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Palladium-Mediated Synthesis of 2-([Biphenyl]-4-yloxy)quinolin-3-carbaldehydes through Suzuki–Miyaura Cross-Coupling and Their in Silico Breast Cancer Studies on the 3ERT Protein

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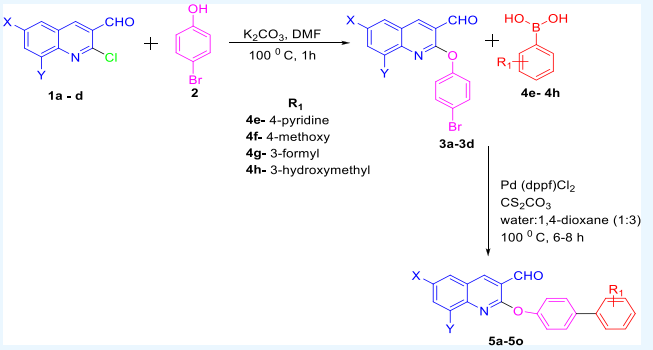
ABSTRACT: A series of novel quinoline appended biaryls have been synthesized (**5a–5o**) by reacting various substituted boronic acids (**4e–4h**) with various substituted 2-(4-bromophenoxy)-quinolin-3-carbaldehydes (**3a–3d**) through carbon–carbon bond formation. Effects of various quinoline appended biaryls (**5a–5o**) on the breast cancer protein 3ERT are moderate to high, as found by in silico molecular docking studies. Comparatively, all quinoline appended biaryls (**5a–5o**) **5h** show better efficacy with a binding energy of −9.39 kcal/mol, and hydrogen bonds are Thr347, Glu353, and Arg394 in the binding pocket. Conclusively, the final novel quinoline appended biaryls (**5a–5o**) have been confirmed with all the spectral studies, and their efficacy has been validated with in silico studies.



INTRODUCTION

Cancer is one of the most feared diseases of the 20th century, and its prevalence and incidence are increasing in the 21st century also.[1] Despite significant advancements in cancer research, breast cancer remains a significant public health concern and a top scientific research goal.[2] The quinolone-based drugs, namely, neratinib and talazoparib are in clinical practice to treat breast cancer. The recent literature shows evidently that quinoline-based compounds are widely used for anticancer treatment, especially breast cancer.[3] Quinolone-based compounds recently reported by Govindarao et al. are found to act against breast cancer cells.[4] Kardile et al. reported the in vitro screening, molecular docking, and absorption, distribution, metabolism, and excretion (ADME) predictions of quinolone derivatives.[5] The derivatives with a quinoline core are also known as potent tubulin assembly inhibitors,[6] mutant epidermal growth factor receptor (EGFR) inhibitors targeting resistance in lung cancer cells,[7] anti-tubulin agents targeting the colchicine binding site,[8] potential anti-hepatoma agents,[9] and various other anticancer activities;[10−13] hence, we intend to synthesize new quinoline derivatives and screen them for their activity against the breast cancer 3ERT protein. The synthesis of biaryls involving carbon–carbon bond formation through palladium-mediated Suzuki–Miyaura cross-coupling plays a key role in the synthetic chemistry to build complex molecules from simple precursors since the formation of biaryls using Suzuki–Miyaura coupling is the most reliable and efficient method.[14] Various quinoline derivatives have been prepared synthetically and extracted from natural resources as well. In synthetic laboratories, Suzuki–Miyaura cross-coupling was hugely applied as a key step in the total synthesis of natural products[6] and in polymer synthesis.[15] The commercial availability of boronic acids is due to their low toxicity and eco-friendly nature as compared with other organometallic reagents; mild reaction conditions are the main advantages of Suzuki–Miyaura cross-coupling. In the view of developing an eco-friendly protocol and making the Suzuki–Miyaura cross-coupling reaction more efficient, different modifications were introduced in reaction media, reaction conditions, substrates, catalysts, and synthetic techniques.[16] Subsequently, other than for treating breast cancer, the quinoline-based compounds are widely used as anticancer,[17] antibacterial,[18] antimalarial,[19] and antifungal[20] agents. Some of the quinoline-based biaryls were used as anthelmintics and were reported to show a free radical scavenging property against DPPH as well[21] (Figure 1). In recent years, the in silico studies have shown to be promising to validate the synthesized compounds toward any biological target. The current study sought to design the quinoline-based

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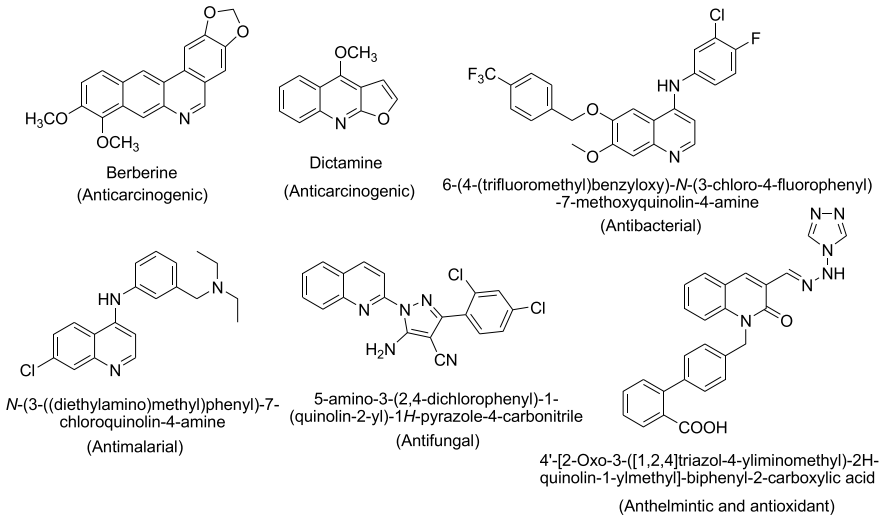

