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NOVEL SUBSTITUTED-3H-[1,2,3]TRIAZOLO-[2,3-b]QUINOLINES AS POTENT ANTIMICROBIAL AGENTS

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ABSTRACT

Novel series of methyl and phenyl substituted-3*H*-[1,2,3]triazolo-[2,3-*b*]quinolines are synthesized by reacting 2-chloro-4-methyl/4-phenyl-quinoline with sodium azide under appropriate reaction conditions which in turn obtained by the chloro substitution of 2-hydroxy-4-methyl/phenyl substituted quinolines. The hitherto synthesised compounds are characterized by IR, NMR and Mass spectroscopy. *In-vitro* screening of the synthesized compounds against microbes (*Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Asperigillus niger and Candida Albicans*) revealed that these scaffolds can act as efficient antimicrobials**.**

Keywords: Triazoloquinolines, N-heterocycles, Azide, *Candida albicans*.

1. INTRODUCTION

Heterocyclic chemistry is of prime importance as a sub-discipline of organic chemistry. In the series of heterocycles, quinoline and isoquinoline derivatives [1] are well known for their pharmaceutical [2-4] and industrial [5] importance. Since the identification of quinine from chinchona tree and utility towards the malaria parasite, several quinoline fused heterocycles such as furoquinolines, thienoquinolines, pyranoquinolines, etc have been synthesized and studied for their biological and medicinal applications that lead to many successful marketable drugs [6]. Triazole, a five-membered heterocyclic compound manifolds its presence in pharmacological [7] and industrial applications [8,9]. Among the triazoles 1,2,3-triazole and 1,2,4-triazole ring systems present as a part of many medicinal agents which has proved the pharmacological importance of this heterocyclic nucleus and also plays a vital role in the drug industry. It is observed from the literature that triazole moiety has great versatility infusing to various ring systems and that N-bridged heterocycles derived from them are associated with different pharmacological activities. Numbers of triazole derivatives as clinical drugs or candidates have been frequently employed for the treatment of various types of diseases [10-16], which have proved the importance of this heterocyclic nucleus in drug design and discovery. Recently, many endeavors were made to involve the triazole in the designing of anticonvulsants, antiviral, antimalarial [14], antimicrobial [15-17], anti-tuberculosis[18], anticonvulsant, antidepressant [19-24], antioxidant [25], anti-inflammatory [26,27] and anti-cancer agents[28,29]. These compounds also show anti-HIV [30], antihistaminic [31, 32], and antiepileptic [33]. Due to the broad spectrum of promising biological activity of triazoles, a number of triazole fused heterocyclic derivatives are prepared and studied for their pharmaceutical properties as feasible new drugs [34-44]. For instance, the synthesized triazolo combined heterocycles such as new imidazo [1,2-a] pyridines carrying suitably substituted 1,2,3-triazoles [45] 5-alkoxy-[1,2,4] triazolo [4,3-a] quinoline [46] and 1,2,4-triazolo [4,3-a] quinoline derivatives [47], 3-alkyl-8-aryl-5,6-dihydro-2-triazolo [3,4-b][1,3,4] thiadiazoles [48], 3-{4-[-nitrophenyl)-5-thioxo-4, 5-dihydro-1H- [1,2,4]triazole-3-yl-methoxy] phenyl} -2-phenyl -3H- quinolin-4-one are reported as good antifungal against *Aspergillus niger[*49] 3- (2, 4- dichlorophenoxymethyl) -7-(3, 4) dichlorophenyl-5H-6-dihydroimidazo [2,1-c] (1,2,4) triazoles found to possess superior *in vitro* antibacterial activity compared to ampicillin and chloramphenicol [50]. Based on the pharmacological importance of both quinoline and triazole nucleus, the combined action of both the nucleus may pave way for an enhanced pharmacological assays. On the insight of the discussed pharmacological importance, there is a continuous exploration of convenient and profitable synthetic methods for the triazolo bearing heterocycles [51-54]. Hence in this

