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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SOME NEW BAYLIS-HILLMAN DERIVED CINNAMYL SUBSTITUTED QUINAZOLINONE DERIVATIVES

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ABSTRACT: A series of new Baylis–Hillman derived cinnamyl substituted quinazolinone derivatives have been synthesized by the condensation reaction between Baylis-Hillman bromides and quinazolinones in a simple and efficient manner in less reaction time with high yields. Methyl quinazolinone yields two isomers of Baylis-Hillman derived *3-N*-cinnamyl substituted quinazoline-4-one derivatives and 4-*O*-cinnamyl substituted quinazoline derivatives, and the structures were confirmed by X-ray crystallography. All the newly synthesized compounds were characterized by their spectral data and evaluated their antibacterial and antifungal activity. The compounds (3a, 4a) without any substitution at the aryl group exhibited good antibacterial activity especially on *S. epidermidis* (gram positive), Replacement of hydrogen atom of the aryl group by CF_3 (3c, 4c) or by fluorine (3g) exhibited significant antibacterial activity on both gram-positive (*S. epidermidis*) and gram-negative (*K. pneumonia*) organisms compared to other compounds. All the compounds exhibited interesting antifungal activity on *C. albicans* microorganism exclusively and inactive on the remaining organisms. Compound 3a and 4f exhibited good antifungal activity compared to the other compounds.

INTRODUCTION: Research in heterocyclic chemistry has gained thrust in recent times because more than half of the biologically active molecules belong to various classes of heterocycles [1-8]. 1, 3-Diaza-heterocycles like pyrimidine and quinazoline derivatives, quinazolinones in particular, have been identified as potential drug molecules against various types of diseases. Innumerable quinazolinone alkaloids isolated from plants, animals, and microorganisms shows different types of pharmacological activities [9-15].

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Rutaecarpine and Evodiamine **Fig. 1**, alkaloidal constituents of the Chinese herbal drugs Wu-Chu-Ru [16, 17] Shih-Hu [18, 19] and Febrifugine [20] alkaloids isolated from roots of the Dichroa Febrifuga plant contain the quinazolinone ring system in their structures.

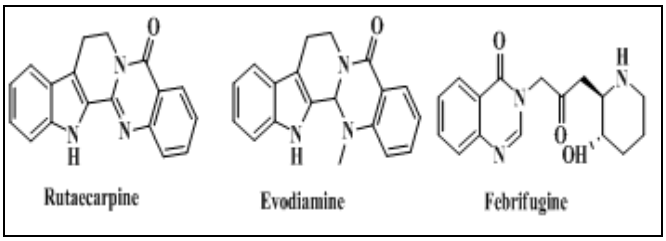


FIG. 1: BIOLOGICALLY ACTIVE QUINAZOLINONE DERIVATIVES

The unique scaffold and pharmacological properties associated with these types of compounds attracted the attention of chemists

towards the syntheses of various types of analogs, and this led to the identification of novel quinazolinone derivatives showing a wide variety of activities like antiallergic, [21] anticonvulsant, [22-24] sedative-hypnotic, [25] antihypertensive [26] and also anticancer [27, 28], *etc*.

Antibacterial and antifungal diseases are very common all over the world. Currently used antimicrobial agents are not effective due to the resistance developed by the microbes, and therefore, it is an ongoing effort to synthesize new antimicrobial agents. Quinazolin-4(3H)-ones with substitution at position 3, has been reported to be associated with anti-microbial properties.[29-36] Examples of these substitutions were substituted phenyl ring moieties [29, 30] bridged phenyl rings [31, 32] heterocyclic rings 33 and aliphatic systems [34, 35].

The Baylis–Hillman reaction [37-41] has attracted the attention of organic chemists as this reaction provides synthetically useful multifunctional molecules. Inspired with the biological profile of quinazolinones and their increasing importance in pharmaceutical and biological fields, and in connection with our research on the design and synthesis of biologically active and pharmacologically important new heterocycles and their derivatives [42-48] it was thought worthwhile to synthesize the title compounds with a view to obtain certain new chemical entities and to have them evaluated for their antimicrobial activity. On the other hand, to the best of my knowledge previously, there is no report, on the synthesis of Baylis-Hillman derived 3-substituted cinnamyl quinazolinone derivatives. In this article, we illustrate the simple and efficient synthesis of Baylis-Hillman derived *3-N*-cinnamyl substituted quinazoline-4-one derivatives and 4-*O*-cinnamyl substituted quinazoline derivatives and screened for their antimicrobial activity.

EXPERIMENTAL:

Materials: All chemicals were of research grade and were used as obtained from Aldrich. The reactions were carried out in a round-bottomed flask of 25 ml capacity at room temperature in an efficient fume hood. The progress of all the reactions was monitored by TLC. Melting points were determined on a MEL-TEMP II melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz, Bruker Avance 300 MHz, 75 MHz spectrometers; TMS was used as an internal standard in $CDCl_3$. Mass spectra were recorded on VG Micro mass 7070 H (EI), QSTAR XL High-resolution mass spectrometer (HRMS), Thermo fining an ESI ion trap Mass Spectrometer and a GC-MS system on an Agilent 6890 series. Commercially available organic compounds were used without further purification except for the solvent, which was distilled by known methods before use. X-ray data were collected at room temperature using a Bruker Smart Apex CCD diffracto meter with graphite mono chromated Mo Kα radiation (λ=0.71073Å) by the ω-scan method [49].

Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Integration and scaling of intensity data were accomplished using the program SAINT [49]. The structures were solved by direct methods using SHELXS97 [50] and refinement was carried out by full-matrix least-squares technique using SHELXL-97 [50]. Anisotropic displacement parameters were calculated for all non-hydrogen atoms. All H atoms were positioned geometrically and treated as riding on their parent C atoms, with C-H = 0.93-0.98 Å, and with U_{iso} (H) = $1.5U_{eq}$(C) for methyl H and $1.2U_{eq}$(c) for other H atoms. The methyl groups were allowed to rotate but not to tip.

General Experimental Procedure: To a solution of quinazolin-4(3H)-one 2a (0.292 g, 2 mmol) in DMF (3 mL), oven dried and ground K_2CO_3 (0.331 g, 1.2 mmol) was added and stirred at room temperature for 10 minutes. Bayllis Hillman bromide (Z)- methyl 2- (bromomethyl)-3-phenylacrylate 1a (0.51 g, 2 mmol) in 2ml DMF was added slowly and stirred at room temperature. Progress of the reaction was monitored by TLC. After completion (1 h), the reaction mixture was diluted with water to remove excess K_2CO_3 and the obtained solid was filtered, washed with water and dried to obtain compound 3a in 95% yield. A similar procedure was adopted for the preparation of other quinazolinone derivatives. In case of compounds 3i-j the obtained solid was further purified by recrystallization with hexane: ethyl acetate (3:1) to get exclusively *Z*-isomer.

In case of compounds 4a-f and 5a-f the obtained solid mixture was further purified by column chromatography (60-120) mesh, with eluent, hexane: ethyl acetate and the pure compounds of 4a-f (8:2) and 5a-f (7:3) were separated.