Figure 1. The reported biologically active quinoline-based molecules.

biaryls and validated them through in silico studies, and these synthesized final compounds (**5a−o**) showed promising impact against the breast cancer target.

EXPERIMENTAL SECTION

Methods and Materials. Melting points (m.p.) reported in this work were recorded in an Elchem microprocessor-based DT apparatus in open capillary tubes. ^{1}H NMR and ^{13}C NMR spectra were recorded in a Bruker 400 MHz nuclear magnetic resonance (NMR) spectrometer with tetramethylsilane (TMS) as an internal reference. The chemical shift values are reported in parts per million (δ, ppm) from internal standard TMS. Mass spectra are obtained from a high-resolution mass spectroscopy (HRMS) (Maxis 10138) analyzer. All reagents were purchased from Aldrich and used as received. Solvents were removed under vacuum. Organic extracts were dried with anhydrous Na_2SO_4. Silica gel $60F_{254}$ aluminum sheets were used in analytical thin-layer chromatography (TLC). Visualization of spots on TLC plates was performed by UV illumination, exposure to iodine vapor, and heating the plates dipped into the $KMnO_4$ stain. In column chromatography, the silica gel with 230−400 mesh size was used for the purification.

*Synthesis of 2-([Biphenyl]-4-yloxy)quinolin-3-carbaldehydes (**5a−o**).* The substituted 2-(4-bromophenoxy)-quinolin-3-carabaldehydes were treated (**3a−d**, 0.1 g, 0.0003 M) with substituted boronic acids (**4e−h**, 0.037 g, 0.0003 M) in the presence of Cs_2CO_3 (0.1 g, 0.0003 M) and [(dppf)$PdCl_2$] (5 mol %) in water/1,4-dioxane (1:3, 4 mL) at 100 °C, and the reaction continued for 6−8 h. After completion of the reaction (confirmed by TLC), the reaction mass was extracted using ethyl acetate and dried, and then the obtained compound was purified by column chromatography using ethyl acetate/hexane (3:7) as an eluent.

*2-(4-(4-Methoxyphenyl)phenoxy)quinoline-3-carbaldehyde (**5b**).* Colorless compound, yield 65%, m.p.: 186−188 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.67 (s, 1H), 8.75 (s, 1H), 7.91 (d, J = 8.00 Hz, 1H), 7.78 (d, J = 8.40 Hz, 1H), 7.71 (dt, J = 1.20, 10.80 Hz, 1H), 7.64 (d, J = 8.40 Hz, 2H), 7.57 (d, J = 8.80 Hz, 2H), 7.47 (q, J = 0.80 Hz, 1H), 7.36 (d, J = 8.40 Hz, 2H), 7.00 (d, J = 8.80 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 189.01, 160.52, 159.15, 152.00, 148.63, 140.60, 137.92, 133.09, 132.76, 129.68, 128.13, 127.87, 127.78, 125.82, 125.19, 120.21, 122.00, 114.27, 55.39. HRMS-ESI (m/z) calcd for $C_{21}H_{14}N_2O_2$ $[M + H]^+$ = 356.1287, found = 356.1290.

Spectral Characterization of 5b. Compound **5b** was characterized by ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H COSY, HSQC, and HRMS (ESI) spectral data. The ^{1}H NMR spectrum of compound **5b** exhibited the following chemical shifts: δ ppm 10.67 (s, 1H), 8.75 (s, 1H), 7.91 (d, J = 8.00 Hz, 1H), 7.78 (d, J = 8.40 Hz, 1H), 7.71 (dt, J = 1.20, 10.80 Hz, 1H), 7.64 (d, J = 8.40 Hz, 2H), 7.57 (d, J = 8.80 Hz, 2H), 7.47 (q, J = 0.80 Hz, 1H), 7.36 (d, J = 8.40 Hz, 2H), 7.00 (d, J = 8.80 Hz, 2H), 3.87 (s, 3H) (Figure 2).

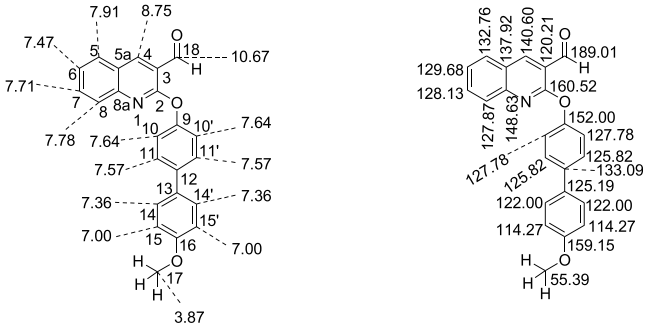

Figure 2. Summary of proton and carbon chemical shift (δ) values of **5b**.

