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Synthesis of some heterocyclic compounds and studies of their antimicrobial efficacy

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ABSTRACT

*Some 1-{4-Chloro-6-[3-(6-methoxy - benzothiazol-2-ylazo)-2,6-dimethyl-quinolin-4-yloxy]-[1,3,5] triazin-2-yl}-(substituted phenyl)-urea **3a-h** were synthesized and studied for their microbial activity. These compounds were prepared by the condensation of substituted phenylurea with [4-(4,6-Dichloro-[1,3,5]triazin-2-yloxy)-2,6-dimethyl-quinolin-3-yl]-(6-methoxy-benzothiazol-2-yl)-diazene **[2]** which is prepared by the reaction between 3-[(6-methoxy-benzothiazol-2-yl)-diazinyl]-2,6-dimethyl-4-hydroxyquinoline **[1]** and cyanuric chloride. 3-[(6-methoxy-benzothiazol-2-yl)-diazinyl]-2,6-dimethyl-4-hydroxyquinoline **[1]** prepared by coupling of 2,6-dimethyl-4-hydroxyquinoline and diazotised 2-amino-6-methoxy benzothiazole. All the compounds were characterized by elemental analysis and spectral studies.*

Key Words: Benzothiazole derivative, Quinoline derivative, Cyanuric chloride, Substituted Phenyl urea, Antimicrobial Activity.

INTRODUCTION

Benzothiazole derivative exhibit a wide range of biological activities[1,2] Benzothiazole moiety exhibits activities such as antiallergic[3], antitumor[4] , antiparstitic, antifungal and antibacterial [5] etc. In bioorganic and medicinal chemistry 2 – aminobenzothiazole derivatives are broadly found with applications in drug discovery and development of the treatments of diabetes[6], epilepsy[7,8], inflammation[9,10], amyotrophic lateral sclerosis[11], analgesic[12], tuberculosis [13] and viral infection[14].

Quinoline derivatives possess wide therapeutic activity, viz; antiseptic, analgesic, trypanocidal, germicidal, amoebicidal, antitubercular, anthelmintic, pyroplasmosis, schistomiasis,

antiserotonin, cytokinin and antispasmodic [15-21]. Urea derivatives of quinoline are used as analgesic and central nervous system depressant and 8-aminoquinolines as antimalarials[22,23].

EXPERIMENTAL SECTION

All reagents were obtained from commercial sources. Solvents were dried and purified with known conventional methods.

Analytical methods

All melting points were taken in open capillary tubes and were uncorrected. Thin layer chromatography was performed on precoated TLC plates with silica gel (Merck GF254) and detection was done by UV lamp (254 nm). The IR spectra were obtained on a Perkin-Elmer BX series FTIR-5000 spectrophotometer using KBr pellets. The ^{1}H NMR spectra in DMSO-d_6 were recorded on Varian Gemini 400 MHz spectrometer and chemical shift were reported as parts per million (δ ppm) down field using TMS as internal standard.

Preparation of Diazotised 2-amino-6-methoxy benzothiazole:

Sodium nitrite (2.07 gm, 0.03 mol) was added to a cold concentrated sulphuric acid (15 ml) and after addition; the mixture was warmed gradually on water bath at 65-70 °C. The solution was cooled to 0-5°C, and then a mixture of propionic acid (8 ml) and acetic acid (12 ml) is added to it. After that 2-amino-6-substituted benzothiazole (5.4 gm, 0.03 mol) was added gradually to a nitrosyl sulphuric acid paste at 0°C, and then stirred for 30 minutes, maintaining the temperature at 10°C. After completion of reaction, excess of nitrous acid was destroyed using sulphamic acid.

Coupling of 2,6-dimethyl-4-hdyroxy quinoline with diazotised 2-amino-6-methoxy benzothiazole: [1]

A solution of 2,6-dimethyl 4-hydroxy quinoline (3.46 gm, 0.02 mole) in 50ml 10% NaOH was cooled at 0-5°C, and then diazotized 2-amino-6-methoxy benzothiazole solution was added slowly to it, keeping temperature 0-5°C. The reaction mixture was further stirred for 3 hours at 0-5°C. The solid product separated was filtered, dried and crystallized from ethanol. Anal. calcd. For $C_{19}H_{16}O_2N_4S$: C,62.62; H,4.43; O,8.78; N,15.37; S,8.80 Found C,62.60; H,4.44; O,8.75; N,15.35; S,8.82.

