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SYNTHESIS AND ANTI-MICROBIAL ACTIVITIES OF SOME 3-(4-PHENYLTHIAZOLE-2-YL) / 3-(3-CARBETHOXY-4,5,6,7-TETRAHYDROBENZOTHIOPHENE-2YL) QUINAZOLIN-4(3H)-ONE

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ABSTRACT

In the present study, a novel quinazolin-4-(3H)-ones were synthesized by condensation of 2-amino-4-phenylthiazole/2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene with 6,8-(un/mono/di)-bromo-2-(methyl/phenyl)-4H-benzo-[1,3]-oxazine-4-ones. The 2-amino-4-phenylthiazole and 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene was synthesized from acetophenone and cyclohexanone respectively. The 6,8-(un/mono/di)-bromo-2-(methyl/phenyl)-4H-benzo-[1,3]-oxazine-4-ones were synthesized from 3,5-(un/mono/di)-bromo anthranilic acid. The chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H-NMR, Mass spectral and Elemental analysis. These compounds were screened for anti-bacterial (*Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Micrococcus luteus* ATCC 4698, *Bacillus cereus* ATCC 11778, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853, *and Klebsiella pneumoniae* ATCC 11298) and anti-fungal (*Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC 46645) activities by paper disc diffusion technique. The minimum inhibitory concentrations (MIC) of the compounds were also determined by agar streak dilution method. Most of the synthesized compounds exhibited mild to moderate anti-bacterial and anti-fungal activities. Among the synthesized compounds, 6,8-Dibromo-2-methyl-3-(4-phenylthiazol-2-yl)-quinazolin-4(3H)-one **(7c)** was found to exhibit the highest anti-bacterial activity and 6,8-Dibromo-2-methyl-3-(3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene-2-yl)-quinazolin-4(3H)-one **(7f)** exhibited highest anti-fungal activity.

Key words: Quinazolin-4-(3H)-one, Thiazole, Benzothiophene, Anti-bacterial and Anti-fungal.

INTRODUCTION

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. Quinazolin-4(3H)-ones[1-5] are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological activities such as, anti-microbial, anti-cancer, anti-convulsant, anti-tubercular, etc. In addition, several physiological activities such as anti-bacterial, fungicidal, anti-spasmodic, analgesic and anti-tubercular of various thiazole[6-8] derivatives have proved their efficacy in combating variety of diseases. A large number of benzothiophene[9-11] derivatives have been found to exhibit a wide variety of pharmaceutical activity such as anti-microbial, anti-cancer and anti-HIV. The above observation stimulated our interest to, synthesize a series of compounds containing quinazolin-4(3H)-one ring system associated with thiazole/benzothiophene moiety and to evaluate their anti-microbial potency.

The synthetic strategy to synthesize the title compounds **(7a-l)** is depicted in scheme-1. In step 1, acetophenone **(1)** is allowed to react with thiourea in presence of bromine to produce 2-amino-4-phenyl thiazole **(2)**. In step 2, cyclohexanone **(3)** was subjected to condensed with ethylcyanoacetate and sulphur to produce 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene **(4)**. In step 3, 3,5-(un/mono/di)-bromo anthranilic acid (X, X_1 = H/Br) **(5)** were allowed to react with acetic

anhydride/benzoyl chloride in dry pyridine for cyclization to produce 6,8-(un/mono/di)-bromo-2-(methyl/phenyl)-4H-benzo-[1,3]-oxazine-4-one **(6)**.

In step 4, the 6,8-(un/mono/di)-bromo-2-(methyl/phenyl)-4H-benzo-[1,3]-oxazine-4-ones **(6)** were allowed to react with 2-amino-4-phenyl thiazole **(2)** / 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene **(4)** in dry pyridine to yield the title compounds **(7a-l)**. Structural elucidation of synthesized compounds was attained by the aid of IR, ^{1}H-NMR, mass spectral and elemental analysis. All the title compounds were screened for their anti-microbial activity against four gram positive bacteria (*Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Micrococcus luteus* ATCC 4698 and *Bacillus cereus* ATCC 11778), three gram negative bacteria (*Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853, *and Klebsiella pneumoniae* ATCC 11298) and two fungi (*Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC 46645). For preliminary screening, the anti-microbial tests were carried out by the paper disc diffusion technique. The minimum inhibitory concentrations (MIC) of the compounds were also determined by agar streak dilution method.

