

QUINOLIN-6-AMINES: SYNTHESIS AND BIOLOGICAL EVALUATION

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ABSTRACT

Some novel 2-((chloromethoxy)methyl)thio-N-substituted phenyl-[1,2,4]triazolo[1,5-a] quinolin-6-amines have been derived from 5-bromocoumarin. All the synthesized compounds have been characterized by elemental and spectral (I.R., ¹H-NMR, Mass) analysis and evaluated for their antimicrobial, insecticidal and anthelmintic activities.

Keywords: Quinolin-6-amines; antimicrobial; insecticidal; anthelmintic

ABSTRAK

Beberapa senyawa baru kuinolin-6-amin tersubstitusi 2-((klorometoksi)metil)tio-N telah dihasilkan sebagai turunan dari 5-bromocoumarin. Semua senyawa yang disintesis telah dikarakterisasi melalui analisis unsur dan spektra (IR, H-NMR dan massa) dan diuji terhadap aktivitas antimikrobia, insentisida dan antelmintak.

Kata Kunci: kuinolin-6-amin; antimikrobia; insektisida; antelmintak

INTRODUCTION

Coumarins belong to a group of compounds known as the benzopyrones, all of which consist of a benzene ring joined to a pyranone ring. During 1820, coumarin [1] was first isolated from the tonka bean and the name coumarin derives from a French word, *coumarou*, for the tonka bean. Due to its sweet odor, it was frequently used in perfumes since 1882. Coumarin and its derivatives extensively used as building block in heterocyclic synthetic chemistry for their versatile biological activities including antibacterial [2-5] antifungal [6-10], herbicidal [11], antitumor [12-13], anti-HIV [14], anticoagulant [15], anticonvulsant [16-17], anti-inflammatory [18-19], antimalarial [20] activities. In addition, these compounds are used as additives in food and cosmetics [21], dyes for tuning lasers [22-25]. On the other side, 1,2,4-triazoles symbolize one of the most biologically active block of compounds possessing a wide spectrum of activities. The 1,2,4-triazole derivatives were allied with various pharmacological activities viz. antiseptic, analgesic, anti-convulsant [26-37], antibiotic [26], antiallergic [26], anti-inflammatory [26-35,38], diuretic [26,30,33], fungicidal [28-29,35-38], insecticidal [28,35,38], herbicidal [28,35,38], antibacterial [28-31,36-37], antiviral [27-30,32-33,35], antidepressant [27,30,34], antimicrobial [27-30,32,35-37], antitumor [28,31,34-35], antihypertensive [30,33,34], and antimigraine

compounds [32]. There are several well known market drugs which possess 1,2,4-triazole group e.g. rizatriptan, nefazodone, vorozole, ribavirin, fluconazole, letrozole and uniconazole etc. These above mentioned observations motivated us to design a synthetic strategy (Scheme-1). Herein we report on the synthesis of a new class of substituted quinolin-6-amines and their biological activity by using a simple synthetic approach from easily available building block materials.