Reaction of 3-[(6-methoxy-benzothiazol-2-yl)-diazinyl]-2,6-dimethyl-4-hydroxy quinoline with cyanuric chloride: [2]

Cyanuric chloride (3.69 gm, 0.02 mol) was dissolved in 60 ml acetone and 3-[(6-methoxy -benzothiazol-2-yl)-diazenyl]-2,6-dimethyl-4-hydroxy quinoline (7.28 gm, 0.02 mol) was dissolved in acetone (60 ml). Cyanuric chloride solution was added slowly to above reaction mixture at 0°C with constant stirring. Then sodium bicarbonate solution (10% w/w) was added to neutralize librated HCl during the reaction. Finally the reaction mixture was poured over crushed ice. The solid separated out was filtered, washed with water and crystallized from alcohol. Anal. calcd. For $C_{22}H_{15}O_2N_7SCl_2$: C,51.57; H,2.95; O,6.25; N,19.14; S,6.26; Cl,13.84. Found C,51.55; H,2.96; O,6.24; N,19.15; S,6.25; Cl, 13.83.

Condensation of Substituted phenyl urea with [4-(4,6-Dichloro-[1,3,5]triazin-2-yloxy)-2,6-dimethyl-quinolin-3-yl]-(6-methoxy-benzothiazol-2-yl)diazene: [3a-h]

[4-(4,6-Dichloro-[1,3,5]-triazin-2-yloxy)-2,6-dimethyl-quinolin-3-yl]-(6-methoxy-benzothiazol-2-yl)-diazene (2.56 gm, 0.005 mol) was dissolved in acetone (25 ml). Substituted phenyl urea (0.005 mol) was dissolved in acetone (10 ml) and added slowly to the above reaction mixture at 35-40°C temperature with constant stirring. Sodium bicarbonate solution (10%) was added to neutralize liberated HCl during reaction. The stirring was continued at the same temperature for

2 hours. Finally the reaction mixture was poured over crushed ice. The solid separated out was filtered, washed with water and crystallized from chloroform. Anal. calcd. For $C_{29}H_{22}O_3N_9SCl$: C,56.91; H,3.62; O,7.84; N,20.60; S,5.24; Cl,5.79. Found C,56.93; H,3.60; O,7.82; N,20.57; S,5.25; Cl, 5.81.

1-{4-Chloro-6-[3-(6-methoxybenzothiazol-2-ylazo)-2,6-dimethyl-quinolin-4-yloxy]-[1,3,5] triazin-2-yl}-(phenyl)-urea (3a)

Yield 72.25%; mp: 108 ^{o}C; FT-IR [ν, cm^{-1}, KBr]: 3416 (NH), 1400 (-CH_3), 2833 (-OCH_3), 1659 (-C=N), 753 (-C-Cl), 1577 (-N=N-), 1263(C-O-C), 1710(C=O). ^{1}H NMR [400 MHz, δ, ppm, DMSO-d_6]: 2.66 (3H, s, -CH_3), 2.86 (3H, s, -CH_3), 3.82 (3H, s, -OCH_3), 6.88-7.97 (11H, m, Ar-H), 8.85 (1H, s, -NH), 9.85(1H, s, -NH). Anal. calcd. For $C_{29}H_{22}O_3N_9SCl$: C,56.91; H,3.62; O,7.84; N,20.60; S,5.24; Cl,5.79. Found C,56.93; H,3.60; O,7.82; N,20.57; S,5.25; Cl, 5.81.

