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Synthesis, characterization and antimicrobial screening of *N*-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloro-substitutedquinoline-3-carboxamides

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Abstract
A sequence of N-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloro-substitutedquinoline-3-carboxamides (6a-n) compounds synthesized and characterized by various analytical techniques. Synthesized compounds were screened for their antibacterial and antifungal activity against different strains and gives moderate to excellent activities. After performing statistical analysis, present research showed significant co-relation of the synthesized compounds.

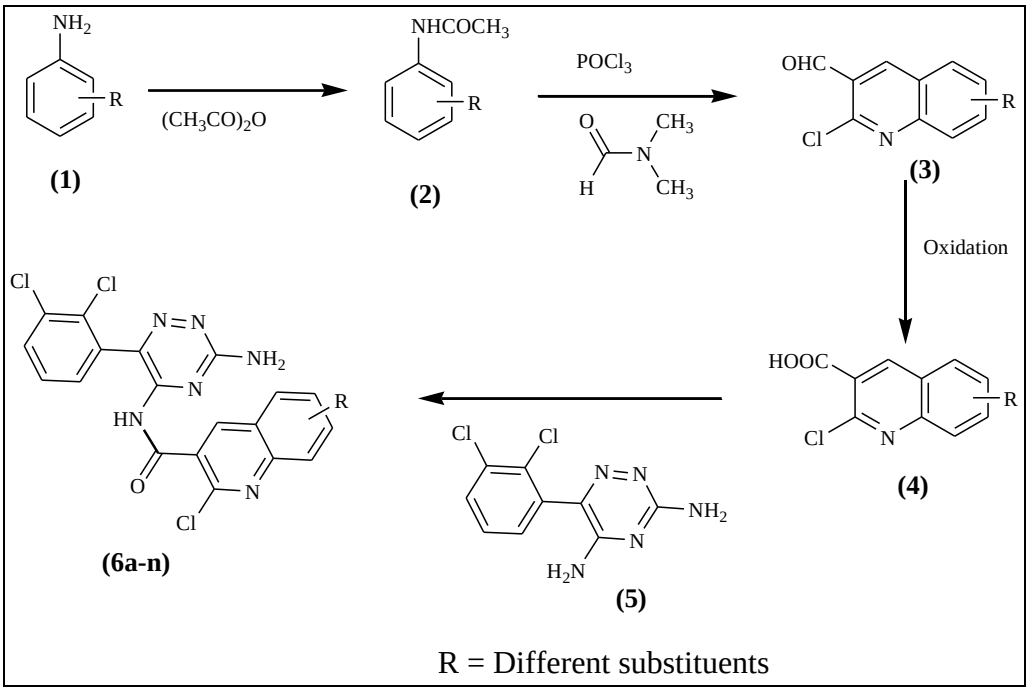
Keywords: Anti-microbial activity, 1, 2, 4-triazine derivatives, Quinoline derivatives

Introduction
The structural modification of biologically active compounds is greatest worldwide method in the medicinal chemistry towards the find out improved therapeutic categories [1]. The major use of heterocyclic compounds in pharmaceutical drug products and other synthetic natural products have made them very useful synthetic goals.

The quinoline moiety is one of the most important heterocyclic ring observed in many pharmaceutically important compounds and also found in natural products and alkaloids. The quinoline nucleus containing derivatives possess various therapeutic categories like antiasthmatic [2], antimalarial [3], antibacterial [4] and many more. Thus, expansion of the novel quinoline derivatives, inventive synthetic routes for the preparation of quinoline derivatives and screening of the synthesized quinoline derivatives for the various therapeutic categories are very much important in the medicinal chemistry and drug discovery from last many decades [5-8].

1,2,4-triazines and their condensed derivatives discloses wide-ranging uses in medicinal and drug discovery. The NCNN group of 1,2,4-triazine ring is an very useful part in various therapeutic catagories. Tirapazamine as antitumor [9], Lamotrigine as anti-epileptic drug [1[0]] and fused 1,2,4-triazines as antimicrobial [11], anti HIV [12], antimycobacterial [13], antiviral [14], anxiolytic [15] and antidepressant [16] agents are already reported in literature. Heterobicyclic nitrogen systems containing 1,2,4-triazine moiety have also shown anticancer activities [17].

Due to medicinal importance of Quinoline and 1,2,4-triazine moieties, we have designed and synthesized a series of *N*-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloro-substitutedquinoline-3-carboxamides (6a-n) (Scheme-1). The structures of compounds synthesized were assigned on the basis of IR, ^{1}H NMR and Mass spectra. These compounds were evaluated for their antibacterial and antifungal screening on different strains of bacteria and fungi respectively.