(E)-methyl2-((4-oxoquinazolin-3(4H)-yl)methyl)-3-phenylacrylate (3a): ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.75 (s, 3H, O-CH_3), 4.99 (s, 2H, N-CH_2), 7.34-7.37 (t, 1H, *J* = 7.78 Hz, H_{Ar}), 7.39-7.44 (q, 3H, *J* = 8.49 Hz, H_{Ar}), 7.52-7.54 (d, 2H, *J* = 7.78, H_{Ar}), 7.60-7.61 (d, 1H, *J* = 7.78 Hz, H_{Ar}), 7.68-7.71 (t, 1H, *J* = 7.78 Hz, H_{Ar}), 7.95 (s, 1H, C=CH), 8.09 (s, 1H, N=CH), 8.14-8.16 (d, 1H, *J* = 7.78 Hz, H_{Ar}).^{13}C NMR (DMSO, 75 MHz): δ 43.56 (O-CH_3), 51.57(N-CH_2), 121.37, 125.74, 126.20, 126.74, 128.14, 128.14, 128.67, 128.92, 133.37, 133.77, 143.13, 143.34, 147.07, 147.47, 159.91 (N-C=O), 166.0 (O-C=O). IR (KBr) in cm^{-1}: 1260 (C-O-C), 1471 (C=N), 1605 (C=C), 1696 (C=O), 2945 (=CH), 3057 (Ar-CH).MS-ESI: m/z 321 $[M+H]^+$. HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{19}H_{17}N_2O_3$: 321.1239; found 321.1252.

(E)-methyl 3- (4- methoxy phenyl) -2-((4-oxoquinazolin-3(4H)-yl) methyl) acrylate (3b): ^{1}H NMR ($CDCl_3$, 300 MHz,): δ 3.78 (s, 3H, O-CH_3), 3.82 (s, 3H, Ar-O-CH_3), 5.04 (s, 2H, N-CH_2), 6.89-6.92 (m, 2H, H_{Ar}), 7.42-7.51 (m, 3H, H_{Ar}), 7.63-7.73 (m, 2H, H_{Ar}), 7.96 (s, 1H, C=CH), 8.07 (s, 1H, N=CH), 8.23-8.27 (d, 1H, *J* = 8.31 Hz, H_{Ar}).^{13}C NMR ($CDCl_3$,75 MHz,): δ 43.74 (O-CH_3), 52.29 (Ar-O-CH_3), 55.29 (N-CH_2), 121.95, 122.80, 126.35, 126.62, 127.02, 127.33, 131.52, 134.11, 145.34, 145.34, 146.28, 147.90, 160.79 (O-Ar-C), 161.22 (O=C-N), 167.31 (O=C-O).IR (KBr) in cm^{-1}: 1258 (C-O-C), 1470 (C=N), 1601 (C=C), 1699 (C=O), 2841 (=CH), 2942 (Ar-CH).MS-ESI: m/z 351 $[M+H]^+$.HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{20}H_{19}N_2O_4Br$: 351.1344; found 351.1359.

(E)-methyl2-((4-oxoquinazolin-3(4H)-yl)methyl)-3 (2 (tri fluoro methyl) phenyl) acrylate (3c):^{1}H NMR ($CDCl_3$, 300 MHz,): δ 3.81 (s, 3H, O-CH_3), 4.77 (s, 2H, CH_2), 7.40-7.49 (m, 2H, H_{Ar}), 7.57-7.64 (m, 2H, H_{Ar}), 7.66-7.76 (m, 3H, H_{Ar}), 8.01 (s, 1H, C=CH), 8.05 (s, 1H, N=CH), 8.17-8.19 (dd, 1H, *J* = 7.93 Hz, H_{Ar}).^{13}C NMR ($CDCl_3$, 75 MHz): δ 43.81 (CH_2), 52.56 (CH_3), 121.95, 125.07, 126.12, 126.19, 126.62, 127.08, 127.38, 128.86, 129.14, 129.14, 129.88, 131.90, 132.79, 134.14, 141.21, 146.88, 160.83 (O=C-N), 166.12 (O=C-O). IR (KBr) in cm^{-1}: 1258 (C-O-C), 1293, 1319, 1473 (C=N), 1606 (C=C), 1679 (N-C=O), 1710 (O-C=O), 2955 (=CH), 3073 (Ar-CH).MS-ESI: m/z 389 $[M+H]^+$.HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{20}H_{16}N_3O_3F_3$: 389.1113; found 389.1117.

(E)-methyl 3- (4-nitro phenyl) -2- ((4-oxo quinazolin-3(4H)-yl)methyl) acrylate (3d): ^{1}H NMR ($CDCl_3$, 300 MHz,): δ 3.78 (s, 3H, O-CH3), 4.95 (s, 2H, N-CH_2), 7.41-7.46 (t, 1H, *J* =8.31 Hz, H_{Ar}), 7.60-7.62 (d, 1H, *J* = 7.55 Hz, H_{Ar}), 7.69-7.73 (t, 1H, *J* = 6.80 Hz, H_{Ar}), 7.81-7.84 (d, 2H, *J* = 8.31 Hz, H_{Ar}), 7.93 (s, 1H, C=CH), 8.08-8.11 (d, 1H, *J* = 8.31 Hz, H_{Ar}), 8.22-8.25 (d, 2H, *J* = 6.80 Hz, H_{Ar}), 8.28 (s, 1H, N=CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 44.28 (O-CH_3), 52.57 (N-CH_2), 121.72, 123.77, 126.41, 127.21, 127.36, 128.82, 129.90, 134.32, 140.85, 141.79, 147.28, 147.68, 147.74, 161.06 (N-C=O), 166.18 (O-C=O). IR (KBr) in cm^{-1}: 1260 (C-O-C), 1472 (C=N), 1517, 1609 (C=C), 1675 (N-C=O), 1707 (O-C=O), 2957 (=CH), 3061 (Ar-CH).MS-ESI: m/z 366 $[M+H]^+$.HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{19}H_{16}N_3O_5$: 366.1089; found 366.1081.

(E)-methyl 3- (naphthalen-1-yl) -2-((4-oxo quinazolin-3(4H)-yl) methyl) acrylate (3e): ^{1}H NMR ($CDCl_3$, 300 MHz,): δ 3.85 (s, 3H, O-CH_3), 4.89 (s, 2H, N-CH_2), 7.36-7.39 (t, 1H, *J* = 7.29 Hz, H_{Ar}), 7.43-7.45 (dd, 2H, *J* = 8.33 Hz, H_{Ar}), 7.47-7.48 (d, 1H, *J* = 7.29 Hz, H_{Ar}), 7.51-7.53 (m, 2H, H_{Ar}), 7.96 (s, 1H), 7.62-7.65 (t, 1H, *J* = 8.33 Hz, H_{Ar}), 7.75 (s, 1H, C=CH), 7.78-7.83 (m, 3H, H_{Ar}), 8.11-8.13 (d, 1H, *J* = 8.33 Hz, H_{Ar}), 8.43 (s, 1H, N=CH).^{13}C NMR ($CDCl_3$, 75 MHz,): δ 44.27 (O-CH_3), 52.86 (N-CH_2), 122.42, 124.36, 125.20, 126.03, 126.43, 126.67, 126.79, 126.86, 127.28, 128.65, 129.55, 131.09, 131.57, 133.44, 133.87, 143.04, 143.90, 146.81, 148.16, 160.99 (N-C=O), 166.80 (O-C=O).IR (KBr) in cm^{-1}: 1274 (C-O-C), 1468 (C=N), 1606 (C=C), 1700 (C=O), 2954 (=CH), 3057 (Ar-CH).MS-ESI: m/z 371 $[M+H]^+$. HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{23}H_{19}N_2O_3$: 371.1395; found 371.1408.