The ^{13}C NMR spectrum exhibits the following chemical shift values: δ ppm 189.01 (C-18), 160.52 (C-2), 159.15 (C-16), 152.00 (C-9), 148.63 (C-8a), 140.60 (C-4), 137.92 (C-5a), 133.09 (C-13), 132.76 (C-5), 129.68 (C-6), 128.13 (C-7), 127.87 (C-8), 127.78 (C-10, 10′), 125.82 (C-11, 11′), 125.19 (C-13), 120.21 (C-3), 122.00 (C-14, 14′), 114.27 (C-15, 15′), 55.39 (C-17). The upfield signal at δ 55.39 was assigned to C-17, and the extreme downfield signal at δ 189.01 ppm was assigned to aldehyde carbon C-18. The C-5a and C-8a carbons were identified as δ 127.87 and 148.63 ppm, respectively. The signals at δ 160.52, 120.21, 152.00, 125.82, 125.19, and 159.15 ppm were due to non-proton-bearing carbons at C-2, C-3, C-9, C-12, C-13, and C-16 (Figure 3). The signals at δ 140.59, 132.76, 129.68, 128.14, 127.88, 127.78, 125.82, 121.99, 114.27, and 55.39 ppm are assigned to C-4, C-6, C-7, C-8, C-10, 10′,

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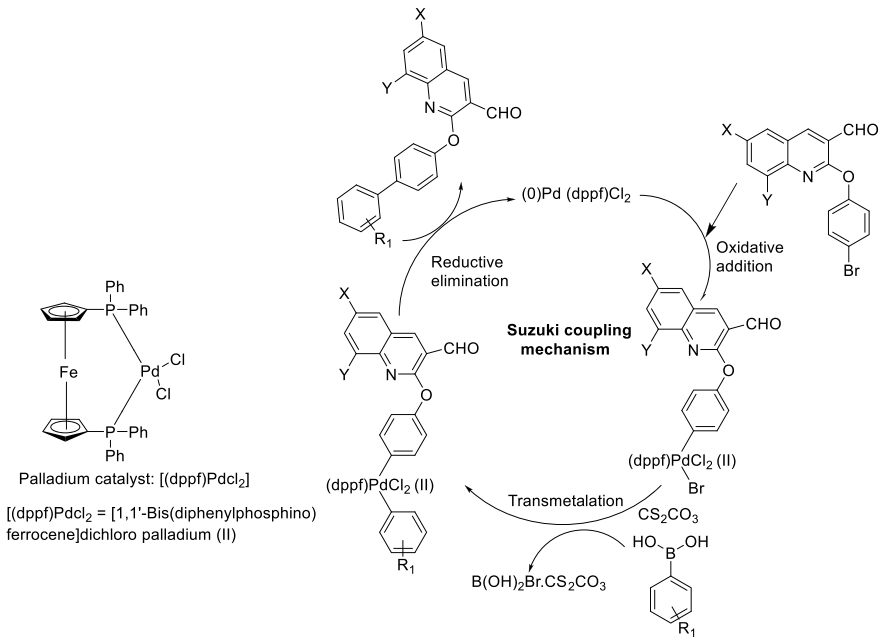

Figure 3. Proposed mechanism for the synthesis of 2-([biphenyl]-4-yloxy)quinolin-3-carbaldehydes (**5a**–**o**).

C-11, 11′, C-14, C-14′, C-15, C-15′, and C-17, respectively, and are confirmed by DEPT-135. The formation of compound **5b** was supported by the observation of the m/z value at 356.1290 in the mass spectrum, and the proton and carbon chemical shift values were assigned based on H,H-COSY and HSQC and are given in Figure 2.

*2-(4-(Pyridin-4-yl)phenoxy)quinolin-3-carbaldehyde (**5a**).* Brown-colored compound, yield 60%, m.p.: 142–146 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.67 (s, 1H), δ 8.78 (s, 1H), δ 8.69 (d, J = 6.00 Hz, 2H), 7.93 (d, J = 8.00 Hz, 1H), δ 7.79–7.71 (m, 4H), 7.57 (d, J = 6.00 Hz, 2H), 7.50 (t, J = 6.80 Hz, 1H), 7.46 (d, J = 8.80 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 188.74, 160.19, 153.90, 150.30, 148.50, 147.67, 140.86, 135.04, 132.91, 129.72, 128.25, 127.82, 126.03, 125.30, 122.49, 121.57, 120.16. HRMS-ESI (m/z) calcd for $C_{21}H_{14}N_2O_2$ $[M + H]^+$ = 327.1134, found = 327.1130.