Scheme 1: Synthesis of N-(3-amino-6-(2,3-dichloro- phenyl)-1,2,4-triazin-5-yl)substituted-carboxamides (6a-n)

Materials and Methods

General

IR spectra were recorded on Perkin Elmer FT-IR spectrophotometer. ^{1}H-NMR spectra was recorded on Bruker DPX-40C instrument at 400 MHz. Chemical shifts are reported in ppm referenced to the residual solvent signal. Mass spectra were recorded on JEOL SX-102. Elemental analysis was performed by Perkin-Elmer 2400-CHN analyzer. Melting points were recorded on Gallenkemp apparatus and were uncorrected. Aluminium coated TLC plates 60 F_{245} (E. Merck) were used for monitoring of reaction and purity of compounds.

Preparation of acetanilide (2) from aniline (1)

50ml of acetic anhydride was taken in a round bottom flask, then 0.01 mole aniline **(1)** was added in it and refluxed it at 90ºC for 4 hrs. After completion of the reaction, the crude compound was separated out and excess amount of acetic anhydride was distilled out. The crude acetanilide was poured in ice-cold water and filtered, washed with cold water, dried and recrystallized from ethanol to get pure acetanilide compound (2). Yield 85%, m.p.: 116°-118 °C; Anal. obs.: C-71.08%, H-6.71%, N-10.36%. Calcd. for C_8H_9NO: C-71.13%, H-6.75%, N-10.41%. The progress of the reaction and the purity of the compound was routinely checked on TLC [Aluminium sheet silica gel 60 F_{245} (E. Merck)] using benzene: ethyl acetate (4:1 v/v) as an irrigator and was developed in an iodine chamber.

Preparation of 2-chloroquinoline-3-carbaldehyde (3) from acetanilide (2)

N, N-Dimethylformamide (0.125 mole) was cooled to 0 °C in a flask equipped with drying tube and phosphoryl chloride (0.35 mole) was added drop-wise with stirring. To this solution was added acetanilide (0.05 mole) and after 5 min, the solution was heated under reflux for 6 hrs at 75 °C. After the completion of the reaction, the mixture was cooled and poured into ice-water and stirred for 30 min. The compound was filtered, washed with water, dried and recrystallized from ethanol. Yield: 93%, m.p.: 145-147°C; Anal. obs.: C-62.68%, H-3.15%, N-7.31%. Calcd. for $C_{11}H_8ONCl$: C-62.75%, H-3.20%, N-7.36%. The progress of the reaction and the purity of the compound were routinely checked on TLC [Aluminium sheet silica gel 60 F_{245} (E. Merck)] using benzene: ethyl acetate (4:1 v/v) as an irrigator and was developed in an iodine chamber.

Preparation of Substituted-2-chloroquinoline-3-carboxylic acid (4) from Substituted-2-chloroquinoline-3-carbaldehyde (3)

0.1 mole of Substituted-2-chloroquinoline-3-carbaldehyde **(3)** dissolved in methanol and potassium dichromate (0.02 mole) added in the reaction mass and stirred it for 2 hours at room temperature. After the completion of the reaction, the reaction mixture was cooled and poured into ice-water and stirred for 30 min. The obtained Substituted-2-chloroquinoline-3-carboxylic acid compound **(4)** was filtered, washed with water, dried and recrystallized from ethanol. Yield: 91%, Purity: 98%.

Preparation and characterization of *N*-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloroquinoline-3-carboxamide (6a-n)

Dissolved 0.1 mole of substituted 2-chloroquinoline-3-carboxylic acid of Formula (4) and DCC (0.04 mole) in ethanol and heated the reaction mass at 90ºC with stirring. After 1 hour, 0.1 mole of Lamotrigine of formula (5) slowly added in to reaction mass. Then catalytic amount of Tetrabutylammonium bromide (0.04 mole) was added as a catalyst and heated the reaction mass for two hours. After the completion of reaction, cooled the reaction mass and distilled out the ethanol. Poured the reaction mass into ice-cold water and filtered to get amide derivative of formula 6a. The obtained *N*-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloroquinoline-3-carboxamide (Formula 6a) is further purified by using ethanol. Yield: 93%. IR (KBr): υ = 3742 (-CONH group), 3445 (Stretching, -NH_2 group), 1614 (C=N), 1560-1486 (C=C, benzene and quinoline ring), 1453 (Bending, –NH_2 group), 890, 787, 744 (C-Cl bond) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 6.8 – 7.10 (m, 3H, Ar-H), 7.28 – 8.3 (m,

5H, Qui-H), 8.82 (s, 1H, O=C-N-H), 6.35 (s, 2H, -NH_2); MS: m/z 445.69 (M^+). Anal. calc. For $C_{19}H_{11}Cl_3N_6O$, M.P. 220-222, C, 51.20; H, 2.49; N, 18.86%. Found: C, 51.26; H, 2.55; N, 18.91%.