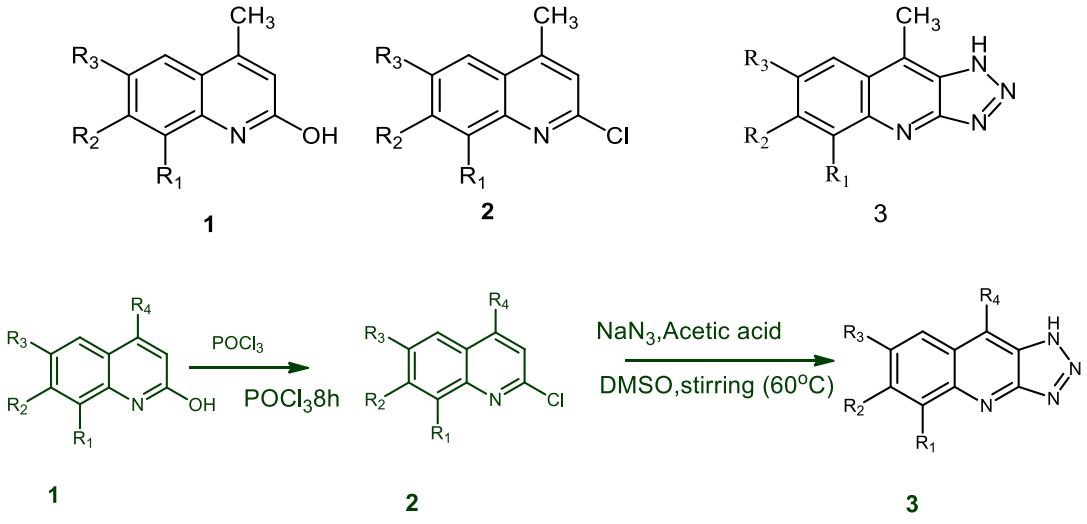
context, we are interested to synthesize the quinoline fused triazole nucleus by a catalyst-free single step addition reaction and thereby to study their antimicrobial activities against some selected bacteria and fungi.

2. EXPERIMENTAL

The synthesized compounds were characterized by spectroscopic analysis. IR, ^{1}H-NMR, ^{13}C-NMR are in support of the formation of the synthesized compounds. CHNS analysis was also carried out. Melting points were measured on a Gallen Kamp capillary melting point apparatus and are calibrated. Chromatographic techniques were used for the purification of targeted compounds. The compounds were recrystallized from chloroform. Chemicals for the experiments are obtained from Sigma Aldrich and used as such.

The targeted molecule (**3**) was obtained from the potential precursors 2-hydroxy-4-methyl quinoline (**1**), through the cyclization of chloroquinoline (**2**).

The precursor, 2-hydroxy quinoline **(1)** was obtained by the cyclization of the 3-oxo-N-[4'-methyl phenyl butanamide] with Con.H_2SO_4 as per the reported procedure [55, 56]. Accordingly, 2g (0.344mmol) of 2-hydroxy compound **(1)** was refluxed with 0.05mL (0.344mmol) of $POCl_3$ and three drops of DMA for 8 hours at 100°C. The compound was then recovered by following the reported procedure [55, 56]. Equal moles of 2-chloro quinoline derivatives (0.6g, 3.149mmol) in DMSO and NaN_3 (0.204g, 3.149mmol) in water were mixed and stirred at 60°C. As the layer separated, about 10mL of acetic acid was added to the reaction mixture. The stirring was further continued. The progress of the reaction was periodically monitored with TLC. The time for the complete reaction was 4 hours. The reaction mixture was poured into ice and the product obtained was washed with water and recrystallized from $CHCl_3$. On recrystallization, a lustrous dirty white precipitate was obtained. The melting point and yield of each product were noted. The reaction sequence was extended to synthesize their derivatives **3(a-n)**