EXPERIMENTAL

Chemistry:

The melting points were determined on a MEL-Temp apparatus by open capillary tube method and are uncorrected. The IR spectra of the compounds were recorded on ABB Bomem FT-IR spectrometer MB 104 with KBr pellets. The ^{1}H-NMR (300 MHz) spectra were recorded on a Bruker 300 NMR spectrometer with TMS as internal references. Mass spectra were recorded on Shimadzu GC MS QP 5000. Microanalyses were obtained with an elemental Analyses system GmbH VarioEL V300 element analyzer. The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (HF_{254}, 200 mesh) aluminium plates (E Merk) using ethyl acetate: n-hexane as developing solvent and visualized in UV chamber. IR, ^{1}H-NMR, Mass spectra and Elemental analysis were consistent with the assigned structures.

Synthesis of 2-amino-4-phenyl thiazole (2):

A mixture consisting of acetophenone **(1)** (0.1 mol) and thiourea (0.2 mol), add bromine (0.2 mol) drop wise very slowly. After the addition of bromine, the reaction mixture was heated on water bath for overnight, and water was added to it and again heated until most of the solid has gone into solution. The reaction mixture was filtered when it is hot and the filtrate was cooled. It was made alkaline with conc. ammonium hydroxide to separate 2-amino-4-phenyl thiazole[12]. The product was filtered, washed with alcohol and dried over P_2O_5. It was recrystallised from ethanol, as colorless needles **(2)**. Yield (84.2%), m.p. 120-122^{0}C .

Synthesis of 2-amino-3-carbethoxy-4,5,6,7-tetrahydro benzothiophene (4):

To a mixture of cyclohexanone **(3)** (0.2 mol), ethylcyanoacetate (0.2 mol) and sulphur (0.2 mol) in ethanol (40 ml), diethylamine (0.2 mol) was added drop wise with stirring. The 2-amino-3-carbethoxy-4,5,6,7-tetrahydro benzothiophene[13] crystals **(4)** obtained are filtered and recrystallized from ethanol. Yield (89.5%), m.p. 119-121^{0}C.

Synthesis of 6,8-(un/mono/di)-bromo-2–(methyl/phenyl)-4H-benzo-(1,3)-oxazin–4-one (6):

For the synthesis of 2-methyl derivative a mixture of 3,5-(un/mono/di)-bromo anthranilic acid **(5a-c)** (0.01mol) and acetic anhydride (0.1mol) was refluxed on gentle flame for 1 – 4 h. The excess of acetic anhydride was distilled off under reduced pressure and the residue was dissolved in petroleum ether and kept aside for1h. The light brown solid **(6a-c)** which obtained was filtered and dried.

For the synthesis of 2-phenyl derivative to a solution of 3,5-(un/mono/di)-bromo anthranilic acid **(5a-c)** (0.1 mol) dissolved in pyridine (60 ml), benzoyl chloride (0.2 mol) was added. The mixture was stirred for 30 min followed by treatment with 5% $NaHCO_3$ (15 ml). The solid **(6d-f)** obtained was recrystallized from ethanol.

Synthesis of title compounds (7a-l):

A mixture of **6a-f** (0.02mol) and **2/4** (0.01mol) in dry pyridine (80 ml) was refluxed for overnight. After refluxing, the excess of solvent was removed and the residue was neutralized with HCl. The solid separated out was washed with water and recrystallised from ethanol to yield title compounds **(7a-l)**. The physical data of the title compounds are depicted in Table-1.