Preparation and characterization of *N*-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloro-6-methyl quinoline-3-carboxamide (6b): Yield: 91%. IR (KBr): υ = 3745 (-CONH group), 3451 (Stretching, -NH_2 group), 2850 (Stretching CH_3 group), 1617 (C=N), 1563-1489 (C=C, benzene and quinine ring), 1459 (Bending, –NH_2 group), 1453 (Bending, CH_3 group), 893, 789, 749 (C-Cl bond) cm^{-1}; ^{1}H- NMR (DMSO-d_6): δ 6.4 – 7.15 (m, 3H, Ar-H), 7.26 – 8.2 (m, 4H, Qui-H), 8.85 (s, 1H, O=C-N-H), 6.38 (s, 2H, -NH_2), 2.34 (s, ,3H, -CH_3); MS: m/z 459.72 (M^+). Anal. calc. For $C_{20}H_{13}Cl_3N_6O$, M.P. 227-229, C, 52.25; H, 2.85; N, 18.28%. Found: C, 52.31; H, 2.91; N, 18.34%.

Preparation and characterization of *N*-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloro-6-ethyl quinoline-3-carboxamide (6c): Yield: 90%. IR (KBr): υ = 3740 (-$CONH_2$), 3442 (Stretching, -NH_2 group), 2895 (Stretching –CH_2 group), 2859 (Stretching CH_3 group),, 1619 (C=N), 1560-1483 (C=C, Benzene and Quinoline ring), 1464 (Bending CH_3 group), 1468 (Bending –CH_2 group), 1464 (Bending CH_3 group), 1457 (Bending –NH_2 group), 893, 782, 749 (C-Cl bond) cm^{-1}; ^{1}H- NMR (DMSO-d_6): δ 6.8 – 7.18 (m, 3H, Ar-H), 7.23 – 8.1 (m, 4H, Qui-H), 8.88 (s, 1H, O=C-N-H), 6.39 (s, 2H, -NH_2), 2,56 (m, 5H, C_2H_5 group),; MS: m/z 473.74 (M^+). Anal. calc. For $C_{21}H_{15}Cl_3N_6O$, M.P. 215-217, C, 53.24; H, 3.19; N, 17.74%. Found: C, 53.30; H, 3.25; N, 17.80%.

Preparation and characterization of *N*-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloro-6-propyl quinoline-3-carboxamide (6d): Yield: 93%. IR (KBr): υ = 3739 (-$CONH_2$), 3441 (Stretching, -NH_2 group), 2890 (Stretching –CH_2 group), 2855 (Stretching CH_3 group), 1620 (C=N),1563-1488 (C=C, benzene and quinine ring), 1464 (Bending –CH_2 group), 1461 (Bending CH_3 group), 1450 (-NH bending –NH_2 group), 891, 780, 752 (C-Cl bond) cm^{-1}; ^{1}H- NMR (DMSO-d_6): δ 6.5– 7.13 (m, 3H, Ar-H), 7.22 – 8.1 (m, 4H, Qui-H), 8.88 (s, 1H, O=C-N-H), 6.31 (s, 2H, -NH_2), 2,56 (m, 7H, C_3H_7 group); MS: m/z 487.77 (M^+). Anal. calc. For $C_{22}H_{17}Cl_3N_6O$, M.P. 235--237, C, 54.17; H, 3.51; N, 17.23%. Found: C, 54.23; H, 3.57; N, 17.28%.

Preparation and characterization of N-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloro-6-metho xyquinoline-3-carboxamide (6e)
Yield: 93.5%. IR (KBr): υ = 3747 (-$CONH_2$), 3449 (Stretching, –NH_2 group), 2955 (Stretching, -OCH_3 group), 1619 (C=N), 1566-1489 (C=C, benzene and quinine ring), 1465 (Bending, -OCH_3 group), 1458 (-NH bending –NH_2 group), 896, 780, 748 (C-Cl bond) cm^{-1}; ^{1}H- NMR (DMSO-d_6): δ 6.6 – 7.16 (m, 3H, Ar-H), 7.25 – 8.34 (m, 4H, Qui-H), 8.87 (s, 1H, O=C-N-H), 6.31 (s, 2H, -NH_2), 3.42 (s, 3H, -OCH_3 group); MS: m/z 475.72 (M^+). Anal. calc. For $C_{20}H_{13}Cl_3N_6O_2$, M.P. 208-210, C, 50.50; H, 2.75; N, 17.67%. Found: C, 50.56; H, 2.81; N, 17.73%.