EXPERIMENTAL SECTION

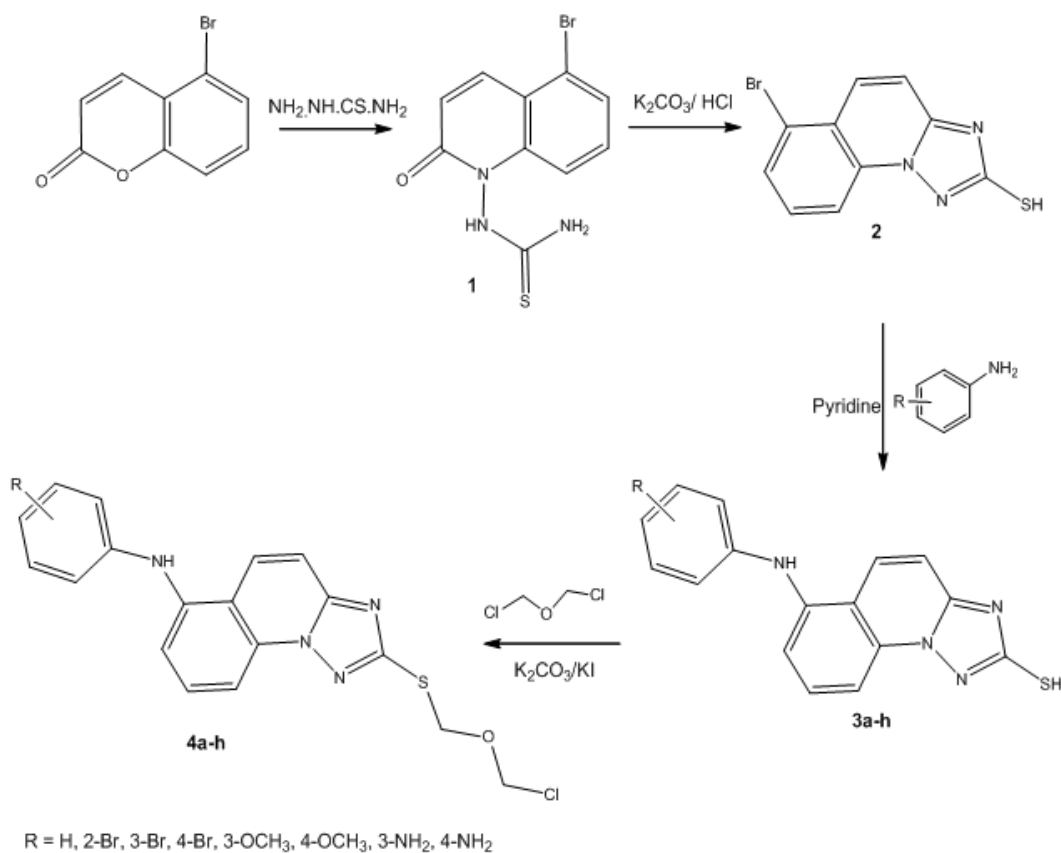
Materials

All the chemicals used for the preparation of desired derivatives, were obtained from Sisco Research Laboratories (SRL), Mumbai, India; Qualigen Fine Chemicals, Mumbai, India; E. Merck Ltd., New Delhi, India. The reference drugs ampicillin trihydrate, fluconazole, cypermethrin and albendazole were procured from Ind-Swift Pharmaceutical, Panjab; Cadilla Pharmaceuticals, Gujarat; Royal Crop Science, Panipat, India.

Instrumentation

The melting points of the compounds were determined in open glass capillaries with the help of

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Scheme 1

thermonic melting points apparatus (Campbell Electronics, Mumbai, India) and are uncorrected. The homogeneity of all the newly synthesized compounds was routinely checked by TLC on silica gel G plates and spots were located by using iodine chamber. Elemental analysis was performed in Heraeus CHN rapid analyzer. The results were found within the $\pm 0.4\%$ of theoretical values. Infrared spectra were recorded on KBr pellets on a Perkin Elmer system 2000 FTIR spectrometer and $^1\text{H-NMR}$ spectra on Bruker DPX 200 using TMS as internal standard.

Characterization of the Synthesized Compounds

The formation of compound 1 was confirmed by the presence of absorption bands at 1625, 1350, 3400, 3150 cm^{-1} due to vibrational movement of C=O, C=S, NH₂, NH of incorporated thiourea group respectively which was further evidenced by the appearance of broad signals in $^1\text{H-NMR}$ spectrum at δ 6.58 and 4.30 due to -NH and -NH₂ groups. Disappearance of adsorption band for C-O-C at 1040 cm^{-1} clears the formation of compound 1. Cyclisation of compound 1 into compound 2 was confirmed by the disappearance of vibration band in I.R. spectrum at 3400 cm^{-1} of NH₂ group and appearance of

bands at 2400, 1625 cm^{-1} for -SH and C=N groups respectively. $^1\text{H-NMR}$ spectra revealed the anilation of compound 2 to compounds 3a-h; by the appearance of broad signal at δ 3.70. Presence of band at 1025 cm^{-1} is the characteristic feature of the existence of compounds 4a-h which was further evidenced by the disappearance of band for SH at 2400 cm^{-1} .

Procedure

Synthesis of 1-(2-oxoquinolin-1(2H)-yl)thiourea 1

A reaction mixture of 5-bromo coumarin (0.01 mol) and thiosemicarbazide (0.01 mol) in pyridine was refluxed for 3 h. The progress of reaction was monitored by TLC. Excess of the solvents was removed under reduced pressure. Residue was washed with water, filtered, dried, triturated with petroleum ether (40-60 °C) to yield compound 1: Yield 83%, m.p.89 °C. IR (KBr) ν_{max} in cm^{-1} : 1290 (N-N), 1350 (C=S), 1530 (C—C of aromatic), 1615 (C=N), 1640 (C=O), 3030 (aromatic CH), 3180 (NH), 3400 (NH₂). $^1\text{H-NMR}$ (CDCl₃) δ : 4.30 (bs, 2H, NH₂), 6.15 (s, 1H, NH), 6.85-7.87 (m, 6H, Ar-H). MS: m/z 298.96 [M]⁺. Elemental analysis (C₁₀H₈N₃SOBr), calcd: C 40.28, H 2.70, N 14.09%, found: C 40.16, H 2.73, N 14.05%.