Anti-microbial activity:

All the title compounds were screened for their anti-bacterial and anti-fungal activities. The anti-bacterial activity of the synthesized compounds was tested against four gram positive bacteria (*Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Micrococcus luteus* ATCC 4698 and *Bacillus cereus* ATCC 11778) and three gram negative bacteria (*Escherichia coli* ATCC 25922 *Pseudomonas aeruginosa* ATCC and *Klebsiella pneumoniae* ATCC 11298) using nutrient agar medium (Hi-Media Laboratories, India). The anti-fungal activities of the compounds were tested against two fungi namely *Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC using sabouraud dextrose agar medium (Hi-Media Laboratories, India). For preliminary screening, the anti-microbial tests were carried out by the paper disc diffusion method. The minimum inhibitory concentrations (MIC) of the compounds were also determined by agar streak dilution method.

Paper disc diffusion technique:

The sterilized[14] (autoclaved at 120 °C for 30min) medium (40-50 °C) was inoculated (1ml/100ml of medium) with the suspension (10^5cfu/ml) of the microorganism (matched to McFarland barium sulphate standard) and poured into a petridish to give a depth of 3-4 mm. The paper impregnated with the test compounds (100µg/ml in dimethyl formamide) was placed on the solidified medium. The plates were pre-incubated for 1 h at room temperature and incubated at 37 °C for 24 and 48 h for anti-bacterial and anti-fungal activities, respectively. Ciprofloxacin (100 µg/disc) and Ketoconazole (100 µg/disc) were used as standard for anti-bacterial and anti-fungal activities, respectively. The observed zone of inhibition is presented in Table-2.

Minimum inhibitory concentration (MIC):

MIC[15] of the compound was determined by agar streak dilution method. A stock solution of the synthesized compound (100 µg/ml) in dimethyl formamide was prepared and graded quantities of the test compounds were incorporated in specified quantity of molten sterile agar (nutrient agar for anti-bacterial activity and sabouraud dextrose agar medium for anti-fungal activity). A specified quantity of the medium (40-50 °C) containing the compound was poured into a petridish to give a depth of 3-4 mm and allowed to solidify. Suspension of the microorganism were prepared to contain approximately 10^5 cfu/ml and applied to plates with serially diluted compounds in dimethyl formamide to be tested and incubated at 37 °C for 24 h and 48 h for bacteria and fungi, respectively. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria or fungi on the plate. The observed MIC is presented in Table-2.

RESULTS AND DISCUSSION

Chemistry:

2-Methyl-3-(4-phenylthiazol-2-yl)-quinazolin-4(3H)-one (7a):

IR (KBr, cm^{-1}): 3017 (Ar-CH), 2915 (CH in CH_3), 1720 (C=O), 1518 (C=N), 1462 (C=C), 653 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 7.20-7.85 (m, 9H; C_5,C_6,C_7,C_8,$C_{2''}$,$C_{3''}$,$C_{4''}$,$C_{5''}$,$C_{6''}$; Ar-H), 6.71 (s, 1H; $C_{5'}$), 0.87 (s, 3H; C_2, -C<u>H</u>$_3$). EI-MS *(m/z)*: 319 (Calcd for $C_{18}H_{13}N_3OS$; 319.38). Anal. Calcd for $C_{18}H_{13}N_3OS$: C, 67.69; H, 4.10; N, 13.16. Found: C, 67.60; H, 4.07; N, 13.11.

6-Bromo-2-methyl-3-(4-phenylthiazol-2-yl)-quinazolin-4(3H)-one (7b):

IR (KBr, cm^{-1}): 3041 (Ar-CH), 2920 (CH in CH_3), 1725 (C=O), 1514 (C=N), 1457 (C=C), 646 (C-S), 568 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.18-8.07 (m, 8H; C_5,C_7,C_8, $C_{2''}$,$C_{3''}$,$C_{4''}$,$C_{5''}$,$C_{6''}$; Ar-H), 6.58 (s, 1H; $C_{5'}$), 0.89 (s, 3H; C_2, -C<u>H</u>$_3$). EI-MS *(m/z)*: 398 (Calcd for $C_{18}H_{12}BrN_3OS$; 398.28). Anal. Calcd for $C_{18}H_{12}BrN_3OS$: C, 54.28; H, 3.04; N, 10.55. Found: C, 54.21; H, 3.00; N, 10.49.