Preparation and characterization of N-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloro-6-ethoxy quinoline-3-carboxamide (6f): Yield: 89%. IR (KBr): υ = 3753 (-$CONH_2$), 3456 (Stretching, –NH_2 group), 2951 (Stretching, -OC_2H_5 group), 1623 (C=N), 1569-1484 (C=C, benzene and quinine ring), 1461 (Bending, -OC_2H_5 group), 1456 (Bending –NH_2 group), 892, 784, 743 (C-Cl bond) cm^{-1}; ^{1}H- NMR (DMSO-d_6): δ 6.3 – 7.19 (m, 3H, Ar-H), 7.22 – 8.24 (m, 4H, Qui-H), 8.80 (s, 1H, O=C-N-H), 6.33 (s, 2H, -NH_2), 3.67 (s, ,3H, -OCH_3); MS: m/z 489.74 (M^+). Anal. calc. For $C_{21}H_{15}Cl_3N_6O_2$, M.P. 252-253, C, 51.50;; H, 3.09; N, 17.16%. Found: C, 51.56; H, 3.15; N, 17.22%.

Preparation and characterization of N-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloro-6-propo xyquinoline-3-carboxamide (6g): Yield: 92%. IR (KBr): υ = 3732 (-$CONH_2$), 3446 (Stretching, -NH_2 group), 2950 (Stretching –OC_3H_7 group), 1625 (C=N),1567-1482 (C=C, benzene and quinine ring), 1473 (Bending –OC_3H_7 group), 1452 (-NH bending –NH_2 group), 896, 787, 755 (C-Cl bond) cm^{-1}; ^{1}H- NMR (DMSO-d_6): δ 6.0– 7.10 (m, 3H, Ar-H), 7.27 – 8.15 (m, 4H, Qui-H), 8.84 (s, 1H, O=C-N-H), 6.37 (s, 2H, -NH_2), 4.33 (m, 7H, OC_3H_7 group); MS: m/z 503.77 (M^+). Anal. calc. For $C_{22}H_{17}Cl_3N_6O_2$, M.P. 248-250, C, 52.45; H, 3.40; N, 16.68%. Found: C, 52.52; H, 3.46; N, 16.74%.

Preparation and characterization of *N*-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2,6-dichloro quinoline-3-carboxamide (6h)
Yield: 90%. IR (KBr): υ = 3738 (-CONH group), 3441 (Stretching, -NH_2 group), 1618 (C=N), 1560-1483 (C=C, benzene and quinoline ring), 1459 (Bending, –NH_2 group), 891, 805, 787, 741 (C-Cl bond) cm^{-1}; ^{1}H- NMR (DMSO-d_6): δ 6.6 – 7.2 (m, 3H, Ar-H), 7.23 – 8.2 (m, 4H, Qui-H), 8.84 (s, 1H, O=C-N-H), 6.32 (s, 2H, -NH_2); MS: m/z 480.13 (M^+). Anal. calc. For $C_{19}H_{10}Cl_4N_6O$, M.P. 206-208ºC, 47.53; H, 2.10; N, 17.50%. Found: C, 47.59; H, 2.16; N, 17.56%.

Preparation and characterization of N-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-6-bromo-2-chloro-quinoline-3-carboxamide (6i)
Yield: 92%. IR (KBr): υ = 3746 (-CONH group), 3446 (Stretching, -NH_2 group), 1620 (C=N), 1563-1486 (C=C, benzene and quinoline ring), 1460 (Bending, –NH_2 group), 902 (C-Br bond), 892, 789, 744 (C-Cl bond) cm^{-1}; ^{1}H- NMR (DMSO-d_6): δ 6.5 – 7.3 (m, 3H, Ar-H), 7.21 – 8.4 (m, 4H, Qui-H), 8.86 (s, 1H, O=C-N-H), 6.34 (s, 2H, -NH_2); MS: m/z 524.59 (M^+). Anal. calc. For $C_{19}H_{10}BrCl_3N_6O$, M.P. 224-226ºC, 43.50; H, 1.92; N, 16.02%. Found: C, 43.56; H, 1.99; N, 16.08%.

Preparation and characterization of N-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloro-6-fluoro-quinoline-3-carboxamide (6j)
Yield: 94%. IR (KBr): υ = 3742 (-CONH group), 3444 (Stretching, -NH_2 group), 1624 (C=N), 1562-1485 (C=C, benzene and quinoline ring), 1468 (Bending, –NH_2 group), 921 (C-F bond), 890, 783, 743 (C-Cl bond) cm^{-1}; ^{1}H- NMR (DMSO-d_6): δ 6.4 – 7.32 (m, 3H, Ar-H), 7.23 – 8.42 (m, 4H, Qui-H), 8.81 (s, 1H, O=C-N-H), 6.32 (s, 2H, -NH_2); MS: m/z 463.68 (M^+). Anal. calc. For $C_{19}H_{10}Cl_3FN_6O$, M.P. 237-239ºC, 49.22; H, 2.17; N, 18.12%. Found: C, 49.28; H, 2.23; N, 18.18%.