Synthesis of 6-bromo-(1,2,4-triazolo)(1,5-a) quinoline-2-thiol 2

Compound 1 (0.01 mol) was mixed with aqueous solution of K_2CO_3 (25% w/w) and stirred at 55 °C for 8 h. On completion, the reaction mixture cooled and acidified with 2% HCl. The crude solid washed with water, filtered, dried and recrystallized with dioxane to obtain compound 2: Yield 76%, m.p.137 °C. IR (KBr) ν_{max} in cm^{-1} : 1288 (N-N), 1533 (C—C of aromatic), 1610 (C=N), 3035 (aromatic CH). 1H -NMR ($CDCl_3$) δ : 6.67-7.56 (m, 5H, Ar-H), 12.70 (s, 1H, HS). MS: m/z 280.94 $[M]^+$. Elemental analysis ($C_{10}H_6N_3SBr$), calcd: C 42.87, H 2.16, N 15.00%, found: C 42.90, H 2.15, N 15.03%.

Synthesis of 6-(substitutedanilino)(1,2,4-triazolo)(1,5-a)quinoline-2-thiol 3a-h

Methanolic solution of compound 2 (0.01 mol) in presence of few drops of pyridine was refluxed with different substituted anilines (0.01 mol) for 5-8 h. On completion of the reaction, excess of solvent was distilled off and thus obtained residue cooled, poured into ice cold water, filtered, dried and triturated with petroleum ether (40-60 °C) and recrystallized with appropriate solvents to furnish the products 3a-h.

6-(Anilino)(1,2,4-triazolo)(1,5-a)quinoline-2-thiol 3a. Yield 76%, m.p.137 °C. IR (KBr) ν_{max} in cm^{-1} : 1288 (N-N), 1533 (C—C of aromatic), 1610 (C=N), 3035 (aromatic CH), 3385 (NH). 1H -NMR ($CDCl_3$) δ : 5.85 (bs, 1H, NH), 6.79-7.64 (m, 10H, Ar-H), 12.55 (s, 1H, HS). MS: m/z 292.08 $[M]^+$. Elemental analysis ($C_{16}H_{12}N_4S$), calcd: C 65.73, H 4.14, N 19.16%, found: C 65.70, H 4.17, N 19.09%.

6-(2-Bromoanilino)(1,2,4-triazolo)(1,5-a)quinoline-2-thiol 3b. Yield 68%, m.p.169 °C. IR (KBr) ν_{max} in cm^{-1} : 1290 (N-N), 1531 (C—C of aromatic), 1615 (C=N), 3030 (aromatic CH), 3377 (NH). 1H -NMR ($CDCl_3$) δ : 5.77 (bs, 1H, NH), 6.68-7.60 (m, 9H, Ar-H), 12.41 (s, 1H, HS). MS: m/z 369.99 $[M]^+$. Elemental analysis ($C_{16}H_{11}N_4SBr$), calcd: C 51.76, H 2.99, N 15.09%, found: C 51.70, H 2.97, N 15.14%.

6-(3-Bromoanilino)(1,2,4-triazolo)(1,5-a)quinoline-2-thiol 3c. Yield 63%, m.p.158 °C. IR (KBr) ν_{max} in cm^{-1} : 1292 (N-N), 1529 (C—C of aromatic), 1611 (C=N), 3032 (aromatic CH), 3380 (NH). 1H -NMR ($CDCl_3$) δ : 5.80 (bs, 1H, NH), 6.65-7.55 (m, 9H, Ar-H), 12.46 (s, 1H, HS). MS: m/z 369.99 $[M]^+$. Elemental analysis ($C_{16}H_{11}N_4SBr$), calcd: C 51.76, H 2.99, N 15.09%, found: C 51.70, H 2.97, N 15.14%.