*2-(4-(3-Formyl-phenyl)phenoxy)quinolin-3-carbaldehyde (**5c**).* Pale yellow-colored compound, yield 63%, m.p.: 168–170 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.68 (s, 1H), 10.12 (s, 1H), 8.78 (s, 1H), 8.16 (s, 1H), 7.90 (q, J = 8.40 Hz, 3H), 7.79–7.70 (m, 4H), 7.65 (t, J = 7.60 Hz, 1H), 7.50 (q, J = 10.8, 1H), 7.44 (d, J = 8.80 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 192.34, 188.85, 160.33, 153.07, 148.55, 140.77, 136.98, 136.71, 133.00, 132.86, 129.81, 129.71, 129.60, 128.74, 128.31, 128.06, 127.84, 125.95, 125.25, 122.35, 120.18. HRMS-ESI (m/z) calcd for $C_{23}H_{15}NO_3$ $[M + H]^+$ = 354.1130, found = 354.1114.

*2-(4-(3-Hydroxymethyl-phenyl)phenoxy)quinolin-3-carbaldehyde (**5d**).* Pale yellow-colored compound, yield 61%, m.p.: 192–194 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.68 (s, 1H), 8.77 (s, 1H), 7.92 (d, J = 8.40 Hz, 1H), 7.79 (d, J = 8.40 Hz, 1H), 7.71 (q, J = 6.80 Hz, 4H), 7.58 (d, J = 7.60 Hz, 1H), 7.48 (q, J = 6.40 Hz, 2H), 7.39 (t, J = 8.40 Hz, 3H), 4.80 (d, J = 4.40 Hz, 2H), 1.77 (t, J = 5.60 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 188.98, 160.45, 152.57, 148.60, 141.48, 140.87, 140.68, 138.02, 132.82, 129.70, 129.11, 128.83, 128.28, 127.86, 126.43, 125.89, 125.74, 125.21, 122.07, 120.19, 65.40. HRMS-ESI (m/z) calcd for $C_{23}H_{17}NO_3$ $[M + H]^+$ = 356.1287, found = 356.1285.

*2-(4-(Pyridin-4-yl)phenoxy)-8-ethylquinolin-3-carbaldehyde (**5e**).* Brown-colored compound, yield 63%, m.p.: 136–138 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.68 (s, 1H), 8.75 (s, 1H), 8.71 (d, J = 3.20 Hz, 2H), 7.77 (q, J = 2.00 Hz, 3H), 7.66 (d, J = 5.20 Hz, 2H), 7.59 (d, J = 6.40 Hz, 1H), 7.51 (dd, J = 2.00, 6.80 Hz, 2H), 7.42 (t, J = 8.00 Hz, 1H), 2.89 (q, J = 7.60 Hz, 2H), 1.14 (t, J = 7.60 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 188.76, 154.56, 146.75, 141.82, 141.22, 134.22, 131.74, 128.02, 127.51, 125.92, 125.33, 122.81, 119.62, 29.70, 14.75. HRMS-ESI (m/z) calcd for $C_{23}H_{18}N_2O_2$ $[M + H]^+$ = 355.1447, found = 355.1435.

*2-(4-(4-Methoxy-phenyl)phenoxy)-8-ethylquinolin-3-carbaldehyde (**5f**).* Colorless compound, yield 60%, m.p.: 180–182 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.70 (s, 1H), 8.73 (s, 1H), 7.75 (d, J = 8.00 Hz, 1H), 7.65–7.55 (m, 5H), 7.39 (t, J = 3.60 Hz, 3H), 7.02 (d, J = 8.40 Hz, 2H), 3.88 (s, 3H), 2.88 (q, J = 7.60 Hz, 2H), 1.13 (t, J = 7.20 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 189.18, 159.59, 159.13, 152.21, 146.92, 141.88, 140.87, 137.64, 133.16, 131.57, 128.09, 127.46, 127.40, 125.66, 125.15, 122.21, 119.62, 114.27, 55.42, 24.68, 14.77. HRMS-ESI (m/z) calcd for $C_{25}H_{21}NO_3$ $[M + H]^+$ = 384.1600, found = 384.1585.

*2-(4-(3-Formyl-phenyl)phenoxy)-8-ethylquinolin-3-carbaldehyde (**5g**).* Pale yellow-colored compound, yield 65%, m.p.: 172–174 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.69 (s, 1H), 10.12 (s, 1H), 8.74 (s, 1H), 8.18 (s, 1H), 7.91 (q, J = 7.60 Hz, 2H), 7.74 (q, J = 8.00 Hz, 3H), 7.65 (t, J = 7.60 Hz, 1H), 7.58 (d, J = 7.20 Hz, 1H), 7.47 (d, J = 8.80 Hz, 2H), 7.40 (t, J = 7.60 Hz, 1H), 2.89 (q, J = 7.60 Hz, 2H), 1.14 (t, J = 7.60 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 192.36, 188.95, 159.38, 153.32, 146.84, 141.85, 141.53, 141.04, 137.00, 136.46, 132.98, 131.65, 129.59, 128.78, 127.94, 127.48, 125.78, 125.24, 122.54, 119.63, 116.18, 24.65, 14.76. HRMS-ESI (m/z) calcd for $C_{25}H_{19}NO_3$ $[M + H]^+$ = 382.1443, found = 382.1421.