Preparation and characterization of N-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloro-6-iodo quinoline-3-carboxamide (6k)
Yield: 94%. IR (KBr): υ = 3747 (-CONH group), 3448 (Stretching, -NH_2 group), 1621 (C=N), 1561-1482 (C=C,

benzene and quinoline ring), 1462 (Bending, –NH_2 group), 937 (C-I bond), 893, 781, 741 (C-Cl bond) cm^{-1}; ^{1}H- NMR (DMSO-d_6): δ 6.42 – 7.31 (m, 3H, Ar-H), 7.22 – 8.41 (m, 4H, Qui-H), 8.83 (s, 1H, O=C-N-H), 6.32 (s, 2H, -NH_2); MS: m/z 571.59 (M^+). Anal. calc. For $C_{19}H_{10}Cl_3IN_6O$, M.P. 210-212ºC, 39.92; H, 1.76; N, 14.70%. Found: C, 39.99; H, 1.82; N, 14.76%.

Preparation and characterization of N-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloro-6-nitro quinoline-3-carboxamide (6l)

Yield: 92%. IR (KBr): υ = 3742 (-CONH group), 3443 (Stretching, -NH_2 group), 1623 (C=N), 1590 (NO_2 group, symmetric stretching), 1560-1487 (C=C, benzene and quinoline ring), 1467 (Bending, –NH_2 group), 1350 (NO_2 group, asymmetric stretching), 892, 780, 738 (C-Cl bond) cm^{-1}; ^{1}H- NMR (DMSO-d_6): δ 6.43 – 7.34 (m, 3H, Ar-H), 7.29 – 8.44 (m, 4H, Qui-H), 8.82 (s, 1H, O=C-N-H), 6.34 (s, 2H, -NH_2); MS: m/z 490.69 (M^+). Anal. calc. For $C_{19}H_{10}Cl_3N_7O_3$, M.P. 252-254ºC, 46.51; H, 2.11; N, 19.98%. Found: C, 46.57; H, 1.82; N, 20.04%.

Preparation and characterization of N-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloro-7-methyl quinoline-3-carboxamide (6m)

Yield: 82%. IR (KBr): υ = 3744 (-CONH group), 3452 (Stretching, -NH_2 group), 2853 (Stretching CH_3 group), 1618 (C=N), 1562-1488 (C=C, benzene and quinine ring), 1458 (Bending, –NH_2 group), 1452 (Bending, CH_3 group), 892, 788, 747 (C-Cl bond) cm^{-1}; ^{1}H- NMR (DMSO-d_6): δ 6.3 – 7.14 (m, 3H, Ar-H), 7.25 – 8.22 (m, 4H, Qui-H), 8.83 (s, 1H, O=C-N-H), 6.37 (s, 2H, -NH_2), 2.33 (s, ,3H, -CH_3); MS: m/z 459.72 (M^+). Anal. calc. For $C_{20}H_{13}Cl_3N_6O$, M.P. 267-269, C, 52.25; H, 2.85; N, 18.28%. Found: C, 52.32; H, 2.93; N, 18.35%.

Preparation and characterization of N-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloro-5,7-dimethyl-quinoline-3-carboxamide (6n)

Yield: 80%. IR (KBr): υ = 3740 (-CONH group), 3457 (Stretching, -NH_2 group), 2851, 2859 (Stretching CH_3 groups), 1610 (C=N), 1561-1484 (C=C, benzene and quinine ring), 1457 (Bending, –NH_2 group), 1442, 1448 (Bending, CH_3 groups), 891, 783, 744 (C-Cl bond) cm^{-1}; ^{1}H- NMR (DMSO-d_6): δ 6.33 – 7.12 (m, 3H, Ar-H), 7.21 – 8.21 (m, 3H, Qui-H), 8.81 (s, 1H, O=C-N-H), 6.32 (s, 2H, -NH_2), 2.34 (d, 3H, -CH_3 group), 2.45 (m, ,3H, -CH_3); MS: m/z 473.74 (M^+). Anal. calc. For $C_{21}H_{15}Cl_3N_6O$, M.P. 273-274, C, 53.24; H, 3.19; N, 17.74%. Found: C, 53.30; H, 3.25; N, 17.80%.