1-{4-Chloro-6-[3-(6-methoxybenzothiazol-2-ylazo)-2,6-dimethyl-quinolin-4-yloxy]-[1, 3, 5] triazin-2-yl}-(2-methyl phenyl)-urea (3b)

Yield 75.34%; mp: 132 ^{o}C; FT-IR [ν, cm-1, KBr]: 3412 (NH) , 1395 (CH_3), 2835 (OCH_3), 1654 (C=N), 758 (C-Cl), 1575 (-N=N-), 1260(C-O-C), 1708(C=O). ^{1}H NMR [400 MHz, δ, ppm, DMSO-d_6]: 2.62 (3H, s, -CH_3), 2.88 (3H, s, -CH_3), 3.80 (3H, s, -OCH_3), 6.84-7.94 (11H, m, Ar-H), 8.81 (1H, s, -NH), 9.88(1H,s,-NH). Anal. calcd. For $C_{30}H_{24}O_3N_9SCl$: C,57.55; H,3.86; O,7.67; N,20.13; S,5.12; Cl,5.66. Found C,57.57; H,3.86; O,7.68; N,20.15; S,5.10; Cl, 5.65.

1-{4-Chloro-6-[3-(6-methoxybenzothiazol-2-ylazo)-2,6-dimethyl-quinolin-4-yloxy]-[1, 3, 5] triazin-2-yl}-(4-methyl phenyl)-urea (3c)

Yield 76.12%; mp: 139 ^{o}C; FT-IR [ν, cm-1, KBr]: 3410 (NH), 1392 (CH_3), 2830 (OCH_3), 1657 (C=N), 755 (C-Cl), 1574 (-N=N-), 1264(C-O-C), 1709(C=O). ^{1}H NMR [400 MHz, δ, ppm, DMSO-d_6]: 2.61 (3H, s, -CH_3), 2.84 (3H, s, -CH_3), 3.81 (3H, s, -OCH_3), 6.84-7.95 (11H, m, Ar-H), 8.86 (1H, s, -NH), 9.81(1H,s,-NH). Anal. calcd. For $C_{30}H_{24}O_3N_9SCl$: C,57.55; H,3.86; O,7.67; N,20.13; S,5.12; Cl,5.66. Found C,57.56; H,3.85; O,7.66; N,20.14; S,5.11; Cl, 5.67.

1-{4-Chloro-6-[3-(6-methoxybenzothiazol-2-ylazo)-2,6-dimethyl-quinolin-4-yloxy]-[1, 3, 5] triazin-2-yl}-(2-methoxy phenyl)-urea (3d)

Yield 71.34%; mp: 116 ^{o}C; FT-IR [ν, cm-1, KBr]: 3415 (NH), 1398 (CH_3), 2834 (OCH_3), 1656 (C=N), 751 (C-Cl), 1578 (-N=N-), 1269(C-O-C), 1702(C=O). ^{1}H NMR [400 MHz, δ, ppm, DMSO-d_6]: 2.65 (3H, s, -CH_3), 2.86 (3H, s, -CH_3), 3.80 (3H, s, -OCH_3), 6.84-7.92 (11H, m, Ar-H), 8.83 (1H, s, -NH), 9.85(1H,s,-NH). Anal. calcd. For $C_{30}H_{24}O_4N_9SCl$: C,56.12; H,3.77; O,9.97; N,19.63; S,4.99; Cl,5.52. Found C,56.11; H,3.76; O,9.98; N,19.65; S,5.00; Cl, 5.53.

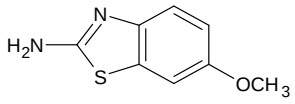
1-{4-Chloro-6-[3-(6-methoxy benzothiazol 2-ylazo)-2,6-dimethyl-quinolin -4-yloxy]-[1, 3, 5] triazin-2-yl}-(4-methoxyphenyl)-urea (3e)

Yield 70.35%; mp: 129 ^{o}C; FT-IR [ν, cm-1, KBr]: 3418 (NH), 1394 (CH_3), 2835 (OCH_3), 1652 (C=N), 758 (C-Cl), 1579 (-N=N-), 1266(C-O-C), 1715(C=O). ^{1}H NMR [400 MHz, δ, ppm, DMSO-d_6]: 2.61 (3H, s, -CH_3), 2.82 (3H, s, -CH_3), 3.87 (3H, s, -OCH_3), 6.89-7.91 (11H, m, Ar-H), 8.88 (1H, s, -NH), 9.89(1H,s,-NH). Anal. calcd. For $C_{30}H_{24}O_4N_9SCl$: C,56.12; H,3.77; O,9.97; N,19.63; S,4.99; Cl,5.52. Found C,56.10; H,3.78; O,9.99; N,19.64; S,4.98; Cl, 5.51.

