (ethyl acetate:hexane, 1:1) to afford pure **11j** (461 mg, 64%). Mp: 253–255 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 6H), 3.85 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H), 6.54 (s, 2H), 6.63 (s, 2H), 7.35 (d, 1H, $J = 7.28$ Hz), 7.52 (s, 1H), 7.61–7.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.4, 58.6, 60.4, 62.7, 112.4, 114.6, 119.6, 120.6, 122.4, 128.5, 138.5, 139.5, 140.8, 142.3, 152.6, 153.8, 157.8, 160.8; MS (ESI): 557 $[M+H]^+$. Anal. Calcd for $C_{27}H_{26}BrNO_7$: C, 58.28; H, 4.71; N, 2.52; Found: C, 58.3; H, 4.72; N, 2.51.

2-(2,2-Bis(3,4,5-trimethoxyphenyl)vinyl)-6-chlorobenzoxazole (11k)

Compound **11k** was prepared by following the method described for the preparation of the **11a**, employing **9** (1.2 mmol, 500 mg, 1.0 eq) with 2-amino-5-chlorophenol **10k** (1.2 mmol, 172 mg, 1.0 eq), $Pb(OAc)_4$ (6 mmol, 266 mg, 5.0 eq) and the crude product was purified by column chromatography (ethyl acetate:hexane, 1:1) to afford pure **11k**, (466 mg, 71%). Mp: 235–237 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 6H), 3.85 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H), 6.54 (s, 2H), 6.63 (s, 2H), 7.23 (d, 1H, $J = 7.26$ Hz), 7.40 (d, 1H, $J = 7.26$ Hz), 7.54 (s, 1H), 7.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.4, 58.6, 60.4, 62.7, 110.6, 114.5, 119.6, 120.6, 125.6, 129.6, 138.6, 139.8, 140.6, 140.9, 146.5, 153.4, 157.6, 161.6; MS (ESI): 512 $[M+H]^+$. Anal. Calcd for $C_{27}H_{26}BrNO_7$: C, 63.34; H, 5.12; N, 2.74; Found: C, 63.36; H, 5.14; N, 2.71.

2-(2,2-Bis(3,4,5-trimethoxyphenyl)vinyl)-5-nitrobenzoxazole (11l)

Compound **11l** was prepared by following the method described for 11a, employing **9** (1.2 mmol, 500 mg, 1.0 eq) with 2-amino-4-nitrophenol **10l** (1.2 mmol, 185 mg, 1.0 eq), $Pb(OAc)_4$ (6 mmol, 266 mg, 5.0 eq) and the crude product was purified by column chromatography (ethyl acetate:hexane, 1:1) to afford pure compound **11l**, (51 mg, 76%). Mp: 238–240 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 6H), 3.85 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H), 6.54 (s, 2H), 6.63 (s, 2H), 7.52 (s, 1H), 7.68 (d, 1H, $J = 7.30$ Hz), 7.89 (d, 1H, $J = 7.30$ Hz), 8.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.4, 58.6, 60.4, 62.7, 112.4, 114.5, 115.7, 117.6, 120.6, 138.6, 139.7, 140.6, 144.5, 145.6, 152.3, 153.7, 157.5, 160.9; MS (ESI): 523 $[M+H]^+$. Anal. Calcd for $C_{27}H_{26}N_2O_9$: C, 62.06; H, 5.02; N, 5.36; Found: C, 62.12; H, 4.99; N, 5.31.

2-(2,2-Bis(3,4,5-trimethoxyphenyl)vinyl)-5-chloro-6-nitrobenzoxazole (11m)

Compound **11m** was prepared by following the method described for 11a, employing **9** (1.2 mmol, 500 mg, 1.0 eq) with 2-amino-4-chloro-5-nitrophenol **10m** (1.2 mmol, 226 mg, 1.0 eq), $Pb(OAc)_4$ (6 mmol, 266 mg, 5.0 eq) and the crude product was purified by column chromatography (ethyl acetate:hexane, 1:1) to afford pure **11m**, (523 mg, 73%). Mp: 249–251 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 6H), 3.85 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H), 6.54 (s, 2H), 6.63 (s, 2H), 7.54 (s, 1H), 7.86 (s, 1H), 8.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.4, 58.6, 60.4, 62.7, 106.7, 114.5, 120.6, 122.7, 132.5, 138.6, 139.8, 140.8, 141.4, 147.6, 148.5, 153.5, 157.6, 160.9; MS (ESI): 557 $[M+H]^+$. Anal. Calcd for $C_{27}H_{25}ClN_2O_9$: C, 58.23; H, 4.52; N, 5.03; Found: C, 58.28; H, 4.49; N, 5.07.