a) R_1=R_2=R_3=H, R_4 =CH_3 b)R_1=CH_3, R_2=R_3=H ,R_4 =CH_3

c) R_2=CH_3 , R_1=R_3=H ,R_4 =CH_3 d) R_3=CH_3 R_1=R_2=H,R_4=CH_3

e) R_1=Cl , R_2=R_3=H ,R_4 =CH_3 f) R_1=OCH_3 R_2=R_3=H ,R_4 =CH_3

g) R_3=OCH_3 R_1=R_2=H, R_4 =CH_3 h) R_1=R_2=R_3=H , R_4 = C_6H_5

i) R_1=CH_3, R_2=R_3=H ,R_4 = C_6H_5 j) R_2=CH_3 , R_1=R_3=H,R_4 = C_6H_5

k) R_3=CH_3 R_1=R_2=H,R_4 = C_6H_5 l) R_1=Cl , R_2=R_3=H ,R_4 = C_6H_5

m) R_1=OCH_3 R_2=R_3=H, R_4 = C_6H_5, n)R_3=OCH_3 R_1=R_2=H, R_4 = C_6H_5

Scheme 1: Synthesis of substituted 3H-[1,2,3]triazolo-[2,3-*b*]quinoline 3(a-n)

2.1. *Invitro* antibacetrial and anti fungal studies

Triazoles are good antimicrobial agents. There are many literature reviews as proof for the animicrobial behaviour of triazolo compounds. In this context we have also tried to study the antibacterial and antifungal nature of a few of our synthesised compounds *viz,* 3a, 3b, 3f,3h, 3i, following the procedure for inoculum method *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomona aeruginosa* were used as organism for the anti bacterial study. *Candida albicans* and *Aspergillus niger* for antifungal studies.

The study was carried out in two different concentrations (50 μg, 100 μg). The zone of inhibition was measured and compared with the standard Ciprofloxacin(10 μg).

3. RESULTS AND DISCUSSION

3.1. Characterization of synthesized compounds

3.1.1. Synthesis of 2-hydroxy-4,6-dimethyl quinoline(1d)

Melting point: 244°C (Lit. MP: 245°C), Yield:3.3g (88.8%). IR(cm^{-1}) (γ_{max}) spectrum of the compound (1d) shows absorption at 1623cm^{-1} for C=N, 3280cm^{-1} for OH. ^{1}H-NMR($CDCl_3$) (δ ppm) spectrum of the compound (1d) showed sharp signal at δ11.6 (1H,OH), δ6.5 (bs,1H, NH-C=O↔C-OH), δ7-7.4 (m,4H,Ar-H). Two singlets for 3 protons at δ1.3 and δ1.7 for 2-CH_3 protons (C_4 and C_6). ^{13}C-NMR ($CDCl_3$) (δ ppm) spectrum of the compound(1d) showed signal at δ 18 and δ 26 for 2-CH_3 carbons and signals at δ 104, 110,118,122,123,136,138,142 and 180 for the carbons C_2-C_{10} of the compound. The 2-hydroxyquinoline (1d) was then converted to its chloro compound by reacting with $POCl_3$.

3.1.2. Synthesis of 2-chloro-4,6-dimethylquinoline (2d)

M.P: 130°C, Yield:1.7g (76.7%), IR(cm^{-1}) (γ_{max}) spectrum of the compound (2d) showed an absorption at 1611cm^{-1}(C=N) and disappearance of the peak at 3280 cm^{-1} for OH. The appearance of the peak at 1031cm^{-1} for chloro establishes the conversion of hydroxyl to chloro. ^{1}H-NMR ($CDCl_3$) (δppm) spectrum of the compound (2d) showed peaks at δ 1.3 and 2.7 for two CH_3 groups in the compound. The peak from δ 7.1 to 7.4 accounts for 4 aromatic protons (C_3, C_5, C_7, and C_8-H). ^{13}C-NMR($CDCl_3$)(δppm) spectrum of the compound (2d) shows the presence of 9 carbon atoms (C_2,C_3,C_4,C_5,C_6,C_7,C_8,C_9) at δ 100, 110, 118, 120, 122,138,140,142, 150 and for 2 CH_3 carbons at δ 20, 30. Hence the conversion of hydroxy to chloro has been confirmed and the compound formed is attested as 2-chloro-4,6-dimethyl quinoline (2d).