Results and Discussion

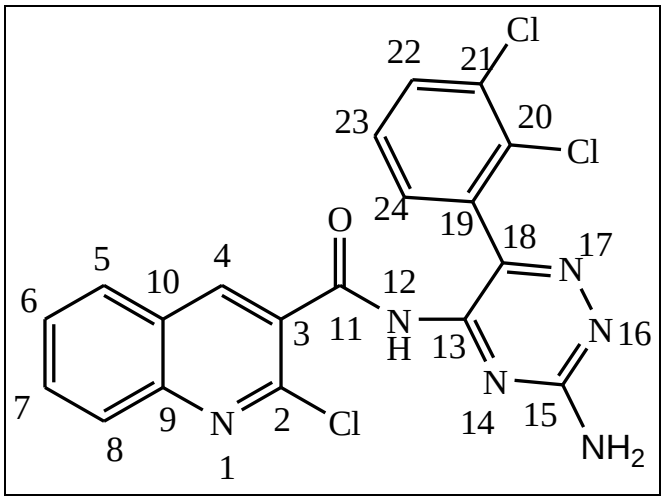
The synthesis of *N*-(3-amino-6-(2,3-dichloro-phenyl)-1,2,4-triazin-5-yl)substituted-carboxamides (6a-n) have been carried out in four steps. First step involves the acetylation of substituted-aniline (1) to give substituted-acetanilide (2). Second step involves preparation of 2-chloroquinoline-3carbaldehyde (3) from substituted-acetanilide (2) by undergoing Villsmeyer-Hack reaction through using Dimethylformamide and phosphoryl chloride. Third step involves preparation of Substituted-2-chloroquinoline-3-carboxylic acid (4) from Substituted-2-chloroquinoline-3-carbaldehyde (3) by involving oxidation reaction. Finally, third step obtained product is reacted with Lamotrigine (5) in presence of DCC and phase transfer catalyst to get *N*-(3-amino-6-(2, 3-dichloro-phenyl)-1, 2, 4-triazin-5-yl) substituted-carboxamides (6a-n) compounds. All the synthesized compounds were characterized by IR, ^{1}H NMR and mass spectra.

IR-data

The IR spectrum of the N-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloroquinoline-3-carboxamide (molecular formula $C_{19}H_{11}Cl_3N_6O$, M.W. 445.69 gm/mol, structure and numbering is given in Formula-6a) over the 3445 cm^{-1} range showed absorption peak corresponding to primary amine stretching vibration absorption peaks, which is attached at number-15 and 3742 cm^{-1} range showed absorption peak corresponding amide stretching vibration absorption peaks, which is formed between number-11 & 12 positions. The moderate intensity absorption at 1614 cm^{-1} corresponds to a >C=N- stretching vibration. The 1560-1486 cm^{-1} absorptions are due to the skeleton vibration of the aryl and heterocyclic rings. The absorption peak at 787 and 744 cm^{-1} are due to the chlorine atom, which are attached with a carbon atom at number - 20 and 21 positions and absorption peak at 890 cm^{-1} is due to the chlorine atom at number-2. The vibration at 1453 cm^{-1} is due to the bending vibration of primary amine groups.

^{1}H-NMR – data

It can be seen from the chemical structure of compound *N*-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloroquinoline-3-carboxamide that protons of primary amine attached at number-15 appeared as 6.38 as singlet. The proton of amide attached at number-12 appeared as singlet at 8.82 ppm. The proton which is attached to number-22, 23 & 24 of aromatic ring appeared between 6.8 to 7.10 ppm. The proton which are attached to quinoline ring appeared between 7.28 to 8.3 ppm.



Scheme 2: Numbering of the N-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)-2-chloroquinoline-3-carboxamide

Antibacterial activity

For the antibacterial activity, the newly synthesized compounds were screened for their antibacterial activity against gram positive bacteria *Staphylococcus aureus* (MTCC-96) and *Streptococcus pyogenes* (MTCC-442) and gram negative *Escherichia Coli* (MTCC-443) and *Pseudomonas aeruginosa* (MTCC-1688)]. Antibacterial activity was carried out by serial broth dilution method [18]. The standard strains used for the antimicrobial activity was procured from Institute of Microbial Technology, Chandigarh. The compounds (6a-n) were screened for their antibacterial

activity in triplicate against with different concentrations as shown in (Table 1). The standard drug used for the antifungal activity is Ampicillin.

- From screening results as mentioned in Table-1 for Anti-bacterial activity *N*-(3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5-yl)substituted-carboxamides, it has been observed that final compounds 6b, 6h, 6i, 6k and 6m possess good activity, while compound PR-7 possesses very good activity & compounds 6a and 6j possess excellent activity against *E. coli* as compared to the standard drug Ampicillin.
- Final compounds 6b, 6c, 6g, 6j, 6l and 6n possess good activity, while compounds 6a, 6i and 6k possess very good activity against *P. aeruginosa* as compared to standard drug Ampicillin.
- Final compounds 6b, 6d, 6g, 6i and 6n possess good activity, while compounds 6a, 6i, 6j and 6k possess very good activity against *S. aureus* as compared to the standard drug Ampicillin.
- Compounds 6a, 6b, 6i, 6j, and 6n were shown to possess good activity against *S. pyogenes* as compared to the standard drug Ampicillin.
- The remaining compounds of the series possess moderate to poor antibacterial activity. The discussion and comparison of antibacterial activity was given with respect to Ampicillin antibiotic.