6-(4-Bromoanilino)(1,2,4-triazolo)(1,5-a)quinoline-2-thiol 3d. Yield 70%, m.p.162 °C. IR (KBr) ν_{max} in cm^{-1} : 1283 (N-N), 1526 (C—C of aromatic), 1617 (C=N), 3024 (aromatic CH), 3373 (NH). 1H -NMR ($CDCl_3$) δ : 5.72 (bs, 1H, NH), 6.60-7.61 (m, 9H, Ar-H), 12.38 (s, 1H, HS). MS: m/z 369.99 $[M]^+$. Elemental analysis ($C_{16}H_{11}N_4SBr$),

calcd: C 51.76, H 2.99, N 15.09%, found: C 51.70, H 2.97, N 15.14%.

6-(3-Methoxyanilino)(1,2,4-triazolo)(1,5-a)quinoline-2-thiol 3e. Yield 66%, m.p.135 °C. IR (KBr) ν_{max} in cm^{-1} : 1279 (N-N), 1527 (C—C of aromatic), 1614 (C=N), 3028 (aromatic CH), 3376 (NH). 1H -NMR ($CDCl_3$) δ : 3.81 (s, 3H, OCH_3), 5.76 (bs, 1H, NH), 6.58-7.55 (m, 9H, Ar-H), 12.44 (s, 1H, HS). MS: m/z 322.09 $[M]^+$. Elemental analysis ($C_{17}H_{14}N_4SO$), calcd: C 63.33, H 4.38, N 17.38%, found: C 63.40, H 4.37, N 17.24%.

6-(4-Methoxyanilino)(1,2,4-triazolo)(1,5-a)quinoline-2-thiol 3f. Yield 71%, m.p.159 °C. IR (KBr) ν_{max} in cm^{-1} : 1284 (N-N), 1530 (C—C of aromatic), 1618 (C=N), 3034 (aromatic CH), 3383 (NH). 1H -NMR ($CDCl_3$) δ : 3.85 (s, 3H, OCH_3), 5.70 (bs, 1H, NH), 6.66-7.62 (m, 9H, Ar-H), 12.51 (s, 1H, HS). MS: m/z 322.09 $[M]^+$. Elemental analysis ($C_{17}H_{14}N_4SO$), calcd: C 63.33, H 4.38, N 17.38%, found: C 63.40, H 4.37, N 17.24%.

6-(3-Aminoanilino)(1,2,4-triazolo)(1,5-a)quinoline-2-thiol 3g. Yield 62%, m.p.121 °C. IR (KBr) ν_{max} in cm^{-1} : 1280 (N-N), 1533 (C—C of aromatic), 1621 (C=N), 3030 (aromatic CH), 3380 (NH). 1H -NMR ($CDCl_3$) δ : 5.67 (bs, 1H, NH), 6.12 (bs, 2H, NH_2), 6.70-7.66 (m, 9H, Ar-H), 12.42 (s, 1H, HS). MS: m/z 307.09 $[M]^+$. Elemental analysis ($C_{16}H_{13}N_5S$), calcd: C 62.40, H 4.27, N 22.84%.

6-(4-Aminoanilino)(1,2,4-triazolo)(1,5-a)quinoline-2-thiol 3h. Yield 65%, m.p.130 °C. IR (KBr) ν_{max} in cm^{-1} : 1278 (N-N), 1531 (C—C of aromatic), 1624 (C=N), 3032 (aromatic CH), 3377 (NH). 1H -NMR ($CDCl_3$) δ : 5.55 (bs, 1H, NH), 6.17 (bs, 2H, NH_2), 6.73-7.60 (m, 9H, Ar-H), 12.48 (s, 1H, HS). MS: m/z 307.09 $[M]^+$. Elemental analysis ($C_{16}H_{13}N_5S$), calcd: C 62.52, H 4.26, N 22.78%, found: C 62.51, H 4.26, N 22.72%.

2-[(chloromethoxy)methylthio-N-substitutedphenyl]-(1,2,4)triazolo(1,5-a)quinolin-6-amine 4a-h

Compound 3a-h (0.01 mol), potassium bicarbonate (0.02 mol), potassium iodide (0.001 mol) was taken in acetonitrile, stirred at room temperature for 30 min, heated 70-80 °C for 2-3 h. The progress of reaction was monitored by TLC for complete disappearance of 3a-h. On completion of reaction, mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was washed with water, brine and then dried over anhydrous sodium sulphate. The dried organic layer was distilled under reduced pressure to furnish compounds 4a-h.