3.1.3. Synthesis of 4,6-dimethyl-3H-[1,2,3] triazolo-[2,3-b]quinoline (3d)

Melting point: 210°C, Yield: 0.5g (80.6%), IR(cm^{-1})(γ_{max}) spectrum of the compound (3d) showed absorption peaks at 1643cm^{-1} C=N and disappearance of peak at 1126 $cm^{-1}$for C-Cl infers the formation of triazoloquinoline. ^{1}H-NMR ($CDCl_3$) δppm) spectrum of the compound showed two singlets at δ 1.7(3H) and δ2.6 (3H) for two methyl groups. The aromatic peak ranges from δ 7 to 7.7 for 3 aromatic protons and a singlet at δ10.1 for NH. ^{13}C-NMR ($CDCl_3$) δppm) spectrum of the compound showed signals at 10 and 20 for two methyl carbons and peaks at δ118, 120, 122, 124, 126, 130, 138, 140, 142 for 9carbons (C_5-C_{13}). Further CHNS analysis of the compound (3d) confirms the molecular formula to be $C_{11}H_{10}N_4$.

All the above discussed spectral and analytical data confirm the compound (3d) to be 4,6-dimethyl-3*H*-[1,2,3]triazolo-[2,3-*b*]quinoline.

3.1.4. 4-methyl-3H-[1, 2,3]triazolo-[2,3-b]quinoline (3a)

Yield: 0.6g (72.2%) Melting point: 113°C, Mol. Formula $C_{10}H_8N_4$, Mol. Weight:184.19, IR(cm^{-1}) (γ_{max}): 2910cm^{-1}(NH),1614cm^{-1} (C=H). ^{1}H-NMR (DMSO) (δppm) δ1.3(s,3H,CH_3),δ6.9-7.5(m,4H-Ar-H), δ 9.00 (bs,1H-NH)

3.1.5. 4,8-dimethyl-3H-[1,2,3]triazolo-[2,3-b] quinoline (3b)

Yield: 0.7g(75.2%), Melting point:220°C, Mol. Formula: $C_{11}H_{10}N_4$, Mol. Weight:198.23. IR(cm^{-1})(γ_{max}): 2900cm^{-1} (NH), 1655cm^{-1}(C=H)

3.1.6. 4,7-dimethyl-3H-[1,2,3]triazolo-[2,3-b] quinoline(3c)

Yield:0.5g(69.4%), Melting point::242°C, Mol. Formula: $C_{11}H_{10}N_4$, Mol. Weight:198.23. IR(cm^{-1})(γ_{max}): 2913cm^{-1} (NH),1640cm^{-1}(C=H), ^{1}H-NMR(DMSO) (δppm)showed a peak atδ11.2 for NH,δ2.5 and δ3.5 for two CH_3 protons.

3.1.7. 8-chloro-4-methyl-3H-[1, 2, 3]triazolo-[2,3-b]quinoline(3e)

Yield: 0.8g (77.6%), Melting point:: 210°C, Mol. Formula: $C_{10}H_7N_4Cl$, Mol. Weight:218.79. IR(cm^{-1}) (γ_{max}) : 2923 cm^{-1}(NH),1643cm^{-1}(C=H)

3.1.8. 8-methoxy-4-methyl-3*H*-[1,2,3]triazolo-[2,3-*b*]quinoline(3f)

Yield: 0.79g (84.9%), Melting point: 216°C, Mol. Formula: $C_{11}H_{10}N_4O$, Mol. Weight:214.22. IR (cm^{-1}): 2972cm^{-1} (NH), 2879cm^{-1} (NH), 1713cm^{-1} (C=O), 1606cm^{-1}(C=N)

3.1.9. 6-methoxy-4-methyl-3*H*-[1,2,3]triazolo-[2,3-*b*]quinolone (3g).