2-(2,2-Bis(3,4,5-trimethoxyphenyl)vinyl)-5,7-dinitrobenzoxazole (11n)

Compound **11n** was prepared by following the method described for 11a, employing **9** (1.2 mmol, 500 mg, 1.0 eq) with 2-amino-4,6-dinitrophenol **10n** (1.2 mmol, 239 mg, 1.0 eq), $Pb(OAc)_4$ (6 mmol, 266 mg, 5.0 eq) and the crude product was purified by column chromatography (ethyl acetate:hexane, 1:1) to afford pure **11n**, (568 mg, 78%). Mp: 247–249 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 6H), 3.85 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H), 6.54 (s, 2H), 6.63 (s, 2H), 7.55 (s, 1H), 8.56–8.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.4, 58.6, 60.4, 62.7, 114.8, 115.7, 119.7, 120.6, 136.6, 138.5, 139.8, 140.6, 140.9, 144.5, 144.9, 153.4, 157.9, 161.8; MS (ESI): 568 $[M+H]^+$. Anal. Calcd for $C_{27}H_{25}N_3O_{11}$: C, 57.14; H, 4.44; N, 7.40; Found: C, 57.18; H, 4.39; N, 7.51.

Biological evaluation

Anticancer activity (MTT assay)

The cytotoxic activity of the compounds was determined using MTT assay. 1×10^4 cells/well were seeded in 200 mL DMEM, supplemented with 10% FBS in each well of 96-well microculture plates and incubated for 24 h at 37 °C in a CO_2 incubator. Compounds, diluted to the desired concentrations in culture medium, were added to the wells with respective vehicle control. After 48 h of incubation, 10 mL MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) (5 mg/mL) was added to each well and the plates were further incubated for 4 h. Then the supernatant from each well was carefully removed, formazon crystals were dissolved in 100 mL of DMSO and absorbance at 540 nm wavelength was recorded.

Molecular docking protocol

The anticancer potency of all the compounds were further screened for molecular docking analysis to explore the approaching of drug candidates towards the protein and binding pattern against EGFR PDB ID: (4hjo) extracted from RSC Protein data bank. The ligand 2D structures were drawn in Chem Bio Draw Ultra 12.0 (www.cambridgesoft.com) and 3D structures were created and optimized by using Gaussian 09 (Pietro et al. 1982), with small basic set **hf/3-21g*** (Frisch et al. 2009). The process of making of protein receptor and ligand inhibitors washed by eliminating the already involved water molecule ligands by using UCSF Chimera 1.12 software.

Auto dock Tools (ADT) (http://mgltools.scripps.edu) version 1.5.6 and Auto dock 4.2 package suite was used for the molecular docking. In the ADT process, the rigid protein receptor EGFR and flexible compounds **11g**, **11l**, **11m** and **11n** were involved and in the preliminary step and it is started by removing the crystal water molecules, non-polar hydrogen atoms of protein structures were merged and gasteiger charges were added to each atom. The distance between donor and acceptor atoms that form a hydrogen bond was fixed as 1.9 Å. For further studies in ADT, initially the PDB structures were converted in PDBQT format, genetic algorithms were used for energy calculations, non-polar hydrogen atoms, rotatable bonds, Gasteiger partial charges, and grid box with dimensions $60 \times 60 \times 60$ Å^3 created around the EGFR protein receptor assigned with the assistance of Auto Dock Tools 1.5.6 and spacing (Angstrom): 0.3750 Å. The population size and the maximum number of evaluations were 150 and 2,500,000 respectively. The output results were used to analyze by Discovery studio 4.1.0. Software. This explores the clear

view of docking studies of **11g**, **11l**, **11m**, and **11n** inhibitors including binding energies of receptor-ligand complex.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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