(E)-ethyl 3- (4-bromo phenyl) -2- ((4-oxoquinazolin-3(4H)-yl) methyl) acrylate (3f): ^{1}H NMR (DMSO-d_6, 300 MHz,): δ 1.26-1.29 (t, 3H, *J* = 7.13 Hz, CH_3), 4.17-4.21 (q, 2H, *J* = 7.13 Hz, O-CH_2), 5.01 (s, 2H, N-CH_2), 7.47-7.50 (t, 1H,

J = 7.92 Hz, H_{Ar}), 7.57-7.61 (q, 4H, *J* = 8.71 Hz, H_{Ar}), 7.63-7.65 (d, 1H, *J* = 7.92 Hz, H_{Ar}), 7.74-7.77 (t, 1H, *J* = 7.92 Hz, H_{Ar}), 7.85 (s, 1H,C =CH), 8.13-8.14 (d, 1H, *J* = 7.92, H_{Ar}), 8.23 (s, 1H, N=CH).^{13}C NMR (DMSO-*d6*, 75 MHz): δ 12.67 (CH_3), 42.69(O-CH_2), 59.72 (N-CH_2), 120.35, 121.73, 124.82, 125.44, 125.82, 129.61, 129.76, 130.29, 131.96, 132.63, 140.93, 146.40, 146.46, 159.19 (N-C=O), 164.48 (O-C=O).IR (KBr) in cm^{-1}: 1256(C-O-C), 1469 (C=N), 1606 (C=C), 1686 (N-C=O), 1715 (O-C=O), 2977 (=CH).MS-ESI: m/z 413 $[M+H]^+$, 415 $[M+2+H]^+$. HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{20}H_{18}N_2O_3Br$: 413.0500; found 413.0521.

(E)-methyl 3- (4- fluoro phenyl) -2- ((4-oxoquinazolin-3(4H)-yl) methyl) acrylate (3g): ^{1}H NMR ($CDCl_3$, 300 MHz,): δ 3.78 (s, 3H, O-CH_3), 4.97 (s, 2H, N-CH_2), 7.09-7.15 (t, 2H, *J* = 8.31 Hz, H_{Ar}), 7.42-7.47 (td, 1H, *J* = 6.80 Hz, H_{Ar}), 7.57-7.61 (q, 2H, *J* = 5.29 Hz, H_{Ar}), 7.63-7.74 (m, 2H, *J* = 8.31 Hz, H_{Ar}), 7.93 (s, 1H, C=CH), 8.10 (s, 1H, N=CH), 8.20-8.23 (d, 1H, *J* = 7.55 Hz, H_{Ar}).^{13}C NMR ($CDCl_3$, 75 MHz): δ 43.94 (O-CH_3), 52.39 (N-CH_2), 115.85, 116.14, 121.91, 125.58, 126.57, 127.12, 127.37, 130.22, 131.46, 134.21, 143.93, 146.83, 147.86, 161.18, 161.48, 164.81 (N-C=O), 166.85 (O-C=O).IR (KBr) in cm^{-1}: 1264 (C-O-C), 1469 (C=N), 1605 (C=C), 1691(C=O), 2951 (=CH), 3050(Ar-CH).MS-ESI: m/z 339 $[M+H]^+$. HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{19}H_{16}N_2O_3F$: 339.1144; found 339.1137.

(E)-methyl 2- ((4- oxo quinazolin-3 (4H)-yl)methyl)-3-(thiophen-2-yl) acrylate (3h): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.79 (s, 3H, O-CH_3), 5.15 (s, 2H, N-CH_2), 7.11-7.14 (dd, 1H, *J* = 5.29 Hz, H_{Ar}), 7.42-7.49 (m, 2H, H_{Ar}), 7.54-7.56 (d, 1H, *J* = 5.29 Hz, H_{Ar}), 7.64-7.73 (m, 2H, H_{Ar}), 8.09 (s, 1H, C=CH), 8.11 (s, 1H, N=CH), 8.25-8.28 (d, 1H, *J* = 8.31 Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 75 MHz,): δ 44.10 (O-CH_3), 52.36 (N-CH_2), 120.85, 122.15, 126.83, 126.93, 127.55, 127.75, 131.39, 133.96, 134.57, 136.78, 137.39, 146.14, 148.14, 161.09 (N-C=O), 166.98 (O-C=O). IR (KBr) in cm^{-1}: 1204 (C-O-C), 1471(C=N), 1607 (C=C), 1672 (N-C=O), 1716 (O-C=O), 2920 (=CH), 3106 (Ar-CH).MS-ESI: m/z 327$[M+H]^+$.HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{17}H_{15}N_2O_3S$: 327.0803; found 327.0814.

(Z)-3- (4-nitro phenyl) -2- ((4- oxo quinazolin 3 (4H)-yl) methyl) acrylo nitrile (3i): ^{1}HNMR ($CDCl_3$, 300 MHz): δ 5.04 (s, 2H, N-CH_2), 7.50-7.54 (t, 1H, *J* = 7.35 Hz, H_{Ar}), 7.65 (s, 1H, C=CH), 7.69-7.71 (d, 1H, *J* = 7.35 Hz, H_{Ar}), 7.77-7.81 (t, 1H, *J* = 8.39 Hz, H_{Ar}), 7.99-8.0 (d, 2H, *J* = 9.44 Hz, H_{Ar}), 8.22-8.24 (d, 2H, *J* = 8.39 Hz, H_{Ar}), 8.27-8.29 (d, 2H, *J* = 8.39 Hz, H_{Ar}), 8.42(s, 1H, N=CH).^{13}C NMR ($CDCl_3$, 75 MHz,): δ 48.29 (N-CH_2), 109.97, 116.10, 121.34, 123.52, 125.99, 126.78, 127.07, 129.63, 134.03, 138.62, 144.06, 146.76, 147.64, 147.76, 159.80 (N-C=O). IR (KBr) in cm^{-1}: 1471 (C=N), 1518, 1605 (C=C), 1666 (N-C=O), 2216 (C≡N), 2995 (=CH), 3036 (Ar-CH). MS-ESI: m/z 338$[M+H]^+$. HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{22}H_{16}N_3O$: 338.1293; found 338.1307.

(Z) - 3- (4-bromo phenyl)- 2- ((4-oxo quinazolin 3(4H)-yl) methyl) acrylo nitrile (3j): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.98 (s, 2H, N-CH_2), 7.44-7.60 (m, 4H, H_{Ar}), 7.67-7.70 (d, 3H, *J* = 8.31 Hz, H_{Ar}), 7.75-7.81 (m, 3H, H_{Ar}), 8.2-8.23 (d, 1H, *J* = 7.93 Hz, H_{Ar}), 8.39 (s, 1H, N=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 49.88 (N-CH_2), 105.19, 117.02, 121.88, 125.82, 126.75, 127.75, 127.84, 130.58, 131.19, 132.27, 134.76, 145.38, 146.94, 147.99, 160.85 (N-C=O). IR (KBr) in cm^{-1}: 1350, 1473 (C=N), 1606 (C=C), 1663 (N-C=O), 2211 (C≡N), 2925 (=CH).MS-ESI: m/z 366 $[M+H]^+$, 368 $[M+2+H]^+$.HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{18}H_{13}N_3OBr$: 366.0241; found 366.0229.

(E)-methyl 2-((2-methyl-4-oxoquinazolin-3(4H)-yl) methyl)-3-phenyl acrylate (4a): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.51 (s, 3H, C-CH_3), 3.70 (s, 3H, O-CH_3), 5.18 (s, 2H, N-CH_2), 7.18-7.37 (m, 5H, H_{Ar}), 7.47-7.49 (d, 1H, *J* = 7.55 Hz, H_{Ar}), 7.60-7.66 (dt, 1H, *J* = 1.51 Hz, *J* = 8.31 Hz, H_{Ar}), 7.87(s, 1H, C=CH), 8.10-8.14 (dd, 1H, *J* = 1.51 Hz, *J* = 8.31 Hz, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.92 (CH_3), 41.37 (O-CH_3), 51.73 (N-CH_2), 119.92, 125.73, 126.03, 126.43, 127.31, 128.09, 128.24, 128.33, 133.62, 133.88, 142.11, 146.62, 154.16, 161.69 (N-C=O), 166.06 (O-C=O). IR (KBr) in cm^{-1}: 1249 (C-O-C), 1387, 1432, 1469 (C=N), 1591(C=C), 1676 (N-C=O), 1710 (O-C=O), 2947 (=CH). MS-ESI: m/z 335$[M+H]^+$. HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{20}H_{19}N_2O_3$: 335.1395; found 335.1399.