Yield: 0.67g (81.7%), Melting point:230°C, Mol. Formula: $C_{11}H_{10}N_4O$, Mol. Weight: 214.22. IR (cm^{-1}) (γ_{max}) 2978cm^{-1}(NH),2885cm^{-1}(NH), 1715cm^{-1}(C=O), 1600cm^{-1}(C=N), ^{1}H-NMR (DMSO) (δppm) δ3.4 (3H-OCH_3), δ2.5(3H-CH_3), δ11(NH)

3.1.10. 4-phenyl-3*H*-[1,2,3]triazolo-[2,3-*b*]quinoline (3h)

Yield: 0.79g (81.4%), Melting point:218°C , Mol. Formula: $C_{15}H_{10}N_4$, Mol. Weight: :246.27. IR (cm^{-1}) (γ_{max}): 2918cm^{-1}(NH), 1617cm^{-1}(C=H)

3.1.11. 8-methyl-4-phenyl-3*H*-[1,2,3]triazolo-[2,3-*b*]quinoline 3(i)

Yield: 0.59g (75.6%), Melting point: 235°C, Mol. Formula: $C_{16}H_{12}N_4$: Mol. Weight: 260.3. IR(cm^{-1}) (γ_{max}) 1643cm^{-1} (C=N), 2924cm^{-1}(NH) , ^{1}H-NMR (DMSO) (δppm) δ10.3 (feeble signal, IH-NH), δ9.2(NH)(bs), δ 6.8-8.3(m,9H),δ1.3(CH_3)

3.1.12. 7-methyl-4-phenyl-3*H*-[1,2,3]triazolo-[2,3-*b*]quinoline 3(j)

Yield: 0.98g (83.7%), Melting point: 233°C, Mol. Formula, $C_{16}H_{12}N_4$, Mol. Weight:260.3. IR(cm^{-1}) (γ_{max}): 1646cm^{-1} (C=N), 2920cm^{-1}(NH)

3.1.13. Synthesis of 6-methyl-4-phenyl-3*H*-[1, 2,3] triazolo-[2,3-*b*]quinoline 3(k)

Yield: 0.79g (89.7%), Melting point: 230°C. Mol. formula of the compound to be $C_{16}H_{12}N_4$. IR(cm^{-1}) (γ_{max})2 920cm^{-1} for NH and 1585$cm^{-1}$for C=N. ^{1}H-NMR ($CDCl_3$)(δppm) δ1.2 for three protons of CH_3, δ 6.9-8 for 9 aromatic protons and δ11 for one NH proton.^{13}C-NMR(DMSO)(δppm) δ 14 for CH_3 carbon, δ101,102,126-143 for15 carbons. Mass spectrum (m/z)showed M^+ peak at 261.29.

3.1.14. 8-chloro-4-phenyl-3*H*-[1,2,3]triazolo-[2,3-*b*]quinoline 3(l).

Yield: 0.92g (78.6%), Melting point: 218°C, Mol. Formula,$C_{15}H_9N_4Cl$: Mol. Weight:280.76. IR(cm^{-1}) (γ_{max}): 2927cm^{-1}(NH), 1649cm^{-1}(C=H).

3.1.15. 8-methoxy-4-phenyl-3*H*-[1,2,3]triazolo-[2,3-*b*]quinoline 3(m).