2-[(chloromethoxy)methylthio-N-phenyl]-(1,2,4)triazolo(1,5-a)quinolin-6-amine 4a. Yield 68%, m.p.135 °C. IR (KBr) ν_{max} in cm^{-1} : 1280 (N-N), 1527 (C—C of aromatic), 1615 (C=N), 3038 (aromatic CH), 3380 (NH). 1H -NMR ($CDCl_3$) δ : 3.00 (s, 2H, CH_2), 5.15 (s, 2H, CH_2-Cl), 5.80 (bs, 1H, NH), 6.95-7.90 (m, 10H, Ar-H). MS: m/z 370.07 $[M]^+$. Elemental analysis

(C₁₈H₁₅N₄SClO), calcd: C 58.30, H 4.08, N 15.11%, found: C 58.26, H 4.07, N 15.27%.

2-[(chloromethoxy)methylthio-N-(2-bromophenyl)]-(1,2,4)triazolo(1,5-a)quinolin-6-amine 4b. Yield 68%, m.p.135 °C. IR (KBr) ν_{\max} in cm⁻¹: 1280 (N-N), 1527 (C—C of aromatic), 1615 (C=N), 3038 (aromatic CH), 3380 (NH). ¹H-NMR (CDCl₃) δ : 3.10 (s, 2H, CH₂), 5.15 (s, 2H, CH₂-Cl), 5.80 (bs, 1H, NH), 6.95-7.90 (m, 9H, Ar-H). MS: m/z 449.97 [M]⁺. Elemental analysis (C₁₈H₁₄N₄SBrClO), calcd: C 48.07, H 3.14, N 12.46%, found: C 48.12, H 3.12, N 12.44%.

2-[(chloromethoxy)methylthio-N-(3-bromophenyl)]-(1,2,4)triazolo(1,5-a)quinolin-6-amine 4c. Yield 53%, m.p.121 °C. IR (KBr) ν_{\max} in cm⁻¹: 1274 (N-N), 1520 (C—C of aromatic), 1626 (C=N), 3028 (aromatic CH), 3372 (NH). ¹H-NMR (CDCl₃) δ : 3.08 (s, 2H, CH₂), 5.21 (s, 2H, CH₂-Cl), 5.88 (bs, 1H, NH), 6.79-7.85 (m, 9H, Ar-H). MS: m/z 449.97 [M]⁺. Elemental analysis (C₁₈H₁₄N₄SBrClO), calcd: C 48.07, H 3.14, N 12.46%, found: C 48.08, H 3.10, N 12.40%.

2-[(chloromethoxy)methylthio-N-(4-bromophenyl)]-(1,2,4)triazolo(1,5-a)quinolin-6-amine 4d. Yield 57%, m.p.140 °C. IR (KBr) ν_{\max} in cm⁻¹: 1277 (N-N), 1524 (C—C of aromatic), 1621 (C=N), 3031 (aromatic CH), 3372 (NH). ¹H-NMR (CDCl₃) δ : 3.12 (s, 2H, CH₂), 5.21 (s, 2H, CH₂-Cl), 5.87 (bs, 1H, NH), 6.75-7.81 (m, 9H, Ar-H). MS: m/z 449.97 [M]⁺. Elemental analysis (C₁₈H₁₄N₄SBrClO), calcd: C 48.07, H 3.14, N 12.46%, found: C 48.05, H 3.10, N 12.38%.

2-[(chloromethoxy)methylthio-N-(3-methoxyphenyl)]-(1,2,4)triazolo(1,5-a)quinolin-6-amine 4e. Yield 56%, m.p.179 °C. IR (KBr) ν_{\max} in cm⁻¹: 1282 (N-N), 1527 (C—C of aromatic), 1616 (C=N), 3038 (aromatic CH), 3375 (NH). ¹H-NMR (CDCl₃) δ : 3.15 (s, 3H, OCH₃), 3.71 (s, 2H, CH₂), 5.15 (s, 2H, CH₂-Cl), 5.80 (bs, 1H, NH), 6.95-7.90 (m, 9H, Ar-H). MS: m/z 401.07 [M]⁺. Elemental analysis (C₁₉H₁₇N₄SClO₂), calcd: C 56.93, H 4.27, N 13.98%, found: C 56.86, H 4.17, N 14.12%.