1-{4-Chloro-6-[3-(6-methoxy benzothiazol 2-ylazo)-2,6-dimethyl-quinolin-4-yloxy]-[1, 3, 5] triazin-2-yl}-(2-chloro phenyl)-urea (3f)

Yield 69.21%; mp: 117 ^{o}C; FT-IR [ν, cm-1, KBr]: 3411 (NH), 1390 (CH_3), 2837 (OCH_3), 1658 (C=N), 754 (C-Cl), 1572 (-N=N-), 1263(C-O-C), 1716(C=O). ^{1}H NMR [400 MHz, δ, ppm, DMSO-d_6]: 2.65 (3H, s, -CH_3), 2.80 (3H, s, -CH_3), 3.86 (3H, s, -OCH_3), 6.86-7.97 (11H, m, Ar-

H), 8.8 (1H, s, -NH), 9.83(1H,s,-NH). Anal. calcd. For $C_{29}H_{21}O_3N_9SCl_2$: C,53.88; H,3.27; O,7.42; N,19.50; S,4.96; Cl,10.97. Found C,53.86; H,3.26; O,7.43; N,19.51; S,4.98; Cl, 10.95.

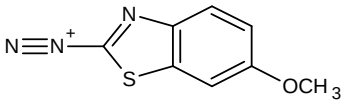


2 - amino 6 -methoxy benzothiazole

Diazotisation/ 0 - 5 °C

$NaNO_2 + H_2SO_4$

Propionic acid

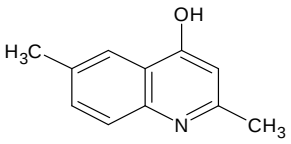


Diazotised 2 - amino 6 -methoxy benzothiazole

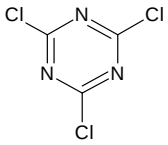
condensation

0 -5 °C

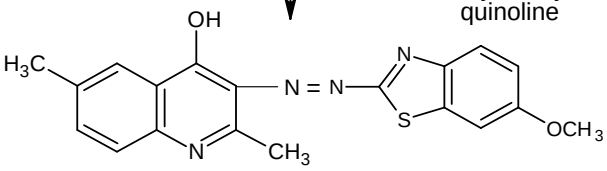
NaOH



2,6 - dimethyl 4 - hydroxy quinoline



2,4,6-trichloro-1,3,5-triazine

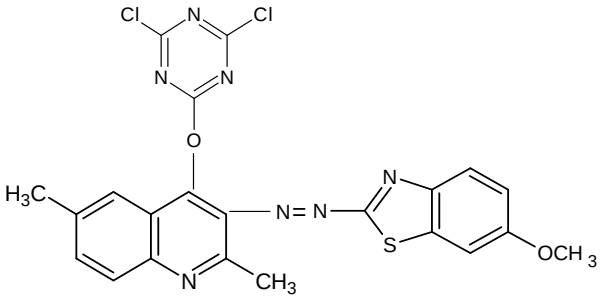


3-[(6-methoxy-benzothiazol-2-yl)-diazinyl]-2,6-dimethyl-4-hydroxy quinoline **[1]**

10% $NaHCO_3$ Sol^n.

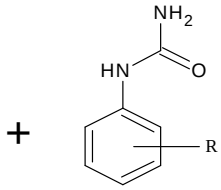
0 - 5 °C

Acetone



[4-(4,6-Dichloro-[1,3,5]triazin-2-yloxy)-2,6-dimethyl-quinolin-3-yl]-(6-methoxy-benzothiazol-2-yl)-diazene

[2]

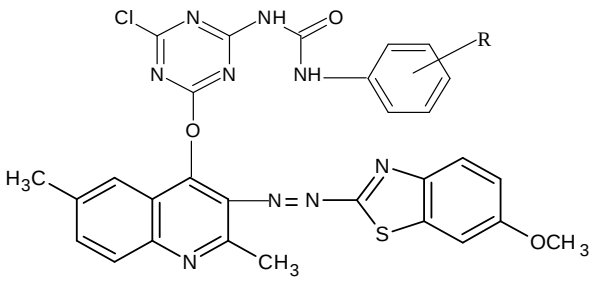


Substitued Phenyl Urea

10% $NaHCO_3$ Sol^n.