(E)-methyl 2- ((2-methyl quinazolin -4-yloxy) methyl)-3-phenyl acrylate (5a): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.67 (s, 3H, C-CH_3), 3.85 (s, 3H, O-CH_3), 5.39 (s, 2H, O-CH_2), 7.33-7.37 (m, 3H, H_{Ar}), 7.41-7.48 (m, 3H, H_{Ar}), 7.73-7.78 (dt, 1H, *J* = 1.51 Hz, *J* = 6.80 Hz, H_{Ar}), 7.81-7.83 (d, 1H, *J* = 7.55 Hz, H_{Ar}), 8.05 (s, 1H, C=CH), 8.08-8.10 (d, 1H, *J* = 7.55 Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.40 (CH_3), 52.3 (O-CH_3), 61.74 (O-CH_2), 114.66, 120.49, 123.54, 126.05, 127.11, 128.81, 129.65, 132.63, 133.40, 134.47, 145.91, 154.03, 161.46 (O-C=O), 165.53 (N-C=N), 166.50 (O-C=N). IR (KBr) in cm^{-1}: 1229 (C-O-C), 1376, 1425, 1494 (C=N), 1575, 1623 (C=C), 1711(O-C=O), 2953 (=CH). MS-ESI: m/z 335$[M+H]^+$. HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{20}H_{19}N_2O_3$: 335.1395; found 335.1397.

(E)-methyl 3-(4-methoxy phenyl)-2-((2-methy l-4-oxoquinazolin-3(4H) yl) methyl) acrylate (4b): ^{1}H NMR (CDCl3, 300 MHz): δ 2.51 (s, 3H, C-CH_3), 3.65 (s, 3H, O-CH_3), 3.75 (s, 3H, ArO-CH_3), 5.21 (s, 2H, N-CH_2), 6.81-6.83 (d, 2H, *J* = 8.58 Hz, H_{Ar}), 7.33-7.36 (m, 3H, H_{Ar}), 7.48-7.49 (d, 1H, *J* = 7.62 Hz, H_{Ar}), 7.61-7.64 (dt, 1H, *J* = 1.91 Hz, *J* = 8.58 Hz, H_{Ar}), 7.81(s, 1H, C=CH), 8.12-8.14 (d, 1H, *J* = 7.62 Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.36 (CH_3), 41.63 (O-CH_3), 52.02 (ArO-CH_3), 55.22 (O-CH_2), 114.01, 125.71, 126.14, 126.41, 126.61, 126.84, 130.80, 134.03, 141.84, 142.58, 147.06, 154.74, 160.09 (O-CAr), 162.22 (N-C=O), 166.70 (O-C=O).IR (KBr) in cm^{-1}: 1260 (C-O-C), 1460 (C=N), 1511, 1600 (C=C), 1680 (N-C=O), 1715 (O-C=O), 2837, 2859 (=CH). MS-ESI: m/z 365$[M+H]^+$. HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{21}H_{21}N_2O_4$: 365.1501; found 365.1514.

(E)-methyl 3- (4-methoxyphenyl) -2- ((2-methyl quinazolin-4-yloxy) methyl) acrylate (5b): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.80 (s, 3H, CH_3), 3.81 (s, 3H, O-CH_3), 3.85 (s, 3H, ArO-CH_3), 5.48 (s, 2H, O-CH_2), 6.87-6.90 (d, 2H, *J* = 8.50 Hz, H_{Ar}), 7.43-7.46 (d, 2H, *J* = 8.69 Hz, H_{Ar}), 7.51-7.56 (t, 1H, *J* = 7.36 Hz, H_{Ar}), 7.83-7.88 (t, 1H, *J* = 7.18 Hz, H_{Ar}), 8.06 (s, 2H), 8.13-8.16 (d, 1H, *J* = 7.93 Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.37(CH_3), 52.25 (O-CH_3), 55.33 (ArO-CH_3), 61.98 (O-CH_2), 101.59, 114.27, 119.92, 123.52, 124.42, 126.08, 126.84, 129.27, 131.68, 133.49, 136.73, 145.88, 152.43, 160.92, 164.14, 166.14, 167.97. IR (KBr) in cm^{-1}: 1260 (C-O-C), 1306, 1372, 1436, 1505 (C=N), 1597 (C=C), 1712 (O-C=O), 2845, 2924 (=CH). MS-ESI: m/z 365 $[M+H]^+$ HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{21}H_{21}N_2O_4$: 365.1501; found 365.1510.

(E)-methyl 2- ((2-methyl -4- oxo quinazolin-3(4H)-yl)methyl)-3-(2-(tri fluoro methyl) phenyl) acrylate (4c): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.50 (s, 3H, CH_3), 3.77 (s, 3H, O-CH_3), 5.02 (s, 2H, N-CH_2), 7.24-7.37 (m, 2H, H_{Ar}), 7.40-7.51 (m, 2H, H_{Ar}), 7.55-7.67 (m, 3H, H_{Ar}), 7.94 (s, 1H, C=CH), 8.05-8.08 (dd, 1H, *J* = 1.51, *J* = 8.31 Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.23(CH_3), 41.97 (O-CH_3), 52.49 (N-CH_2), 120.15, 125.78, 125.84, 125.92, 125.98, 126.19, 126.48, 126.75, 127.91, 128.49, 130.08, 131.06, 131.66, 132.56, 134.13, 138.68, 147.00, 154.48 (N-C=O), 166.05 (O-C=O). IR (KBr) in cm^{-1}: 1237 (C-O-C), 1316, 1375, 1416, 1492 (C=N), 1575 (C=C), 1671 (N-C=O), 1714 (O-C=O), 2954 (=CH), 3070 (ArCH). MS-ESI: m/z 403 $[M+H]^+$. HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{21}H_{18}N_2O_3F_3$: 403.1275; found 403.1275.

(E)-methyl 2-((2-methyl quinazolin - 4 yloxy) methyl)-3-(2-(tri fluoro methyl) phenyl) acrylate (5c): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.63 (s, 3H, CH_3), 3.89 (s, 3H, O-CH_3), 5.22 (s, 2H, N-CH_2), 7.40-7.48 (m, 4H, H_{Ar}), 7.68-7.83 (m, 3H, H_{Ar}), 8.01-8.03 (d, 1H, *J* = 7.55 Hz, H_{Ar}), 8.22-8.23 (d, 1H, *J* = 1.51 Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.31 (CH_3), 52.45 (O-CH_3), 61.42 (O-CH_2), 114.49, 121.99, 123.35, 125.62, 126.01, 126.12, 126.19, 127.15, 128.45, 128.92, 129.24, 130.19, 130.35, 131.83, 133.37, 141.85, 151.57, 163.49 (O-C=O), 165.71 (N=C-N), 166.27 (O-C=N). IR (KBr) in cm^{-1}: 1237 (C-O-C), 1316, 1375, 1416, 1492 (C=N), 1575, 1621(C=C), 1714 (O-C=O), 2954 (=CH), 3070 (Ar-CH). MS-ESI: m/z 403$[M+H]^+$. HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{21}H_{18}N_2O_3F_3$: 403.1269; found 403.1273.