*2-(4-(3-Hydroxymethyl-phenyl)phenoxy)-8-ethylquinolin-3-carbaldehyde (**5h**).* Colorless compound, yield 62%, m.p.: 198–200 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.69 (s, 1H), 8.73 (s, 1H), 7.75 (d, J = 8.00 Hz, 1H), 7.70 (d, J = 8.40 Hz,

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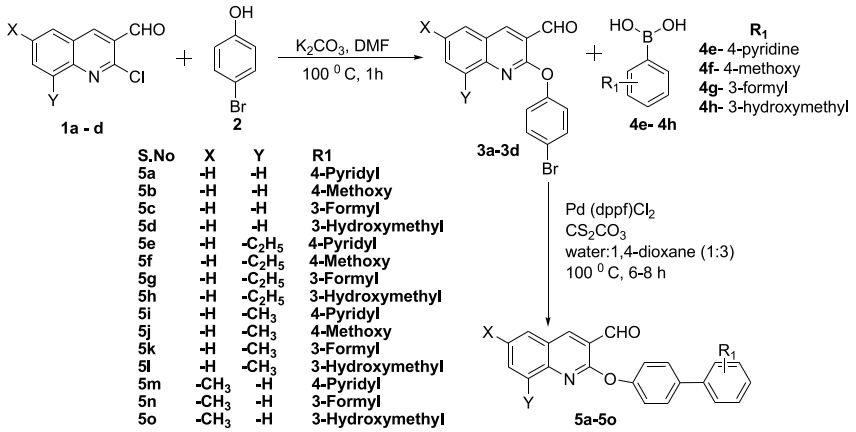
Scheme 1. Synthesis and Its Mechanism of 2-([Biphenyl]-4-yloxy)quinolin-3-carbaldehydes (5a−o)



S.No	X	Y	R1
5a	-H	-H	4-Pyridyl
5b	-H	-H	4-Methoxy
5c	-H	-H	3-Formyl
5d	-H	-H	3-Hydroxymethyl
5e	-H	$-C_2H_5$	4-Pyridyl
5f	-H	$-C_2H_5$	4-Methoxy
5g	-H	$-C_2H_5$	3-Formyl
5h	-H	$-C_2H_5$	3-Hydroxymethyl
5i	-H	$-CH_3$	4-Pyridyl
5j	-H	$-CH_3$	4-Methoxy
5k	-H	$-CH_3$	3-Formyl
5l	-H	$-CH_3$	3-Hydroxymethyl
5m	$-CH_3$	-H	4-Pyridyl
5n	$-CH_3$	-H	3-Formyl
5o	$-CH_3$	-H	3-Hydroxymethyl

3H), 7.58 (t, J = 10.00 Hz, 2H), 7.47 (t, J = 7.60 Hz, 1H), 7.40 (q, J = 8.40 Hz, 4H), 4.80 (s, 2H), 2.88 (q, J = 7.20 Hz, 2H), 1.62 (s, 1H), 1.14 (t, J = 7.60 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 189.07, 159.50, 152.83, 146.89, 141.88, 141.50, 140.93, 137.75, 131.59, 129.11, 127.89, 127.46, 126.40, 125.86, 125.70, 125.68, 125.19, 122.28, 119.64, 65.41, 24.66, 14.76. HRMS-ESI (m/z) calcd for $C_{25}H_{19}NO_3$ $[M + H]^+$ = 384.1600, found = 384.1584.

*2-(4-(Pyridin-4-yl)phenoxy)-8-methylquinolin-3-carbaldehyde (**5i**).* Pale yellow-colored compound, yield 64%, m.p.: 130−132 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.69 (s, 1H), 8.75 (s, 1H), 8.69 (d, J = 3.20 Hz, 2H), 7.76 (q, J = 2.00 Hz, 3H), 7.59 (q, J = 3.60 Hz, 3H), 7.52 (q, J = 2.00 Hz, 2H), 7.39 (t, J = 8.00 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 188.80, 159.09, 154.39, 149.33, 147.30, 141.12, 136.03, 134.33, 133.10, 127.99, 127.47, 125.75, 125.22, 122.61, 121.77, 119.66, 17.37. HRMS-ESI (m/z) calcd for $C_{22}H_{16}N_2O_2$ $[M + H]^+$ = 341.1290, found = 341.1290.

*2-(4-(4-Methoxy-phenyl)phenoxy)-8-methylquinolin-3-carbaldehyde (**5j**).* Colorless compound, yield 61%, m.p.: 176−178 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.69 (s, 1H), 8.72 (s, 1H), 7.74 (d, J = 8.00 Hz, 1H), 7.63 (q, J = 2.00 Hz, 2H), 7.58 (t, J = 8.80 Hz, 3H), 7.42 (d, J = 8.80 Hz, 2H), 7.36 (t, J = 7.60 Hz, 1H), 7.01 (d, J = 8.80 Hz, 2H), 3.87 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 189.14, 159.49, 159.15, 152.19, 147.47, 140.79, 137.59, 136.08, 133.12, 132.93, 128.07, 127.40, 125.49, 125.06, 122.03, 119.69, 114.28, 55.40, 17.38. HRMS-ESI (m/z) calcd for $C_{24}H_{19}NO_3$ $[M + H]^+$ = 370.1443, found = 370.1432.