Yield: 0.67g (75.2%), Melting point: 220°C, Mol. Formula: $C_{16}H_{12}N_4O$, Mol. Weight:276.29. IR(cm^{-1}) (γ_{max}): 2981cm^{-1}(NH), 2874cm^{-1}(NH), 1721cm^{-1}(C=O), 1607cm^{-1}(C=N)

3.1.16. 6-methoxy-4-phenyl-3*H*-[1,2,3] triazolo-[2,3-*b*] quinoline 3(n)

Yield: 0.42g (60.8%), Melting point: 240°C, Mol. Formula: $C_{16}H_{12}N_4O$, Mol. Weight:276.29. IR(cm^{-1}) (γ_{max}): 2984cm^{-1}(NH), 2869cm^{-1}(NH), 1711cm^{-1}(C=O), 1612cm^{-1}(C=N)

3.2. Antimicrobial studies

Antimicrobial studies of the selected compounds and their activities are tabulated in Table 1. The zone of inhibition was measured.

From Table 1 it is evidenced that at 50 μg/mL, compound 3h and 3f are highly active against *Bacillus subtilis* whereas at 100μg concentration samples 3a and 3f show more antibacterial property against *Pseudomonas aeruginosa* and *Bacillus subtilis* respectively. All other compounds showed moderate antibacterial activity against these bacteria which is explained in Fig 1.

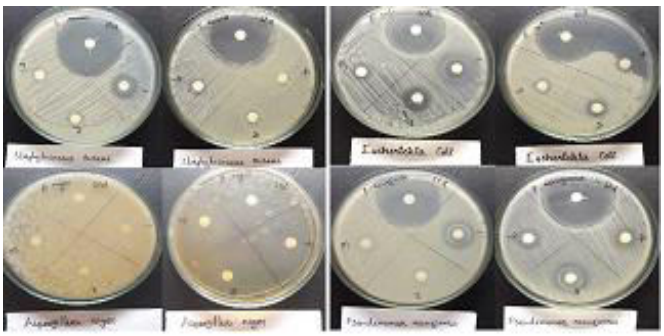


Fig.1: Antibacterialial activity of Triazolo compounds

From Table 2, it is concluded that the compound 3h and 3i are highly active against *Candida albicans* at 100 µg concentration followed by samples 3a and 3f at the same concentration. At 50µg, sample 3b is active against *Aspergillus niger*. On an average rate, all the samples are active against *Candida albicans* than against *Aspergillus niger*. Is also evidenced in Fig.2

Table 1: Antibacterial behavior of triazolo compounds

Organisms	STD Ciprofloxacin 10µg	Zone of Inhibition(mm) Triazolo compounds in µg									
		3a		3h		3b		3i		3f	
		50	100	50	100	50	100	50	100	50	100
Staphylococcus aureus	30	16	18	9	10	8	09	8	09	8	10
Bacillus subtilis	26	17	18	20	21	8	10	14	16	20	22
Escherichia coli	29	15	19	18	20	10	12	10	12	10	13
Pseudomona aeruginosa	32	18	22	9	10	7	09	10	13	18	21

Table 2: Antifungal behavior of Triazolo compounds

Organisms	Standard Fluccanazole (10µg/disc)	Zone of Inhibition(mm) Samples (100µg/disc)									
		3a		3h		3b		3i		3f	
		50	100	50	100	50	100	50	100	50	100
Candida albicans	12	10	11	10	12	09	10	10	12	10	11
Aspergillus niger	09	08	08	09	10	10	11	08	09	10	11

Fig. 2: Antifungal activity of Triazolo compounds

4. CONCLUSION

Triazoloquinoline *viz* 4-methyl-3*H*-[1,2,3] triazolo [2,3-*b*] quinoline achieved by reacting 2-chloro-4-methyl-quinoline and sodium azide. 2-chloro-4-methylquinoline was obtained by treating 2-hydroxy-4-methylquinoline and $POCl_3$. Similarly,4-phenyl-3*H*-[1,2,3] triazolo-[2,3-*b*] quinoline and their derivatives also were synthesized by following the same procedure. Antimicrobial studies show the synthesized compounds posses good antifungal and antibacterial activity.

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