(E)-methyl 2-((2-methyl-4-oxo quinazolin-3 (4H)-yl) methyl) - 3-(4-nitrophenyl) acrylate (4d): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.62 (s, 3H, CH_3), 3.80 (s, 3H, O-CH_3), 5.11 (s, 2H, N-CH_2), 7.30-7.35 (t, 1H, *J* = 7.55 Hz, H_{Ar}), 7.42-7.45 (d, 3H, *J* = 9.07 Hz, H_{Ar}), 7.59-7.64 (t, 1H, *J* = 8.31 Hz, H_{Ar}), 7.84 (s, 1H, C=CH), 7.96-8.0 (m, 3H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.44 (CH_3), 42.28 (O-CH_3), 52.58 (N-CH_2), 119.85, 123.34, 126.45, 126.49, 126.56, 128.75, 130.18, 134.40,

139.56, 140.83, 147.13, 146.86, 154.05, 161.96 (N-C=O), 165.95 (O-C=O). IR (KBr) in cm^{-1}: 1257 (C-O-C), 1340, 1509 (C=N), 1595 (C=C), 1677 (N-C=O), 1712 (O-C=O), 2953 (=CH). MS-ESI: m/z 380 $[M+H]^+$. HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{20}H_{17}N_3O_5$: 380.1246; found 380.1264.

(E)-methyl 2-((2-methyl quinazolin- 4 - yloxy) methyl)-3-(4-nitrophenyl) acrylate (5d): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.67 (s, 3H, CH_3), 3.89 (s, 3H, O-CH_3), 5.35 (s, 2H, O-CH_2), 7.42-7.49 (m, 1H, H_{Ar}), 7.52-7.54 (d, 2H, *J* = 8.31 Hz, H_{Ar}), 7.75-7.85 (m, 2H, H_{Ar}), 8.01-8.03 (d, 2H, *J* = 8.31 Hz, H_{Ar}), 8.19-8.24 (m, 2H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.32 (CH_3), 52.66 (O-CH_3), 61.12 (O-CH_2), 114.36, 123.14, 123.94, 126.24, 127.21, 129.36, 130.18, 130.66, 133.66, 136.08, 142.53, 151.61, 163.52 (O-C=O), 165.61 (N-C=N), 166.66 (O-C=N). IR (KBr) in cm^{-1}: 1225 (C-O-C), 1342, 1424 (C=N), 1520, 1578, 1625 (C=C), 1719 (O-C=O), 2954. MS-ESI: m/z 380 $[M+H]^+$. HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{20}H_{17}N_3O_5$: 380.1246; found 380.1247.

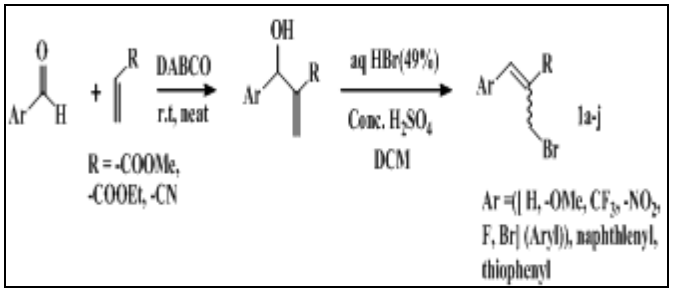
(E)-methyl 2-((2-methyl-4-oxoquinazolin-3 (4H)-yl)methyl)-3-(naphthalen-1-yl) acrylate (4e): ^{1}H NMR ($CDCl_3$, 300 MHz,): δ 2.26 (s, 3H, CH_3), 3.80 (s, 3H, O-CH_3), 5.06 (s, 2H, N-CH_2), 7.22-7.45 (m, 6H, H_{Ar}), 7.50-7.78 (m, 4H, H_{Ar}), 7.94-8.0 (d, 1H, *J* = 7.93 Hz, H_{Ar}), 8.25 (s, 1H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 75 MHz,): δ 22.94 (CH_3), 41.92 (O-CH_3), 52.29 (N-CH_2), 119.98, 124.25, 124.85, 125.73, 125.93, 126.05, 126.19, 126.49, 126.63, 128.33, 128.87, 129.74, 131.21, 133.02, 133.78, 135.59, 140.92, 146.57, 154.10, 161.65 (N-C=O), 167.21 (O-C=O). IR (KBr) in cm^{-1}: 1253 (C-O-C), 1340, 1387, 1436, 1472 (C=N), 1598 (C=C), 1677 (N-C=O), 1715 (O-C=O), 2951 (=CH). MS-ESI: m/z 385 $[M+H]^+$.HRMS (ESI):m/z, $(M+H)^+$ calculated for $C_{24}H_{20}N_2O_3$: 385.1552: found 385.1559.

(E)-methyl 2- ((2-methyl quinazolin-4-yloxy) methyl) -3-(naphthalen-1-yl) acrylate (5e): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.52 (s, 3H, CH_3), 3.90 (s, 3H, O-CH_3), 5.34 (s, 2H, O-CH_2), 7.34-7.44 (m, 2H, H_{Ar}), 7.46-7.51 (d, 3H, *J* = 7.18 Hz, H_{Ar}), 7.69-7.85 (m, 4H, H_{Ar}), 7.90-7.95 (t, 1H, *J* = 5.67 Hz, H_{Ar}), 7.99-8.05 (d, 1H, *J* = 8.12 Hz, H_{Ar}), 8.59 (s, 1H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.17 (CH_3), 52.37 (O-CH_3), 61.94 (O-CH_2), 114.50, 123.43, 124.45, 125.27, 125.96, 126.37, 126.73, 126.86, 128.59, 128.78, 129.31, 129.74, 131.46, 131.71, 133.37, 138.58, 144.21, 151.36, 163.63 (O-C=O), 165.87 (N-C=N), 167.13 (O-C=N). IR (KBr) in cm^{-1}: 1232 (C-O-C), 1370, 1493 (C=N), 1574, 1622 (C=C), 1711 (O-C=O), 2926 (C=CH), 3055 (Ar CH). MS-ESI: m/z 385 $[M+H]^+$. HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{24}H_{21}N_2O_3$: 385.1552; found 385.1561.

(E)-ethyl 3- (4-bromo phenyl) -2-((2-methyl-4-oxo quinazolin -3 (4H)- yl) methyl) acrylate (4f):^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.15-1.22 (t, 3H, *J* = 7.18 Hz, CH_3) 2.53 (s, 3H, CH_3), 4.09-4.18 (q, 2H, *J* = 7.18 Hz, CH_2), 5.14 (s, 2H, N-CH_2), 7.23-7.26 (d, 2H, *J* = 8.50 Hz, H_{Ar}), 7.34-7.42 (q, 3H, *J* = 8.31 Hz, H_{Ar}), 7.47-7.50 (d, 1H, *J* = 8.12 Hz, H_{Ar}), 7.62-7.67 (t, 1H, *J* = 7.18 Hz, H_{Ar}), 7.76 (s, 1H, C=CH), 8.07-8.10 (d, 1H, *J* = 7.93 Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.99 (CH_3), 23.36 (CH_3), 41.80 (CH_2), 61.26 (N-CH_2), 120.26, 126.28, 126.52, 126.74, 128.76, 130.07, 131.67, 133.21, 134.11, 140.86, 146.97, 154.27, 159.98, 161.92 (N-C=O), 165.76 (O-C=O). IR (KBr) in cm^{-1}: 1319 (C-O-C), 1383, 1474 (C=N), 1591(C=C), 1674 (N-C=O), 1716 (O-C=O), 2965, 2989 (=CH). MS-ESI: m/z 427 $[M+H]^+$, 429 $[M+2+H]^+$. HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{21}H_{20}N_2O_3Br$: 427.0657; found 427.0653.