2-[(chloromethoxy)methylthio-N-(4-methoxyphenyl)]-(1,2,4)triazolo(1,5-a)quinolin-6-amine 4f. Yield 51%, m.p.188 °C. IR (KBr) ν_{\max} in cm⁻¹: 1278 (N-N), 1521 (C—C of aromatic), 1620 (C=N), 3035 (aromatic CH), 3380 (NH). ¹H-NMR (CDCl₃) δ : 3.23 (s, 3H, OCH₃), 3.68 (s, 2H, CH₂), 5.10 (s, 2H, CH₂-Cl), 5.93 (bs, 1H, NH), 6.91-7.88 (m, 9H, Ar-H). MS: m/z 401.07 [M]⁺. Elemental analysis (C₁₉H₁₇N₄SClO₂), calcd: C 56.93, H 4.27, N 13.98%, found: C 56.90, H 4.20, N 14.01%.

2-[(chloromethoxy)methylthio-N-(3-aminophenyl)]-(1,2,4)triazolo(1,5-a)quinolin-6-amine 4g. Yield 59%, m.p.116 °C. IR (KBr) ν_{\max} in cm⁻¹: 1270 (N-N), 1528 (C—C of aromatic), 1625 (C=N), 3024 (aromatic CH), 3376 (NH). ¹H-NMR (CDCl₃) δ : 3.10 (s, 2H, CH₂), 4.15 (bs, 2H, NH₂), 5.02 (s, 2H, CH₂-Cl), 5.87 (bs, 1H, NH), 6.75-7.81 (m, 9H, Ar-H). MS: m/z 385.08 [M]⁺.

Elemental analysis (C₁₈H₁₆N₅SClO), calcd: C 56.03, H 4.18, N 18.15%, found: C 56.11, H 4.14, N 18.28%.

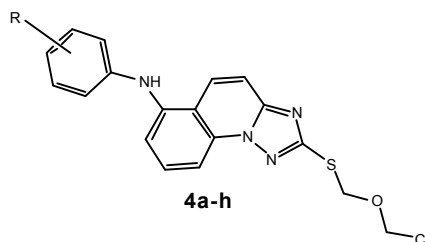
2-[(chloromethoxy)methylthio-N-(4-aminophenyl)]-(1,2,4)triazolo(1,5-a)quinolin-6-amine 4h. Yield 49%, m.p.145 °C. IR (KBr) ν_{\max} in cm⁻¹: 1278 (N-N), 1533 (C—C of aromatic), 1628 (C=N), 3028 (aromatic CH), 3371 (NH). ¹H-NMR (CDCl₃) δ : 3.07 (s, 2H, CH₂), 4.12 (bs, 2H, NH₂), 5.10 (s, 2H, CH₂-Cl), 5.99 (bs, 1H, NH), 6.64-7.80 (m, 9H, Ar-H). MS: m/z 385.08 [M]⁺. Elemental analysis (C₁₈H₁₆N₅SClO), calcd: C 56.03, H 4.18, N 18.15%, found: C 56.00, H 4.20, N 18.20%.

PHARMACOLOGY

Compounds 4a-h were evaluated for antimicrobial, insecticidal and antihelmintic activity (Table 1, 2, and 3).

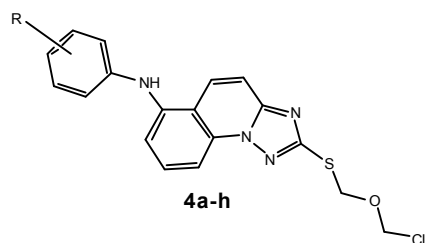
Antimicrobial Screening

All the newly synthesized compounds 4a-h were screened for their antibacterial and antifungal activity. All the bacterial as well as fungal strains were clinical isolates, identified with conventional morphological and biochemical methods. The microorganisms employed antibacterial studies were *Staphylococcus aureus*, *Escherichia coli* and *Klebsiella pneumoniae*. Disk diffusion method [39-40] was used for determination of the preliminary antibacterial activity. Disks measuring 6.25 mm in diameter were punched from Whatman no. 1 filter paper. Batches of 100 disks were dispensed to each screw-capped bottle and sterilized by dry heat at 140 °C for an hour. The test compounds were prepared with different concentrations using DMF. One milliliter containing 100 times the amount of chemical in each disk was added to each bottle, which contained 100 disks. Disks of each concentration were for placed in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37 °C for 24 h. Ampicillin trihydrate and fluconazole were used as standard drugs. Solvent and growth controls were kept and zones of inhibition were noted. The bacterial inhibition values (mm) of the tested compounds against the tested bacterial strains are recorded in Table 1. On the other hand, the newly prepared quinoline compounds were screened for their in vitro antifungal activity against *Aspergillus fumigatus* (plant isolate), *Candida albicans* and *Candida glabrata* in DMF by the serial plate dilution method [41-42]. Sabouraud's agar media were prepared by dissolving peptone (1 g), D-glucose (4 g), and agar (2 g) in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of the spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a