35 - 40 °C

Acetone



1-{4-Chloro-6-[3-(6-methoxy - benzothiazol-2-ylazo)-2,6-dimethyl-quinolin-4-yloxy]-[1,3,5] triazin-2-yl}-(substituted phenyl)-urea **[3a - h]**

Where, R = -CH_3, -OCH_3, -OC_2H_5, -Cl, -H.

1-{4-Chloro-6-[3-(6-methoxy benzothiazol-2-ylazo)-2,6-dimethyl-quinolin -4-yloxy]-[1, 3, 5] triazin-2-yl}-(4-chloro phenyl)-urea (3g)

Yield 70.18%; mp: 154 ^{o}C; FT-IR [ν, cm-1, KBr]: 3416 (NH), 1399 (CH_3), 2835 (OCH_3), 1655 (C=N), 753 (C-Cl), 1576 (-N=N-), 1266(C-O-C), 1722(C=O). ^{1}H NMR [400 MHz, δ, ppm, DMSO-d_6]: 2.66 (3H, s, -CH_3), 2.82 (3H, s, -CH_3), 3.82 (3H, s, -OCH_3), 6.80-7.90 (11H, m, Ar-H), 8.89 (1H, s, -NH), 9.84(1H,s,-NH). Anal. calcd. For $C_{29}H_{21}O_3N_9SCl_2$: C,53.88; H,3.27; O,7.42; N,19.50; S,4.96; Cl,10.97. Found C,53.87; H,3.28; O,7.44; N,19.52; S,4.97; Cl, 10.96.

1-{4-Chloro-6-[3-(6-methoxy benzothiazol-2-ylazo) -2,6-dimethyl-quinolin-4-yloxy]-[1, 3, 5] triazin-2-yl}-(4-ethoxy phenyl)-urea (3h)

Yield 76.80%; mp: 141 ^{o}C; FT-IR [ν, cm-1, KBr]: 3411 (NH), 1397 (CH_3), 2833 (OCH_3), 1654 (C=N), 756 (C-Cl), 1576 (-N=N-), 1266(C-O-C), 1716(C=O). ^{1}H NMR [400 MHz, δ, ppm, DMSO-d_6]: 2.69 (3H, s, -CH_3), 2.84 (3H, s, -CH_3), 3.85 (3H, s, -OCH_3), 6.84-7.95 (11H, m, Ar-H), 8.87 (1H, s, -NH), 9.87(1H,s,-NH). Anal. calcd. For $C_{31}H_{26}O_4N_9SCl$: C,56.75; H,3.99; O,9.75; N,19.21; S,4.89; Cl,5.40. Found C,56.76; H,3.96; O,9.73; N,19.20; S,4.90; Cl, 5.41.

RESULTS AND DISCUSSION

First 2-amino-6-methoxy-benzothiazole diazotized using conc. H_2SO_4 and Sodium nitrite and than condensed with 2,6-dimethyl-4-hydroxyquinoline to give 3-[(6-methoxy-benzothiazol-2-yl)-diazinyl]-2,6-dimethyl 4-hydroxy quinoline **[1]. 1a-h** reacts with cyanuric chloride to yield [4-(4,6-Dichloro-[1,3,5]triazin-2-yloxy)-2,6-dimethyl-quinolin-3-yl]-(6-methoxy-benzothiazol-2-yl)diazene **[2],** it was further reacts with substituted phenylurea to give corresponding compound **3a-h.**