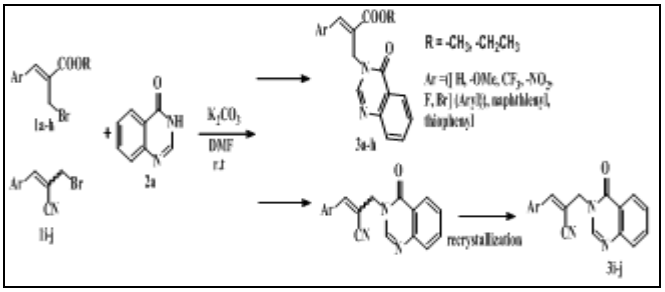
(E)-ethyl 3-(4-bromo phenyl) -2 - ((2-methyl quinazolin-4-yloxy) methyl) acrylate (5f): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29 (t, 3H, *J* = 6.79 Hz, CH_3) 2.68 (s, 3H, CH_3), 4.27-4.34 (q, 2H, *J* = 6.79 Hz, CH_2), 5.36 (s, 2H, O-CH_2), 7.32-7.37 (d, 2H, *J* = 8.31 Hz, H_{Ar}), 7.41-7.47 (dt, 1H, *J* = 1.51 Hz, *J* = 8.31 Hz,H_{Ar}), 7.48-7.52 (d, 2H, *J* = 9.06 Hz, H_{Ar}), 7.73-7.79 (dt, 1H, *J* = 1.51 Hz, *J* = 8.31 Hz, H_{Ar}), 7.81-7.85 (d, 1H, *J* = 7.55 Hz, H_{Ar}), 7.95 (s, 1H, C=CH), 8.03-8.08 (d, 1H, *J* = 8.31 Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.45 (CH_3), 26.38 (CH_3), 61.22 (CH_2), 61.46 (CH_2), 114.57, 123.35, 124.17, 126.04, 127.25, 128.26, 131.06, 132.08, 133.39, 143.93, 151.66, 163.56 (O-C=O), 165.84 (O-C=N), 166.42 (N-C=N). IR (KBr) in cm^{-1}: 1248 (C-O-C), 1322, 1366, 1420, 1491 (C=N), 1576 (C=C), 1637, 1720 (O-C=O), 2921, 2973 (=CH). MS-ESI: m/z 427 $[M+H]^+$. HRMS (ESI): m/z, $(M+H)^+$ calculated for $C_{21}H_{20}N_2O_3Br$: 427.0657; found 427.0663.

RESULTS AND DISCUSSION: Baylis-Hillman bromides (cinnamyl bromides) 1a-j used in the reactions were synthesized according to the literature procedure [51] **Scheme 1**. Quinazolin-4(3H)-one (2a) and 2-methylquinazolin-4(3H)-one (2b) were prepared based on the earlier procedure [52, 53] from anthranilic acid and formamide, acetamide respectively in microwave.



SCHEME 1: SYNTHESIS OF CINNAMYL BROMIDES FROM BAYLIS-HILLMAN ADDUCTS

The Baylis-Hillman derived 3-cinnamyl substituted quinazolinone derivatives were prepared by the reaction between Baylis-Hillman bromides 1a-j and quinazolin-4(3H)-one (2a), in presence of a base. During the optimization studies, the reaction was carried out with cinnamyl bromide 1a with quinazolinone 2a in different bases such as NaH, KOH, K_2CO_3, in DMF, NaOMe in MeOH, and in NEt_3. It was observed that with K_2CO_3, in DMF the desired 3-cinnamyl quinazolinone derivative 3a was obtained at ambient temperature in 1h with 95 % yield **Scheme 2**. In order to evaluate the generality of this method, several analogues of 3-cinnamyl substituted quinazolinone derivatives 3b-j were synthesized by the reaction of quinazolin-4(3H)-one (2a) with different Baylis-Hillman cinnamyl bromides 1b-j **Scheme 2**. The reactions proceeded very efficiently with good yields in less reaction time (40–60 min) **Table 1**. Withdrawing substituted Baylis-Hillman bromides produce the corresponding 3-cinnamyl substituted quinazolinone derivatives in less reaction time with high yields compared to compounds with donating substituent. The structures of 3a-j were firmly established by well-defined ^{1}H-NMR, ^{13}C-NMR, IR, and HRMS. As the ester-substituted Baylis-Hillman bromides are with a *Z*-stereochemistry, they produced 3-cinnamyl substituted quinazolinone derivatives 3a-h with *E*-stereochemistry exclusively which is confirmed by the crystal structure of 3c.



SCHEME 2: SYNTHESIS OF 3-CINNAMYL SUBSTITUTED QUINAZOLINONE DERIVATIVES

Single-Crystal X-ray Diffraction Analysis of Compound 3c: $C_{20}H_{15}F_3N_2O_3$. M = 388.34, monoclinic, space group $P2_1/c$, a = 13.063(4) Å, b = 9.952(3) Å, c = 14.528(5) Å, β = 107.551(5)°, V = 1800.8(10) Å^3, Z = 4, D_c = 1.432 Mg m-3, λ= 0.71073Å, μ(Mo Kα) = 0.118mm-1, F000 = 800, T = 294(2) K. Total number of measured reflections is 14269. Final refinement to convergence on F^2 gave R= 0.0385 (2381 obs. data only) and Rw = 0.1080, GOF = 1.058. Intensity data were measured on Bruker Smart Apex with a CCD area detector. CCDC 885544 contains supplementary Crystallographic data for the structure.

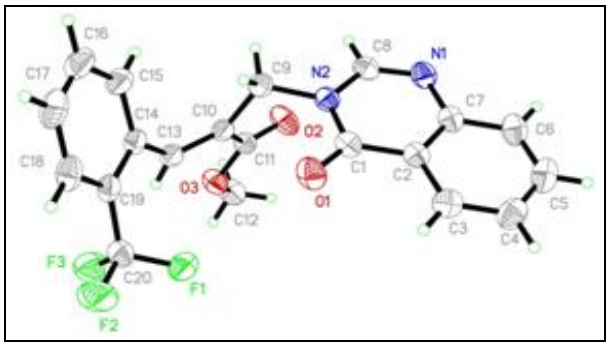


FIG. 2: ORTEP REPRESENTATION OF COMPOUND 3c WITH THERMAL DISPLACEMENT ELLIPSOIDS AT THE 30% PROBABILITY

The cyano substituted Baylis-Hillman bromides are with a mixture of *E* and *Z*-isomers in which *E*-isomer as major product based on earlier reports; they produced 3-cinnamyl substituted quinazolinone derivatives 3i-j with *Z* and *E*-isomers. These compounds were recrystallized with a mixture of hexane and ethyl acetate (3:1) to produce *Z*-isomer exclusively. It was confirmed by the crystal structure obtained for compound 3i. Hence the compounds used for bio-evaluation are with *E*-stereochemistry for compounds 3a-h and with *Z*- stereochemistry for compounds 3i-j.

Single-Crystal X-ray Diffraction Analysis of Compound 3i: $C_{18}H_{12}N_4O_3$. M = 332.32, monoclinic, space group $P2_1/c$, a = 15.5743(15) Å, b = 8.5548(9) Å, c = 12.3161(12) Å, β = 104.611 (2)°, V = 1587.9(3) $Å^3$, Z = 4, D_c = 1.390 Mg m-3, λ= 0.71073Å, μ (Mo Kα) = 0.098mm^{-1}, F000 = 688, T = 294(2) K. Total number of measured reflections is 14757. Final refinement to convergence on F^2 gave R= 0.0368 (2434 obs. data only) and Rw = 0.0998, GOF = 1.024. Intensity data were measured on Bruker Smart Apex with CCD area detector. CCDC 885543 contains supplementary Crystallographic data for the structure.