Table-1. Antimicrobial screening of 2-[(chloromethoxy)methylthio-N substituted phenyl]-(1,2,4)triazolo(1,5-a)quinolin-6-amine 4a-h.

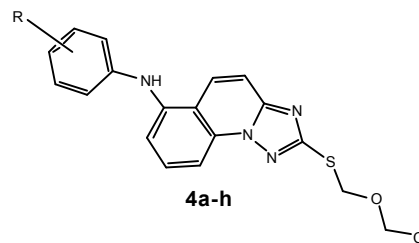
Compound	Antibacterial activity (mm)			Antifungal activity (mm)			
	R	<i>S. aureus</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>A. fumigatus</i>	<i>C. albicans</i>	<i>C. glabrata</i>
4a.	H	-	-	-	6	-	-
4b.	2-Br	-	6	5	-	6	-
4c.	3-Br	-	-	6	6	-	6
4d.	4-Br	-	6	-	-	-	8
4e.	3-OCH ₃	-	5	-	8	6	10
4f.	4-OCH ₃	6	6	10	14	10	8
4g.	3-NH ₂	-	5	-	5	-	5
4h.	4-NH ₂	-	5	6	6	6	6
Ampicillin trihydrate		16	16	20	-	-	-
Fluconazole		-	-	-	20	15	15
DMF (control)		-	-	-	-	-	-

- means no activity

Table-2. Insecticidal activity of 2-[(chloromethoxy)methylthio-N-substitutedphenyl]-(1,2,4)triazolo(1,5-a)quinolin-6-amine 4a-h at two different concentrations (KD value in min.).

Comp.	R	Time [min.]	
		1%	2%
4a.	H	20	14
4b.	2-Br	15	8
4c.	3-Br	18	12
4d.	4-Br	16	12
4e.	3-OCH ₃	16	10
4f.	4-OCH ₃	19	12
4g.	3-NH ₂	18	10
4h.	4-NH ₂	10	6
Cypermethrin		7	5

suspension of the corresponding species. Agar media (20 mL) was poured into each petri dish. Excess suspension was decanted and the plates were dried by placing in an incubator at 37 °C for 1 h. Using an agar punch wells were made into each well labeled. A control

Table-3. Anthelmintic activity of 2-[(chloromethoxy)methylthio-N-substitutedphenyl]-(1,2,4)triazolo(1,5-a)quinolin-6-amine 4a-h against *Pheretima posthuma* (paralytic and lethal time in min.).

Comp.	R	Paralytic time (min.)	Lethal time (min.)
4b.	2-Br	18	24
4c.	3-Br	18	22
4d.	4-Br	10	15
4e.	3-OCH ₃	14	18
4f.	4-OCH ₃	12	16
4g.	3-NH ₂	16	20
4h.	4-NH ₂	8	10
Albendazole		5	8

was also prepared in triplicate and maintained at 37 °C for 3–4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone. The fungicidal inhibitory (mm) values of the tested

compounds against the tested fungal species are recorded in Table 1.

Insecticidal Study

Periplaneta americana was taken for insecticidal study and 1 and 2% solutions of the derivatives 4a-h were injected in the abdominal of *P. americana* with the help of micro syringe. The time of death had been noted as KD (Knock promising to moderate activity) value. Cypermethrin was used as standard drug. At the time of death the antennae of *P. americana* became motionless, the appendages shrunk and folded towards the ventral side and cockroach lay dorsally [43] (Table 2).

Anthelmintic Activity

Indian adult earthworms (*Pheretima posthuma*) were collected from moist soil and washed with normal saline to remove all faecal matter and used for the anthelmintic activity. All the synthesized derivatives 4a-h were dissolved in minimum amount of DMF and the volume adjusted to 10 mL with saline water. All solutions of synthesized derivatives and drugs solutions were freshly prepared. Groups of six earthworms were released into desired formulations and the paralytic and lethal time noted. Albendazole was used as standard drug. Observations were made for the time taken for paralysis and death of individual worms. Paralysis was said to occur when the worms did not receive even in normal saline. Death was concluded when the worms lost their motility followed by fading away of their body color [44-47] (Table 3).