New series of compounds [3a-h] was confirmed on the basis of elemental analysis and spectroscopic investigation. IR spectrum of **[1]** revealed characteristic bands at 3500-3250 (-OH) , 2850-2815 cm^{-1} (-OCH_3), 1680-1650 cm^{-1} (-C=N), 1400-1360 cm^{-1} (-CH_3) , 1630-1575 cm^{-1} (-N=N-) and confirmatory by ^{1}H NMR Signal at δ 5.5 (1H, s, -OH cm^{-1}), IR spectrum of **[2]** revealed characteristic bands at 800-600 cm^{-1} (-C-Cl) and there is no band observe at 3500-3250 cm^{-1} which is prove –OH group absent and it reacts with –Cl group of cyanuric chloride and strong band observe at 1270-1250 cm^{-1} due to ether linkage formation(-C-O-C-) . Further, IR spectroscopic investigation of **3a-h** revealed bands at 3500-3300 cm^{-1} -NH and 1630-1575 cm^{-1} (-C=N) while additional peak appears due to substitution in the aromatic ring showing absorption band at 1400-1360 cm^{-1} (-CH_3), 2850-2815 cm^{-1} (-OCH_3), 1270-1250 cm^{-1} (-C-O-C), 1730-1650 cm^{-1} (-C=O), 800-600 cm^{-1} (-C-Cl). ^{1}H NMR signal at δ 8.6 (1H, s, -NH) and δ 9.9 (1H, s, -NH) and additional signal appear due to substitution in aromatic ring showing common signals at δ 2.6 (3H, s, -CH_3) , δ 2.8 (3H, s, -CH_3), δ 3.7 (3H, s, -OCH_3) and δ (6.8-7.9, m, aromatic protons).

Antimicrobial activity

Antibacterial activity

Antibacterial activities of all the compounds were studied against Gram-positive bacteria [*Staphylococcus aureus & Streptococcus pyogenes*] and Gram-negative bacteria [*salmonella typhi* & *Escherichia coli*] at a concentration of 100μg/mL by agar cup plate method. The test compounds were dissolved in DMF at a concentration of 100 μg/mL using Ciprofloxacin as a standard for comparison control experiment was carried out. The area of inhibition of zone measured in mm. An examination of the data reveals that all compounds showed antibacterial activity. Results are presented in Table-1.

Antifungal activity

The synthesized compounds were also screened for their antifungal activity against *Candida albicans , Aspergillus niger using* the agar cup plate diffusion method by dissolving in DMF at a concentration of 100 μg/mL. The zone of inhibition was at after 7 days and 20 °C and it was compared with Greseofulvin and Nystatin as standard drugs as shown in Table.

Zone of Inhibition (in mm)						
Compd.	Antibacterial activity				Antifungal activity	
	Gram Positive		Gram Negative			
	S. Aureus	*S. Pyogenes*	*E.Coli*	*S.Typhi*	*C.albicans*	*A.Niger*
3a	12(0.63)	13(0.72)	15(0.71)	14(0.70)	17(0.77)	18(0.81)
3b	14(0.73)	13(0.72)	16(0.76)	14(0.70)	18(0.81)	19(0.86)
3c	13(0.68)	14(0.77)	17(0.80)	15(0.75)	18(0.81)	18(0.81)
3d	16(0.84)	15(0.83)	18(0.85)	17(0.85)	19(0.86)	18(0.81)
3e	17(0.89)	16(0.88)	19(0.90)	16(0.80)	20(0.90)	19(0.86)
3f	16(0.84)	14(0.77)	17(0.80)	15(0.75)	19(0.86)	17(0.77)
3g	15(0.73)	13(0.72)	18(0.85)	16(0.80)	20(0.90)	18(0.81)
3h	16(0.84)	15(0.83)	19(0.90)	16(0.80)	18(0.81)	19(0.86)
Std.1	19	18	21	20	22	22

**= average zone of inhibition in mm,*
(Activity index) = Inhibition zone of the sample / Inhibition zone of the standard,
For antibacterial activity: Std. 1 = Ciprofloxacin and
For antifungal activity: Std. 1= Nystatin

CONCLUSION

The antimicrobial activity of 1-{4-Chloro - 6 - [3 - (6-methoxy benzothiazol 2-ylazo) -2,6-dimethyl- quinolin -4-yloxy]-[1, 3, 5] triazin-2-yl}-(substituted phenyl)-urea **[3a-h]** was carried out against some strain bacteria. The results show that the synthesized compounds were toxic against the bacteria. The comparison of the antibacterial and antifungal activity of these compounds with standard drugs shows that the presence of methoxy and halogen (-Cl) groups in the phenyl ring increases the antimicrobial activity. Their potency has been found to be lower than that of standard drugs, but their acute toxicity is significantly lower.

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