6,8-Dibromo-2-methyl-3-(4-phenylthiazol-2-yl)-quinazolin-4(3H)-one (7c):

IR (KBr, cm^{-1}): 3032 (Ar-CH), 2926 (CH in CH_3), 1764 (C=O), 1522 (C=N), 1453 (C=C), 666 (C-S), 583 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.05-7.99 (m, 7H; C_5,C_7,$C_{2''}$,$C_{3''}$,$C_{4''}$,$C_{5''}$,$C_{6''}$; Ar-H), 6.65 (s, 1H; $C_{5'}$), 0.95 (s, 3H; C_2, -C<u>H</u>$_3$). EI-MS *(m/z)*: 477 (Calcd for $C_{18}H_{11}Br_2N_3OS$; 477.17). Anal. Calcd for $C_{18}H_{11}Br_2N_3OS$: C, 45.31; H, 2.32; N, 8.81. Found: C, 45.22; H, 2.26; N, 8.77.

2-Methyl-3-(3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene-2-yl)-quinazolin-4(3H)-one (7d):

IR (KBr, cm^{-1}): 3040 (Ar-CH), 2935 (CH in CH_3), 1722 (C=O), 1519 (C=N), 1448 (C=C), 669 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 7.53-8.05 (m, 4H; C_5,C_6,C_7,C_8; Ar-H), 4.37 (tet, 2H; -C<u>H</u>$_2$), 1.57-2.67 (m, 8H; $C_{4'}$,$C_{5'}$,$C_{6'}$,$C_{7'}$), 1.45 (tri, 3H; -C<u>H</u>$_3$), 0.84 (s, 3H; -C<u>H</u>$_3$). EI-MS *(m/z)*: 368 (Calcd for $C_{20}H_{20}N_2O_3S$; 368.45). Anal. Calcd for $C_{20}H_{20}N_2O_3S$: C, 65.20; H, 5.47; N, 7.60. Found: C, 65.13; H, 5.42; N, 7.55.

6-Bromo-2-methyl-3-(3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene-2-yl)-quinazolin-4(3H)-one (7e):
IR (KBr, cm^{-1}): 3018 (Ar-CH), 2912 (CH in CH_3), 1724 (C=O), 1532 (C=N), 1463 (C=C), 651 (C-S), 574 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.47-7.99 (m, 3H; C_5,C_7,C_8; Ar-H), 4.33 (tet, 2H; -C<u>H</u>$_2$), 1.53-2.60 (m, 8H; $C_{4'}$,$C_{5'}$,$C_{6'}$,$C_{7'}$), 1.39 (tri, 3H; -C<u>H</u>$_3$), 0.87 (s, 3H; -C<u>H</u>$_3$). EI-MS *(m/z)*: 447 (Calcd for $C_{20}H_{19}BrN_2O_3S$; 447.35). Anal. Calcd for $C_{20}H_{19}BrN_2O_3S$: C, 53.70; H, 4.28; N, 6.26. Found: C, 53.61; H, 4.26; N, 6.19.

6,8-Dibromo-2-methyl-3-(3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene-2-yl)-quinazolin-4(3H)-one (7f):
IR (KBr, cm^{-1}): 3046 (Ar-CH), 2920 (CH in CH_3), 1715 (C=O), 1524 (C=N), 1450 (C=C), 643 (C-S), 580 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.69-8.06 (m, 2H; C_5,C_7; Ar-H), 4.26 (tet, 2H; -C<u>H</u>$_2$), 1.59-2.61 (m, 8H; $C_{4'}$,$C_{5'}$,$C_{6'}$,$C_{7'}$), 1.35 (tri, 3H; -C<u>H</u>$_3$), 0.89 (s, 3H; -C<u>H</u>$_3$). EI-MS *(m/z)*: 526 (Calcd for $C_{20}H_{18}Br_2N_2O_3S$; 526.24). Anal. Calcd for $C_{20}H_{18}Br_2N_2O_3S$: C, 45.65; H, 3.45; N, 5.32. Found: C, 45.61; H, 3.39; N, 5.28.