Table 1: Anti-Bacterial Activity *N*-(3-Amino-6-(2,3-Dichloro- Phenyl)-1,2,4-Triazin-5-Yl)Substituted-Carboxamides

Sr. No.	Compound Code	Minimal Inhibitory Concentrations For Bacteria (MIC_B) in µg/ml±SD			
		***E. coli* MTCC-443**	***P. aeru.* MTCC 1688**	***S. aureus* MTCC-96**	***S. pyogenus* MTCC-442**
1	6a	25±2.23	50±3.03	100±3.43	100±3.29
2	6b	100±3.63	100±3.73	250±3.43	100±3.09
3	6c	250±3.53	100±3.21	500±3.04	200±3.24
4	6d	200±3.34	500±3.05	250±3.64	1000±4.13
5	6e	1000±2.25	500±3.78	500±2.64	250±3.24
6	6f	250±4.14	500±3.02	500±4.14	1000±3.53
7	6g	50±4.63	100±3.66	250±2.52	500±2.83
8	6h	100±4.16	200±3.51	250±4.14	250±4.15
9	6i	100±4.72	50±3.53	100±3.78	100±3.23
10	6j	25±2.51	100±2.55	100±3.63	100±3.53
11	6k	100±2.54	50±2.54	100±3.43	200±4.09
12	6l	250±3.56	100±2.51	500±3.60	500±4.04
13	6m	100±2.55	500±3.54	500±3.64	250±4.34
14	6n	250±2.66	100±3.63	250±3.24	100±3.45
Ampicillin		100±4.34	100±4.15	250±4.13	100±2.55
±SD = Standard deviation					

Antifungal activity

- The same novel compounds were tested for antifungal activity in triplicate against Candida albicans, Aspergillus Niger and Aspergillus Clavatus at various concentrations. The standard drug used for the antifungal activity in Griseofulvin.
- From screening results as mentioned in Table-2 for Anti-fungal activity *N*-(3-amino-6-(2,3-dichloro- phenyl)-1,2,4-triazin-5-yl) substituted-carboxamides, it has been observed that final compounds 6b, 6e, 6f, 6h, and 6l possess good activity, and compounds 6i and 6k possess very good activity & compounds 6a and 6j possess an excellent activity against *C. albicans* as compared to the standard drug Griseofulvin.
- Compounds 6a, 6j and 6k possess good activity against *A. niger* as compared to the standard drug Griseofulvin.
- Compounds 6a, 6i, 6k and 6m possess good activity against *A. clavatus* as compared to the standard drug Griseofulvin.
- The remaining compounds of the entire series possess only moderate to poor antifungal activity. The discussion and comparison of antifungal activity was compared with Griseofulvin.

Table 2: Anti-Fungal Activity *N*-(3-Amino-6-(2,3-Dichloro-Phenyl)-1,2,4-Triazin-5-Yl)Substituted-Carboxamides

Sr. No.	Compound Code	Minimal Inhibitory Concentrations For Fungi (MIC_F) in µg/ml±SD		
		***C. albicans* MTCC 227**	***A. niger* MTCC 282**	***A. clavatus* MTCC 1323**
1	6a	100±4.34	100±2.54	100±3.44
2	6b	500±3.42	500±3.03	200±3.23
3	6c	1000±3.03	500±3.34	500±4.64
4	6d	1000±3.60	200±3.54	500±3.03
5	6e	500±3.23	500±3.5	200±4.13
6	6f	500±2.34	500±3.64	500±3.53
7	6g	1000±4.15	200±3.04	500±3.23
8	6h	500±3.02	1000±3.03	500±3.51
9	6i	200±3.54	500±3.23	100±2.54
10	6j	100±3.21	100±2.51	500±4.04
11	6k	200±3.21	100±2.51	100±4.04
12	6l	500±2.23	1000±2.51	500±4.34
13	6m	1000±2.58	500±2.58	100±3.23
14	6n	1000±2.22	1000±3.62	500±2.63
Griseofulvin		500±4.12	100±4.32	100±2.14
±SD = Standard deviation				

Statistical analysis

The standard deviation value is expressed in terms of ±SD. On the basis of the calculated value by using ANOVA method, it has been observed that the differences below 0.0001 level ($p \leq 0.0001$) were considered as statistically significant.

Conclusion

The present synthesized compounds are novel confirmed by literature search and among them few of the compounds are possesses good to excellent antibacterial activity against gram positive bacteria like *E. coli., S. Aureus* and gram negative bacteria like *P. aeruginosa a*nd *S. pyogenes*, while few exhibited very good antifungal activity against *C. albicans, A. niger* and *A. clavatus*. The novel synthesized compounds 6a, 6i and 6j gives very good antibacterial and antifungal activities. From the results, we are in conclusion that quinoline nucleus containing halogen derivatives are very significant for activity against both bacterial and fungal species. The results of the present research on novel quinoline based 1,2,4-triazine derivatives can be useful for the other interesting development of novel molecules with known or unknown therapeutic categories.