RESULT AND DISCUSSION

Chemistry

Synthesis was carried out by conventional methodology as sketched in scheme-1. Synthetic designing was started by the reaction of 5-bromo coumarin with thiosemicarbazide in presence of triethylamine (TEA) to obtain 1-(2-oxoquinolin-1(2*H*)-yl)thiourea 1 which further on cyclised into 6-bromo-(1,2,4-triazolo)(1,5-a) quinoline-2-thiol i.e. compound 2. The latter was anilated by the reaction of different substituted aromatic amines to afford 6-(substituted phenylamino)(1,2,4-triazolo)(1,5-a)quinoline-2-thiol; 3a-h. Condensation reaction of compounds 3a-h with bis(chloromethyl) ether produced target derivatives, 2-[(chloro methoxy)methylthio-*N*-substitutedphenyl]-(1,2,4) triazolo(1,5-a)quinolin-6-amine; 4a-h.

Biological evaluation

The synthesized substituted quinolines 4a-h evaluated for antimicrobial, insecticidal and anthelmintic activity. *Staphylococcus aureus*, *Escherichia coli*, *Klasiella pneumoniae*, *Aspergillus fumigatus* (plant isolate), *Candida albicans*, *Candida glabrata* pathogens were used for antimicrobial activity. Insecticidal activity performed against *Periplaneta americana*. *Pheretima posthuma* were used for the anthelmintic activity. All screened derivatives were found active against gram negative bacterial strains except derivative 4f. Derivative 4f demonstrated inhibitory profile against all gram positive as well as gram negative pathogens. Quinoline derivative 4f and 4h showed significant biological activity. Compound 4a was found active against *A. fumigatus* while compound 4b inhibited the growth of *E. coli*, *K. pneumoniae* and *C. albicans*. Derivative 4c showed no inhibition against *S. aureus*, *E. coli* and *C. albicans*. It was active against *K. pneumoniae*, *A. fumigatus* and *C. glabrata*. Compound 4d asserted inhibition against *E. coli* and *C. glabrata* only. Compound 4e illustrated improved microbial inhibition. It inhibited the growth of *E. coli*, *A. fumigatus* and *C. albicans*, *C. glabrata*. Growths of all bacterial and fungal strains were inhibited by the compound 4f with good potency. No inhibitory action against *S. aureus*, *K. pneumoniae* and *C. albicans* was elicited by derivative 4g. Compound 4h was active against all pathogens except *S. aureus*. It demonstrated poor antimicrobial array. Insecticidal activity results explored that among the tested compounds 4a-f, compound 4h showed significant insecticidal potential in term of KD values with respect to used standards. Anthelmintic activity screening figures depicted mild to moderate potential of quinoline derivatives 4a-h. Paralytic and lethal time result summary elucidated the efficacy of derivative 4h than the others tested derivatives.

CONCLUSION

Biological evaluation results revealed that 2-[(chloromethoxy)methyl]thio-*N*-(4-methoxyphenyl)[1,2,4] triazolo[1,5-a]quinolin-6-amine i.e. 4f displayed significant biological activity. Screening data explored that 2-[(chloromethoxy)methyl]thio-*N*-(4-methoxyphenyl) [1,2,4]triazolo[1,5-a]quinolin-6-amine showed broad antibacterial as well as antifungal spectrum in comparison to used standard drugs.

While, among the all tested compounds; compound 4h i.e. 2-[(chloromethoxy)methyl]thio-*N*-(4-aminophenyl)[1,2,4]triazolo[1,5-a]quinolin-6-amine also showed moderate insecticidal as well as anthelmintic activity. On the basis of SAR, it is elicited that 2-[(chloromethoxy)methyl]thio-*N*-(4-methoxyphenyl)[1,2,4]

triazolo[1,5-a] quinolin-6-amine, bearing 4-methoxy substitution caused better efficacy against the all used pathogens while on the other hand derivative 4h i.e. 2-((chloromethoxy)methyl)thio-N-(4-aminophenyl)[1,2,4]triazolo[1,5-a]quinolin-6-amine bearing 4-amino group resulted into better insecticidal as well as anthelmintic activity. So 4-methoxy substitution and 4-amino enhance biological activity of the derived quinolines.

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