2-Phenyl-3-(4-phenylthiazol-2-yl)-quinazolin-4(3H)-one (7g):
IR (KBr, cm^{-1}): 3048 (Ar-CH), 2932 (CH in CH_3), 1726 (C=O), 1513 (C=N), 1446 (C=C), 655 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 7.11-8.13 (m, 14H; C_5,C_6,C_7,C_8,$C_{2''}$,$C_{3''}$,$C_{4''}$,$C_{5''}$, $C_{6''}$,$C_{2'''}$,$C_{3'''}$,$C_{4'''}$,$C_{5'''}$,$C_{6'''}$; Ar-H), 6.68 (s, 1H; $C_{5'}$). EI-MS *(m/z)*: 381 (Calcd for $C_{23}H_{15}N_3OS$; 381.45). Anal. Calcd for $C_{23}H_{15}N_3OS$: C, 72.42; H, 3.96; N, 11.02. Found: C, 72.39; H, 3.89; N, 10.99.

6-Bromo-2-phenyl-3-(4-phenylthiazol-2-yl)-quinazolin-4(3H)-one (7h):
IR (KBr, cm^{-1}): 3036 (Ar-CH), 2926 (CH in CH_3), 1722 (C=O), 1520 (C=N), 1460 (C=C), 647 (C-S), 564 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.09-8.01 (m, 13H; C_5,C_7,C_8,$C_{2''}$, $C_{3''}$,$C_{4''}$,$C_{5''}$,$C_{6''}$,$C_{2'''}$,$C_{3'''}$,$C_{4'''}$,$C_{5'''}$,$C_{6'''}$; Ar-H), 6.61 (s, 1H; $C_{5'}$). EI-MS *(m/z)*: 460 (Calcd for $C_{23}H_{14}BrN_3OS$; 460.35). Anal. Calcd for $C_{23}H_{14}BrN_3OS$: C, 60.01; H, 3.07; N, 9.13. Found: C, 59.91; H, 3.02; N, 9.09.

6,8-Dibromo-2-phenyl-3-(4-phenylthiazol-2-yl)-quinazolin-4(3H)-one (7i):
IR (KBr, cm^{-1}): 3024 (Ar-CH), 2939 (CH in CH_3), 1720 (C=O), 1526 (C=N), 1452 (C=C), 670 (C-S), 577 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.29-8.22 (m, 12H; C_5,C_7,$C_{2''}$,$C_{3''}$, $C_{4''}$,$C_{5''}$,$C_{6''}$,$C_{2'''}$,$C_{3'''}$,$C_{4'''}$,$C_{5'''}$,$C_{6'''}$; Ar-H), 6.73 (s, 1H; $C_{5'}$). EI-MS *(m/z)*: 539 (Calcd for $C_{23}H_{13}Br_2N_3OS$; 539.24). Anal. Calcd for $C_{23}H_{13}Br_2N_3OS$: C, 51.23; H, 2.43; N, 7.79. Found: C, 51.17; H, 2.41; N, 7.75.