*2-(4-(3-Formyl-phenyl)phenoxy)-8-methylquinolin-3-carbaldehyde (**5k**).* Colorless compound, yield 60%, m.p.: 162−164 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.72 (s, 1H), 10.15 (s, 1H), 8.76 (s, 1H), 8.20 (s, 1H), 7.96 (dt, J = 1.20, 7.60 Hz, 1H), 7.91 (d, J = 7.60 Hz, 1H), 7.76 (q, J = 8.00 Hz, 3H), 7.67 (t, J = 7.60 Hz, 1H), 7.61 (d, J = 7.20 Hz, 1H), 7.53 (dt, J = 2.40, 9.20 Hz, 2H), 7.40 (t, J = 7.60 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 192.36, 188.97, 159.29, 153.25, 147.38, 141.50, 140.97, 136.98, 136.41, 136.06, 133.03, 132.97, 129.58, 128.79, 127.95, 127.93, 127.44, 125.63, 125.14, 122.39, 119.66, 17.39. HRMS-ESI (m/z) calcd for $C_{24}H_{17}NO_3$ $[M + H]^+$ = 368.1287, found = 368.1256.

*2-(4-(3-Hydroxymethyl-phenyl)phenoxy)-8-methylquinolin-3-carbaldehyde (**5l**).* Colorless compound, yield 63%, m.p.: 206−208 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.69 (s, 1H), 8.72 (s, 1H), 7.74 (d, J = 8.00 Hz, 1H), 7.69 (t, J = 8.80 Hz, 3H), 7.58 (t, J = 8.40 Hz, 2H), 7.46 (q, J = 8.80 Hz, 3H), 7.37 (q, J = 1.60 Hz, 2H), 4.80 (s, 2H), 2.46 (s, 3H), 1.26 (t, J = 7.20 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 189.09, 159.41, 152.77, 147.43, 141.49, 140.89, 140.86, 137.69, 136.07, 132.97, 129.11, 127.90, 127.42, 126.39, 125.85, 125.68, 125.54, 125.08, 122.12, 119.67, 65.42, 17.38. HRMS-ESI (m/z) calcd for $C_{24}H_{19}NO_3$ $[M + H]^+$ = 370.1443, found = 370.1434.

*2-(4-(Pyridin-4-yl)phenoxy)-6-methylquinolin-3-carbaldehyde (**5m**).* Brown-colored compound, yield 61%, m.p.: 138−140 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.65 (s, 1H), 8.69 (s, 2H), 7.76 (q, J = 1.60 Hz, 2H), 7.68 (d, J = 8.80 Hz, 3H), 7.64 (d, J = 4.00 Hz, 2H), 7.57 (dd, J = 1.60, 8.60 Hz, 1H), 7.46 (q, J = 2.00 Hz, 2H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 188.78, 159.65, 154.57, 148.56, 146.90, 140.25, 136.05, 135.22, 134.13, 128.54, 128.39, 127.49, 125.37, 122.55, 121.98, 120.11, 21.33. HRMS-ESI (m/z) calcd for $C_{22}H_{16}N_2O_2$ $[M + H]^+$ = 341.1290, found = 341.1291.

*2-(4-(3-Formyl-phenyl)phenoxy)-6-methylquinolin-3-carbaldehyde (**5n**).* Colorless compound, yield 60%, m.p.: 170−172 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.66 (s, 1H), 10.11 (s, 1H), 8.68 (s, 1H), 8.15 (s, 1H), 7.89 (q, J = 8.00 Hz, 2H), 7.72 (d, J = 8.40 Hz, 2H), 7.65 (q, J = 8.40 Hz, 3H), 7.56 (d, J = 8.80 Hz, 1H), 7.43 (d, J = 8.40 Hz, 2H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 192.30, 188.94, 159.91, 153.25, 147.00, 141.51, 140.05, 136.99, 136.55, 135.85, 135.10, 132.96, 129.57, 128.66, 128.51, 128.27, 128.05, 127.53, 125.28, 122.26, 120.14, 21.32. HRMS-ESI (m/z) calcd for $C_{24}H_{17}NO_3$ $[M + H]^+$ = 368.1287, found = 368.1286.

*2-(4-(3-Hydroxymethyl-phenyl)phenoxy)-6-methylquinolin-3-carbaldehyde (**5o**).* Colorless compound, yield 65%, m.p.: 202−204 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.66 (s, 1H), 8.68 (s, 1H), 7.67 (t, J = 8.80 Hz, 5H), 7.56 (t, J = 7.60 Hz, 2H), 7.46 (t, J = 7.60 Hz, 1H), 7.38 (t, J = 7.60 Hz, 3H), 4.79 (s, 2H), 2.51 (s, 3H), 1.26 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 189.08, 160.03, 152.77, 147.06, 141.47, 140.92, 139.96, 137.88, 135.76, 135.05, 129.09, 128.49, 128.24, 127.56, 126.43, 125.84, 125.73, 125.25, 121.97, 120.17, 65.42, 21.31. HRMS-ESI (m/z) calcd for $C_{24}H_{19}NO_3$ $[M + H]^+$ = 370.1443, found = 370.1435.