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References

1. Daniel A. A Historical Overview of Natural Products in Drug Discovery. Metabolites 2012;2(2):303-336.
2. Roma G, Braccio MD, Chia M. 1,8-Naphthyridines IV. 9-Substituted N,N-dialkyl-5-(alkylamino or cycloalkylamino) [1,2,4]triazolo[4,3-a][1,8]naphthyridine-6-carboxamides, new compounds with anti-aggressive and potent anti-inflammatory activities. Eur. J. Med. Chem 2000;35:1021-1035.
3. Larsen RD, Corley EG, King AO, Carroll JD, Davis TR, Reide PJ. Practical route to a new class of LTD4 receptor antagonists. J. Org. Chem 1996;61:3398-3405.
4. Dube D, Blouin M, Brideau C, Chan C, Desmarais S, Either D *et al*. Quinolines as potent 5-lipoxygenase inhibitors: Synthesis and biological profile of L-746,530. Bioorg. Med. Chem. Lett 1998;8:1255-1260.
5. Balasubramanian M, Keay JG. Pyridine and their Benzo Derivatives: Application in Comprehensive Heterocyclic Chemistry, vol. 5, Pergamon, Oxford 1996, 245-300.
6. Ranu BC, Hajira A, Dey SS, Jana U. Efficient microwave-assisted synthesis of quinolines and dihydroquinolines under solvent-free conditions. Tetrahedron 2003;59:813-819.
7. Wada Y, Mori T, Ichikawa J. A Facile Synthesis of 2,4-Disubstituted 3-Fluoroquinolines via Intramolecular Cyclization of o-Cyanomethylamino-β,β-difluorostyrenes. Chem. Lett 2003;32:1000-1001.
8. Kobayashi K, Yoneda K, Mizumoto T, Umakoshi H, Morikawa O, Konishi H. Synthesis of 3-methoxyquinolines via cyclization of 1-isocyano-2-(2-lithio-2-methoxyethenyl)benzenes. Tetrahedron Lett. 2003;44:4733-4736.
9. Wouters BG, Wang LH, Brown JM. Tirapazamine: A New Drug Producing Tumor Specific Enhancement of Platinum-Based Chemotherapy in Non-Small-Cell Lung Cancer. Ann Oncol 1999;10(5):S29-33. doi: 10.1093/annonc/10.suppl_5.s29.
10. David W, Richard B, Stanley R. Effect of Antiepileptic Drug Comedication on Lamotrigine Clearance. Arch Neurol 2005;62(9):1432-1436. doi:10.1001/archneur.62.9.1432.
11. Arshad M, Taki AK, Meraj AK. 1,2,4-triazine derivatives: Synthesis and biological applications. International Journal of Pharma Sciences and Research (IJPSR) 2014;5:149-162.
12. Mohammed SI, Makki RM, Abdel-Rahman, Khalid AK. Fluorine Substituted 1,2,4-Triazinones as Potential Anti-HIV-1 and CDK2 Inhibitors.. Journal of chemistry. 2014, 14. ID 430573| https://doi.org/10.1155/2014/430573
13. Rajeev Kumar, Sirohi TS, Hariram Singh, Ramji Yadav, Roy RK, Chaudhary A *et al*. 1,2,4-triazine Analogs as Novel Class of Therapeutic Agents.. Mini Rev Med Chem 2014;14(2):168-207. Doi: 10.2174/1389557514666140131111837.
14. Rusinov VL, Egorov IN, Chupakhin ON, Belanov EF, Bormotov NI, Serova OA. Synthesis and antiviral activity of 1,2,4-triazine derivatives. Pharmaceutical Chemistry Journal 2012;45:655-659.
15. Mullick P, Khan SA, Begum T, Verma SP. Synthesis of 1,2,4-triazine derivatives as potential anti-anxiety and anti-inflammatory agents. Acta Poloniae Pharmaceutica ñ Drug Research 2009;66(4):379-385.
16. Shelke SM, Bhosale SH, Mahadik KR. 3-(5*H*-[1,2,4] Triazino [5,6-*b*]indol-3-ylthio)-*N*-(substituted henyl) propionamides: Synthesis and antidepressant activity evaluation. Der Pharma Chemica 2010;2:169-177.
17. Mohamed AEZ, Ahmed IES. An Efficient Synthesis of 1,2,4-triazine-6-one Derivatives and Their in vitro Anticancer Activity. International Journal of Pharmacology 2016;12:188-194.
18. Rattan A. Antimicrobials in Laboratory Medicine (first ed.), B.I. Churchill Livingstone Pvt. Ltd 2000.