2-Phenyl-3-(3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene-2-yl)-quinazolin-4(3H)-one (7j):
IR (KBr, cm^{-1}): 3032 (Ar-CH), 2922 (CH in CH_3), 1718 (C=O), 1514 (C=N), 1455 (C=C), 665 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 7.21-7.97 (m, 9H; C_5,C_6,C_7,C_8,$C_{2''}$,$C_{3''}$,$C_{4''}$,$C_{5''}$, $C_{6''}$; Ar-H), 4.34 (tet, 2H; -C<u>H</u>$_2$), 1.60-2.58 (m, 8H; $C_{4'}$,$C_{5'}$,$C_{6'}$,$C_{7'}$), 1.37 (tri, 3H; -C<u>H</u>$_3$). EI-MS *(m/z)*: 430 (Calcd for $C_{25}H_{22}N_2O_3S$; 430.52). Anal. Calcd for $C_{25}H_{22}N_2O_3S$: C, 69.75; H, 5.15; N, 6.51. Found: C, 69.71; H, 5.12; N, 6.42.

6-Bromo-2-phenyl-3-(3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene-2-yl)-quinazolin-4(3H)-one (7k):
IR (KBr, cm^{-1}): 3019 (Ar-CH), 2917 (CH in CH_3), 1726 (C=O), 1518 (C=N), 1454 (C=C), 649 (C-S), 561 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.27-8.05 (m, 8H; C_5,C_7,C_8,$C_{2''}$,$C_{3''}$, $C_{4''}$,$C_{5''}$,$C_{6''}$; Ar-H), 4.31 (tet, 2H; -C<u>H</u>$_2$), 1.58-2.62 (m, 8H; $C_{4'}$,$C_{5'}$,$C_{6'}$,$C_{7'}$), 1.39 (tri, 3H; -C<u>H</u>$_3$). EI-MS *(m/z)*: 509 (Calcd for $C_{25}H_{21}BrN_2O_3S$; 509.41). Anal. Calcd for $C_{25}H_{21}BrN_2O_3S$: C, 58.94; H, 4.16; N, 5.50. Found: C, 58.90; H, 4.11; N, 5.47.

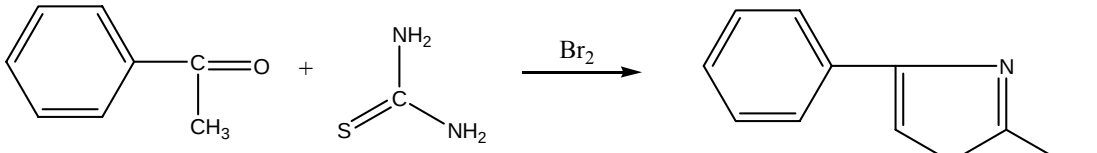
6,8-Dibromo-2-phenyl-3-(3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene-2-yl)-quinazolin-4(3H)-one (7l):
IR (KBr, cm^{-1}): 3041 (Ar-CH), 2924 (CH in CH_3), 1715 (C=O), 1524 (C=N), 1450 (C=C), 663 (C-S), 573 (C-Br). ^{1}H-NMR ($CDCl_3$) δ: 7.34-8.17 (m, 7H; C_5,C_7,$C_{2''}$,$C_{3''}$,$C_{4''}$, $C_{5''}$,$C_{6''}$; Ar-H), 4.26 (tet, 2H; -C<u>H</u>$_2$), 1.53-2.61 (m, 8H; $C_{4'}$,$C_{5'}$,$C_{6'}$,$C_{7'}$), 1.36 (tri, 3H; -C<u>H</u>$_3$). EI-MS *(m/z)*: 588 (Calcd for $C_{25}H_{20}Br_2N_2O_3S$; 588.31). Anal. Calcd for $C_{25}H_{20}Br_2N_2O_3S$: C, 51.04; H, 3.43; N, 4.76. Found: C, 51.01; H, 3.40; N, 4.72.

Anti-microbial activity:
Most of the synthesized compound exhibited mild to moderate anti-microbial activity against the tested microorganism. Compounds **7c** and **7f** were found to possess significant anti-bacterial and anti-fungal activity when compared to standard drug (Ciprofloxacin and

Ketoconazole for anti-bacterial and anti-fungal respectively). The entire synthesized compound exhibited mild to moderate anti-microbial activity with an MIC range of 24.1 to 47.6 µg/ml.