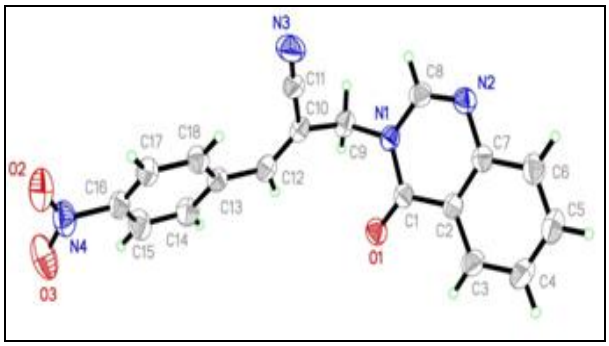


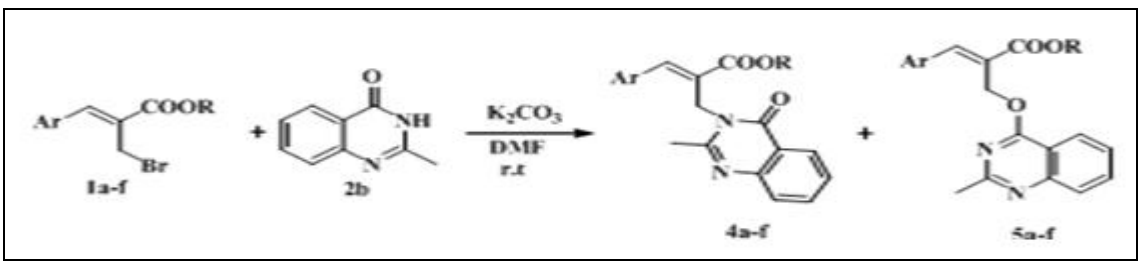
FIG. 3: ORTEP REPRESENTATION OF COMPOUND 3i WITH THERMAL DISPLACEMENT ELLIPSOIDS AT THE 30% PROBABILITY

TABLE 1: VARIOUS QUINAZOLINONE DERIVATIVES SYNTHESIZED

Compound	Ar	R	Mp (°C)	Time(min)	Yield[a] (%)
3a	C_6H_5	CH_3	90-92	60	95
3b	4-$OMeC_6H_4$	CH_3	88-90	60	90
3c	2-$CF_3C_6H_4$	CH_3	118-120	45	92
3d	4-$NO_2C_6H_4$	CH_3	128-130	40	95
3e	C_8H_7 Naphthalen1-yl	CH_3	108-110	60	91
3f	4-BrC_6H_4	CH_2CH_3	103-105	45	94
3g	4-FC_6H_4	CH_3	128-130	40	92
3h	C_4H_3S Thiophene 2-yl	CH_3	114-116	45	90
3i	4-$NO_2C_6H_4$	-	118-120	45	80[b]
3j	4-BrC_6H_4	-	116-118	50	75[b]

[a]isolated yields, [b]isolated yields after recrystallization

To demonstrate the general utility of the method, 2-methylquinazolin-4(3H)-one, different Baylis-Hillman derived cinnamyl 2-methylquinazolin-4(3H)-one derivatives were prepared **Scheme 3** **Table 2**. Baylis-Hillman bromide esters 1a-f and 2-methylquinazolin-4(3H)-one (2b), were reacted in the presence of a base K_2CO_3 in DMF at room temperature and the reactions were completed within 1 h. TLC monitoring of the reaction shows complete consumption of the reactants and appearance of two new products. The reaction was quenched with water and the obtained solid was filtered, washed again with water and dried. The two new products were separated by column chromatography and fully characterized by IR, ^{1}HNMR, ^{13}C-NMR, and HRMS and shown in **Table 2**. Amongst the two products, the more polar products 4a-f were identified as 3-*N*-cinnamyl substituted 2-methyl quinazolin4-one compounds and the less polar products 5a-f were identified as4-*O*-cinnamyl substituted 2-methylquinazoline compounds. These indicate alkylation of 2-methyl quinazolin-4(3H)-one produces two isomers, one with *N*-substitution and another with *O*-substitution. The percentage formation of *N*-isomer is almost equal to *O*-isomer identified from the isolated yields formed. The formation of *O*-isomer may be due to the steric effect and electronic factor of methyl substitution at the 2-position with the cinnamyl bromide during alkylation. The two isomers formed in the reaction were confirmed by X-ray crystallography.



SCHEME 3: SYNTHESIS OF CINNAMYL SUBSTITUTED 2-METHYL QUINAZOLINONE DERIVATIVES

TABLE 2: VARIOUS 2-METHYL QUINAZOLINE AND QUINAZOLINONE DERIVATIVES SYNTHESIZED

Ar	R	Time (min)	Entry	Mp(°C)	Yield [a] (%)	Entry	Mp (°C)	Yield [a] (%)
C_6H_5	CH_3	60	4a	90-92	47	5a	128-130	48
4-$OMeC_6H_4$	CH_3	60	4b	85-87	45	5b	160-162	45
2-$CF_3C_6H_4$	CH_3	45	4c	103-105	48	5c	115-117	48
4-$NO_2C_6H_4$	CH_3	45	4d	128-130	47	5d	158-160	47
C_8H_7 Naphthalen 1-yl	CH_3	50	4e	133-135	45	5e	140-142	45
4-BrC_6H_4	CH_2CH_3	50	4f	136-138	47	5f	144-146	47

[a]isolated yields

Single-Crystal X-ray Diffraction Analysis of Compound 4f: $C_{21}H_{19}BrN_2O_3$. M = 427.29, triclinic, space group P^{-1}, a = 8.7956(6)Å, b = 10.4379(7)Å, c = 11.0152(7)Å, α = 79.103(1) °,β = 71.464(1)°, γ = 84.907(1) °, V = 941.08(11)Å^3, Z = 2, D_c = 1.508 Mg m-3, λ= 0.71073Å, μ(Mo Kα) = 2.208 mm^{-1}, F000 = 436, T = 294(2) K. Total number of measured reflections is 9099. Final refinement to convergence on F^2 gave R= 0.0267 (3001 obs. data only) and Rw = 0.0681, GOF = 1.054. Intensity data were measured on Bruker Smart Apex with CCD area detector. CCDC 826451 contains supplementary Crystallographic data for the structure.

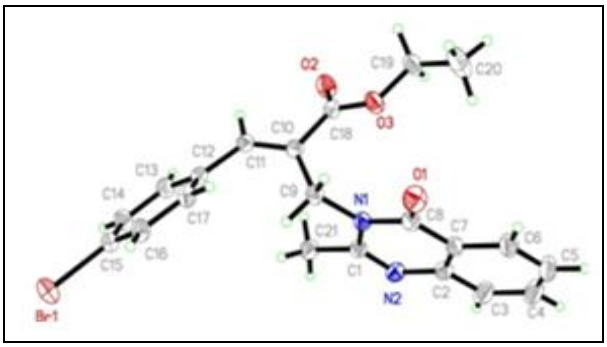


FIG. 4: ORTEP REPRESENTATION OF COMPOUND 4f WITH THERMAL DISPLACEMENT ELLIPSOIDS AT THE 30% PROBABILITY

Single-Crystal X-ray Diffraction Analysis of Compound 5e: $C_{24}H_{20}N_2O_3$. M = 384.42, monoclinic, space group $P2_1/n$, a = 12.0764(12) Å, b = 8.6922(9) Å, c = 18.7930(19) Å, β = 100.867(2)°, V = 1937.3(3) Å^3, Z = 4, D_c = 1.318 Mg m-3, λ= 0.71073Å, μ (Mo Kα) = 0.088mm-1, F000 = 808, T = 294(2) K. Total number of measured reflections is 18042. Final refinement to convergence on F^2 gave R= 0.0358 (3071 obs. data only) and Rw = 0.0978, GOF = 1.051. Intensity data were measured on Bruker Smart Apex with CCD area detector. CCDC 885542 contains supplementary Crystallographic data for the structure.