RESULTS AND DISCUSSION

The molecules **3a−3d** have been synthesized using the literature,[22,23] which in turn are converted into 2-([biphenyl]-4-yloxy)quinolin-3-carbaldehydes (**5a−5o**) by palladium-mediated Suzuki−Miyaura cross-coupling of various substituted 2-(4-bromophenoxy)quinolin-3-carabaldehydes (**3a−3d**,

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Table 1. Optimization of Scheme 1 under Various Catalysts, Solvents, Bases, and Temperatures[a]

s. no	bases	solvents	temperature (°C)	Pd catalyst	yield (%)	time (h)
1	K_2CO_3	DMSO	100	$Pd(OAc)_2$	NR	48
2	K_2CO_3	DMF	100	$Pd(OAc)_2$	NR	48
3	K_2CO_3	CAN	82	$Pd(OAc)_2$	NR	48
4	Na_2CO_3	DMSO	100	$PdCl_2(PPh_3)_2$	NR	48
5	Na_2CO_3	DMF	100	$PdCl_2(PPh_3)_2$	NR	48
6	Na_2CO_3	CAN	82	$PdCl_2(PPh_3)_2$	NR	48
7	Cs_2CO_3	DMSO	100	$Pd(PPh_3)_4$	NR	48
8	Cs_2CO_3	DMF	100	$Pd(PPh_3)_4$	NR	48
9	Cs_2CO_3	CAN	82	$Pd(PPh_3)_4$	NR	48
10	KO^{t}Bu	DMSO	100	[(dppf)$PdCl_2$]	45−50	24
11	KO^{t}Bu	DMF	100	[(dppf)$PdCl_2$]	40−45	24
12	KO^{t}Bu	CAN	82	[(dppf)$PdCl_2$]	NR	48
13	NaO^{t}Bu	DMSO	100	[(dppf)$PdCl_2$]	40−45	24
14	NaO^{t}Bu	DMF	100	[(dppf)$PdCl_2$]	35−40	24
15	NaO^{t}Bu	CAN	82	[(dppf)$PdCl_2$]	NR	48
16	Cs_2CO_3	ethanol	80	[(dppf)$PdCl_2$]	NR	48
17	Cs_2CO_3	methanol	70	[(dppf)$PdCl_2$]	NR	48
18	Cs_2CO_3	water	100	[(dppf)$PdCl_2$]	NR	48
19	Cs_2CO_3	1,4-dioxane	100	[(dppf)$PdCl_2$]	50−55	24
20	Cs_2CO_3		150	[(dppf)$PdCl_2$]	NR	24
21	Cs_2CO_3	water/1,4-dioxane (1:3)	100	[(dppf)$PdCl_2$]	60−65	6−8

[a]DMSO = dimethyl sulfoxide, DMF = dimethylformamide, ACN = acetonitrile, and NR = no reaction.

0.1 g, 0.0003 M) with substituted boronic acids (**4e−4h**, 0.037 g, 0.0003 M) in the presence of Cs_2CO_3 (0.1 g, 0.0003 M) and [(dppf)$PdCl_2$] (5 mol %) in water/1,4-dioxane (1:3, 4 mL) at 100 °C and stirred for 6−8 h (Scheme 1). Initially, (dppf)$PdCl_2$ was treated with substituted 2-(4-bromophenoxy)quinolin-3-carabaldehydes (**3a−d**), in which Pd(0) turns into Pd(II) through the process of oxidative addition in a nitrogen atmosphere. In the next step of transmetalation, various substituted boronic acids (**4e−h**) are reacted with the Pd(II) intermediate in the presence of CS_2CO_3, in which Pd(II) has been reduced to Pd(0) by reductive elimination. In this step, (dppf)$PdCl_2$ also retains its original structure along with the formation of the desired products 2-([biphenyl]-4-yloxy)quinoline-3-carbaldehydes (**5a−o**) (Figure 3). Initially, the reaction was screened with various palladium catalysts such as $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, and [(dppf)$PdCl_2$] as well as different bases like K_2CO_3, Na_2CO_3, Cs_2CO_3, KOtBu, NaOtBu, and Cs_2CO_3 in different solvents such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF), acetonitrile (ACN), and water/1,4-dioxane (1:3). Suzuki coupling was not proceeded to afford the desired product when ethanol, methanol, and water are used as a solvent medium in the presence of catalysts such as $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, and $Pd(PPh_3)_4$. When ACN was used as a solvent even in the presence of [(dppf)$PdCl_2$], the reaction did not proceed. The reaction was observed to proceed under the solvent-free condition as a neat reaction, but the conversion of the product was not observed even after a long time at high temperatures (Table 1). The maximum yield was observed when [(dppf)$PdCl_2$] was used as a catalyst, Cs_2CO_3 as a base, and water/1,4-dioxane (1:3) as a solvent medium (Scheme 1), and all the optimization conditions are described in Table 1.

All the newly synthesized 2-([biphenyl]-4-yloxy)quinolin-3-carbaldehydes (**5a−m**) were characterized and confirmed by ^{1}H NMR, ^{13}C NMR, DEPT-135, ^{1}H-^{1}H COSY, HSQC, and HRMS (ESI). Compound **5b** is considered as a representative compound, and its spectral characterization is described below. According to the characterization of the representative compound, all other remaining compounds were characterized.