SCHEME-1

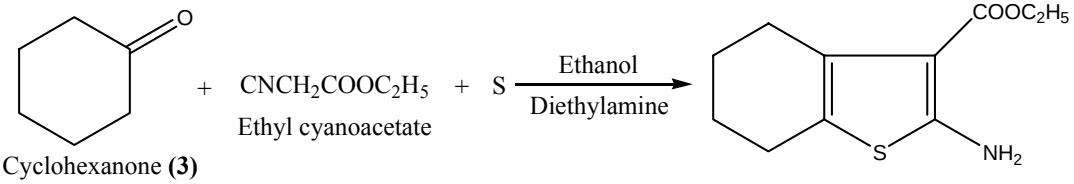
STEP-1:



Acetophenone **(1)** Thiourea

2-Amino-4-phenyl thiazole **(2)**

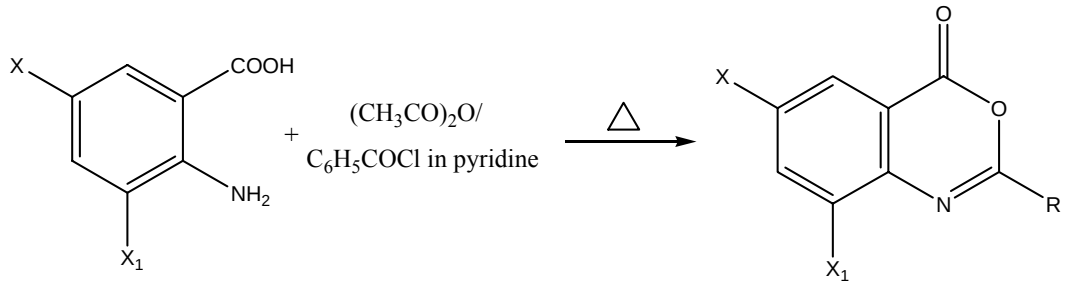
STEP-2:



Cyclohexanone **(3)**

2-Amino-3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene **(4)**

STEP-3:



3,5-(Un/mono/di)-bromo anthranilic acid

X, X_1 = H, Br

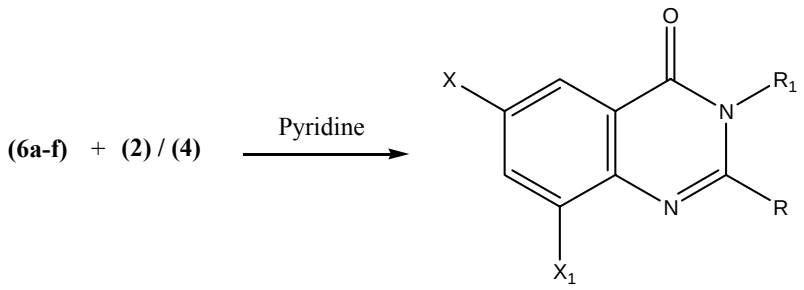
(5a-c)

6,8-(Un/mono/di)bromo-2-(methyl/phenyl)-4H-benzo-[1,3]-oxazin-4-one

R= CH_3, C_6H_5

(6a-f)

STEP-4:



Title compounds **(7a-l)**

Table-1: Physical data of the synthesized compounds

Comp	X	X_1	R	R_1	Mol. Formula	M.W	m.p (^{0}C)	Yield (%)
7a	H	H	CH_3	C_9H_6NS	$C_{18}H_{13}N_3OS$	319	160-162	85
7b	Br	H	CH_3	C_9H_6NS	$C_{18}H_{12}BrN_3OS$	398	272-275	79
7c	Br	Br	CH_3	C_9H_6NS	$C_{18}H_{11}Br_2N_3OS$	477	221-223	77
7d	H	H	CH_3	$C_{11}H_{13}O_2S$	$C_{20}H_{20}N_2O_3S$	368	109-110	81
7e	Br	H	CH_3	$C_{11}H_{13}O_2S$	$C_{20}H_{19}BrN_2O_3S$	447	91-93	76
7f	Br	Br	CH_3	$C_{11}H_{13}O_2S$	$C_{20}H_{18}Br_2N_2O_3S$	526	64-66	74
7g	H	H	C_6H_5	C_9H_6NS	$C_{23}H_{15}N_3OS$	381	79-82	69
7h	Br	H	C_6H_5	C_9H_6NS	$C_{23}H_{14}BrN_3OS$	460	194-196	66
7i	Br	Br	C_6H_5	C_9H_6NS	$C_{23}H_{13}Br_2N_3OS$	539	105-107	65
7j	H	H	C_6H_5	$C_{11}H_{13}O_2S$	$C_{25}H_{22}N_2O_3S$	430	83-85	67
7k	Br	H	C_6H_5	$C_{11}H_{13}O_2S$	$C_{25}H_{21}BrN_2O_3S$	509	139-141	61
7l	Br	Br	C_6H_5	$C_{11}H_{13}O_2S$	$C_{25}H_{20}Br_2N_2O_3S$	588	112-114	64

Table-2: Anti-microbial activity of the synthesized compounds(100 μg/ml)

Compound	Invitro activity - zone of inhibition in mm (MIC in μg/ml)								
	S.aureus	*S.epidermidis*	*M.luteus*	*B.cereus*	*E.coli*	*P.aeuriginosa*	*K.pneumoniae*	*A.niger*	*A.fumigatus*
7a	18(42.1)	20(33.7)	17(43.2)	15(41.3)	20(36.8)	14(38.7)	16(40.5)	13(43.4)	15(42.6)
7b	20(37.5)	23(28.3)	19(40.3)	18(39.7)	21(34.5)	17(39.4)	18(37.4)	14(42.3)	16(40.2)
7c	24(30.6)	27(24.1)	24(33.5)	21(36.4)	25(32.1)	20(37.6)	23(38.7)	20(37.7)	17(38.8)
7d	16(42.1)	17(37.6)	17(41.8)	16(40.2)	14(41.6)	11(45.8)	12(43.5)	20(35.3)	22(30.9)
7e	18(40.5)	16(37.9)	19(37.5)	15(42.6)	16(38.9)	15(40.7)	14(42.1)	19(36.1)	24(31.7)
7f	19(39.3)	18(35.1)	20(38.4)	17(38.5)	18(37.3)	18(35.3)	15(41.3)	24(29.9)	25(30.1)
7g	17(42.6)	20(34.9)	18(40.7)	14(45.1)	13(43.7)	15(40.5)	16(39.8)	13(43.2)	14(43.4)
7h	18(41.4)	22(31.5)	20(39.1)	16(41.8)	17(38.2)	18(34.7)	19(37.2)	15(39.9)	17(39.6)
7i	21(38.2)	25(30.3)	23(33.7)	19(37.9)	21(35.6)	20(34.1)	22(34.5)	18(40.1)	19(39.7)
7j	15(42.9)	14(39.3)	15(44.3)	11(47.6)	13(40.3)	14(42.3)	11(44.6)	18(38.5)	17(38.5)
7k	16(43.3)	19(35.7)	16(42.1)	13(45.7)	14(42.5)	16(39.9)	14(40.7)	21(32.7)	20(33.8)
7l	18(41.7)	18(36.4)	17(42.8)	14(46.3)	15(40.7)	18(35.2)	16(38.9)	22(31.3)	21(32.3)
Ciprofloxacin	26(0.2)	28(0.4)	27(0.3)	23(0.4)	29(0.1)	25(0.3)	27(0.1)	-	-
Ketoconazole	-	-	-	-	-	-	-	29(5.9)	30(0.4)
DMF	-	-	-	-	-	-	-	-	-

Out of the synthesized compounds, brominated derivatives exhibited more activity than unsubstituted one. In addition, thiazole derivatives exhibited more anti-bacterial activity than anti-fungal activity. Whereas, benzothiophene derivatives exhibited more anti-fungal activity than anti-bacterial activity.

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