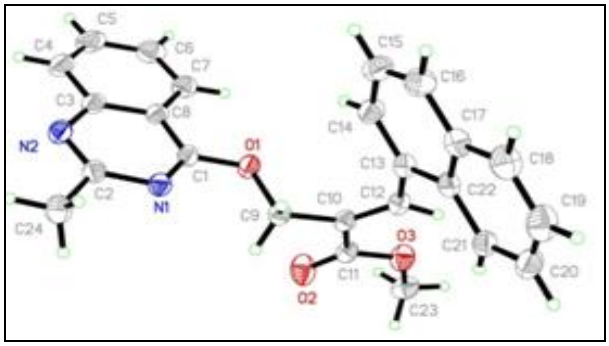


FIG. 5: ORTEP REPRESENTATION OF COMPOUND 5e WITH THERMAL DISPLACEMENT ELLIPSOIDS AT THE 30% PROBABILITY

These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html[or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

Biological Evaluation: All the synthesized compounds are screened for their antimicrobial activity by both dilution method recommended by the National Committee for Clinical Laboratory (NCCL) standards [54]. The minimum inhibitory concentrations (MIC) of various substituted quinazolinone and methyl quinazolinone derivatives were tested against three representative Gram-positive organisms *viz*. *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylo coccus epidermidis* and three Gram-negative organisms viz. *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia* against standards penicillin and streptomycin. The minimum inhibitory concentration (MIC) values are presented in **Table 3**. It has been observed that the test compounds exhibited moderate antibacterial activity, against all the tested organisms. The compound 3a, without any substituent at the aryl group exhibited good antibacterial activity especially on *S. epidermidis* (gram positive). Replacement of hydrogen at the ortho position of the aryl group by CF_3 (3c) and the

para position of the aryl group by fluoro (3g) exhibited significant activity on both gram-positive (*S. epidermidis*) and gram-negative *(K. pneumonia)* organisms. Baylis-Hillman derived 3-cinnamyl substituted quinazolinone derivatives with ester group 3a-h are more active compared to cyano substituted Baylis- Hillman derived 3-cinnamyl substituted quinazolinone derivatives 3i-j.*N*-cinnamyl substituted 2-methylquinazoline compounds 4a-fare showing better antibacterial activity compared to the *O*-cinnamyl substituted 2-methyl quinazolinone compounds 5a-f. 4a and 4c are showing moderate antibacterial activity. Hence the compounds with fluorine, CF_3 substituents have significant antibacterial activity compared to the other compounds.

TABLE 3: ANTIBACTERIAL ACTIVITY OF QUINAZOLINONE AND METHYL QUINAZOLINONE DERIVATIVES

Compound	MIC (µg/mL)					
	B. subtilis	***S. aurues***	***S. epidermidis***	***E. coli***	***P. aeroginosa***	***K. pneumoniae***
3a	100	100	50	100	100	100
3b	100	100	100	100	100	100
3c	100	100	50	100	100	50
3d	100	100	100	100	100	100
3e	100	100	100	100	100	100
3f	100	100	100	100	100	100
3g	100	100	50	100	100	50
3h	100	100	100	100	100	100
3i	100	100	100	100	100	100
3j	100	100	100	100	100	100
4a	100	100	50	100	100	100
4b	100	100	100	100	100	100
4c	100	100	50	100	100	50
4d	100	100	100	100	100	100
4e	100	100	100	100	100	100
4f	100	100	100	100	100	100
5a	100	100	100	100	100	100
5b	100	100	100	100	100	100
5c	100	100	100	100	100	100
5d	100	100	100	100	100	100
5e	100	100	100	100	100	100
5f	100	100	100	100	100	100
Penicillin	1.562	1.562	3.125	12.5	12.5	6.25
Streptomycin	6.25	6.25	3.125	6.25	1.562	3.125

All the compounds are also screened for their antifungal activity against *Yeast* and *Filamentous fungi viz*. *Candida albicans*, *Candida rugosa*, *Saccharomyces cerevisiae*, *Aspergillus niger*, *Rhizopus oryzae* concerning standard Amphotericin B (50 µg) by Agar well diffusion method [55]. Zone of inhibition (mm) was determined for all the compounds. The screening results indicate that all the compounds are showed moderate antifungal activity against *C. albicans* and inactive on the remaining organisms **Table 4**. All the compounds exhibited interesting antifungal activity on *C. albicans* microorganism, however with a degree of variation. Compounds 3a and 4f exhibited good antifungal activity compared to the other compounds.

TABLE 4: ANTIFUNGAL ACTIVITY OF QUINAZOLINONE AND METHYL QUINAZOLINONE DERIVATIVES

Compound	Zone of Inhibition in mm									
	C .albicans		***C. rugosa***		***S. cerevisiae***		***A. niger***		***R. oryzae***	
	50µg	**100µg**	**50µg**	**100µg**	**50µg**	**100µg**	**50µg**	**100µg**	**50µg**	**100µg**
3a	10	14	0	0	0	0	0	0	0	0
3b	7	10	0	0	0	0	0	0	0	0
3c	8	10	0	0	0	0	0	0	0	0
3d	7	10	0	0	0	0	0	0	0	0
3e	9	10	0	0	0	0	0	0	0	0
3f	9	11	0	0	0	0	0	0	0	0

3g	8	11	0	0	0	0	0	0	0	0
3h	8	10	0	0	0	0	0	0	0	0
3i	8	10	0	0	0	0	0	0	0	0
3j	7	10	0	0	0	0	0	0	0	0
4a	8	11	0	0	0	0	0	0	0	0
4b	8	11	0	0	0	0	0	0	0	0
4c	7	10	0	0	0	0	0	0	0	0
4d	8	11	0	0	0	0	0	0	0	0
4e	8	11	0	0	0	0	0	0	0	0
4f	8	12	0	0	0	0	0	0	0	0
5a	7	10	0	0	0	0	0	0	0	0
5b	7	9	0	0	0	0	0	0	0	0
5c	7	10	0	0	0	0	0	0	0	0
5d	8	11	0	0	0	0	0	0	0	0
5e	7	10	0	0	0	0	0	0	0	0
5f	8	11	0	0	0	0	0	0	0	0
Amphotericin-B (50µg)	23.5		21		22		25		24	

CONCLUSION: We developed a new simple and efficient method for the synthesis of a series of new Baylis-Hillman derived *N*-cinnamyl substituted quinazolinone and 2-methylquinazolinone derivatives, and *O*-cinnamyl substituted 2-methyl quinazoline derivatives in good yields. All the synthesized compounds were evaluated for their antimicrobial activity. All compounds are found to be active against all bacterial test strain. Amongst ester substituted compounds, (3a, 3c, 3g and 4a, 4c) shows good antibacterial activity in comparison to cyano substitution. Similarly, compounds with fluorine substituents are active on both gram-positive *(S. epidermidis)* and gram-negative *(K. pneumoniae)* organisms. All the compounds show moderate anti-fungal activity against *C. albicans*. Compound 3a, 4f shows high antifungal activity than the other compounds.

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