In Silico Binding Studies of Quinoline-Based Biaryl Compounds (5a−o) with Breast Cancer Protein 3ERT. *Methodology.* AutoDock software was applied to dock the breast cancer protein with synthesized compounds (**5a−o**). Through this software the compounds screened were found to show the binding energy ranges from −8.04 to −9.39 kcal/mol. The computational studies demonstrated that the proposed structures have an affinity toward the breast cancer protein and may conceivably establish a fascinating novel class of anticancer drugs, which deserve investigation. This confirms the tight binding between the enzyme and leads, which may pave the way for the discovery of new-generation breast cancer drugs. The docking was carried out in AutoDock 4.2 software using the PyMOL plugin to identify the lead candidates. The protein molecule was selected for breast cancer and downloaded from the PDB database, ID: 3ERT. All the water molecules were removed. The polar hydrogens were added to the receptor and merged with the nonpolar hydrogens. The specified grid maps were generated, and the space was adjusted to defaults in AutoDock. The grid dimension was adjusted to 60 × 60 × 60 points, and the coordinates X = 21.8, Y = 3.6, and Z = 21.4 were processed. Finally, AutoGrid and AutoDock were run successfully. The docking analysis was validated using the binding energy in kcal/mol and hydrogen bonds. The 2D plots were generated using Discovery studio Ver 21.1.0.

Molecular Docking Analysis. All the synthetic compounds and gefitinib[24] (reference compound) were docked with the breast cancer target (PDB ID: 3ERT) (Table 2). The docking score ranges between −8.04 and −9.39 kcal/mol for the screened synthetic compounds. The binding energy of the reference compound gefitinib is −6.86 kcal/mol, and the synthesized compounds were observed to show better binding energy than the reference compound. Among the screened compounds, only five compounds such as **5h**, **5g**, **5d**, **5l**, and

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Table 2. Docking Energies of Synthetic Compounds (5a−o) toward the Breast Cancer Target Protein 3ERT

s. no	compound name	binding energy (kcal/mol)	hydrogen bond interactions
1	**5a**	−8.04	Thr347
2	**5b**	−7.76	
3	**5c**	−8.77	Trp393, Lys449
4	**5d**	**−9.16**	Thr347, Glu353
5	**5e**	−8.52	Thr347
6	**5f**	−8.85	His524
7	**5g**	**−9.33**	Thr347
8	**5h**	**−9.39**	Thr347, Glu353, Arg394
9	**5i**	−8.32	Thr347
10	**5j**	−8.36	
11	**5k**	−8.85	Trp393, Lys449
12	**5l**	**−9.13**	Thr347, Glu353, Arg394
13	**5m**	−8.27	Thr347, Arg394
14	**5n**	−8.92	Thr347, Arg394
15	**5o**	**−9.06**	Thr347, Glu353

5o had better binding energies of −9.39, −9.33, −9.16, −9.13, and −9.06 kcal/mol, respectively. The hydrogen bonding resides on amino acid residues such as Thr347, Glu353, and Arg394; compared to all other molecules, **5h** showed better binding energy that is above −9.39 kcal/mol. The interacting residues are Thr347, Glu353, and Arg394, which were shared between the ligands and the protein, and the key residues could be targeted to design better molecules for breast cancer treatment (Figure 4).

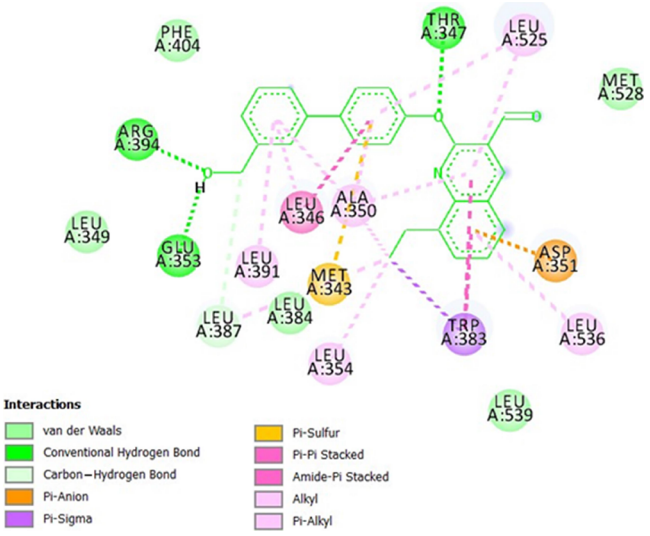

Figure 4. Docking image of amino acid residues of the protein 3ERT interacting with **5h** ligand.

CONCLUSIONS

A series of 2-([biphenyl]-4-yloxy)quinolin-3-carbaldehydes (**5a−5o**) have been synthesized by coupling various 2-(4-bromophenoxy)quinolin-3-carabaldehydes (**3a−3d**) with different boronic acids (**4e−4h**) under the palladium-mediated Suzuki−Miyaura cross-coupling reaction conditions, and all the reactions were found to afford better yield within 6−8 h. The optimized yield was observed while employing [(dppf)-$PdCl_2$] as a Pd catalyst along with Cs_2CO_3 as a base in water/1,4-dioxane (1:3) mixture as a solvent. All the newly synthesized derivatives have been subjected to in silico studies toward the breast cancer protein 3ERT, and all the compounds are found to show better to moderate efficacy based on their finest binding energy values.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c06418.

Spectral and docking images (PDF)

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Notes

The authors declare no competing financial interest.

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