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Research Article

DESIGN AND SYNTHESIS OF 1, 2, 3-TRIAZOLE QUINOLINE ANALOGUES *VIA* CLICK CHEMISTRY APPROACH AND THEIR ANTIMICROBIAL, ANTIOXIDANT ACTIVITIES

SACHIN P. SHIRAME[1], SHRAVAN Y. JADHAV[1], RAGHUNATH B. BHOSALE*[1]

[1]Organic Chemistry Research Laboratory, School of Chemical Sciences, Solapur University, Solapur 413255, Maharashtra, India.
Email: bhosale62@yahoo.com, sachinshirame@gmail.com

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ABSTRACT

Synthesis of new 1, 2, 3-triazole quinoline derivatives 3a-k using 1, 3-dipolar cycloaddition (click chemistry) reaction of 8-azido-2, 6-dimethoxy-4-methyl-5-(3-trifluoromethyl) phenoxy quinoline with substituted alkynes (3a-k) in the presence of Cu(I) catalyst has been achieved in very high yields. The newly synthesized compounds were characterized by IR, NMR and Mass spectroscopy and evaluated for their antioxidant (H_2O_2 and OH radical scavenger) and antimicrobial activity. Among the synthesized compounds, the compounds 3h and 3k was found to be an excellent H_2O_2 radical scavenger as compared to standard ascorbic acid whereas 3f and 3h was found to be good hydroxyl radical scavenger as compared to standard ascorbic acid. Compounds 3a, 3d, 3e, 3f and 3h have shown good antifungal activity as compared to standard drugs griseofluvin and compounds 3b, 3c, 3f and 3h have shown to be moderate antibacterial activity as compared to standard drugs Streptomycin.

Keywords: Click chemistry, Quinoline, Antibacterial, Antifungal and Antioxidant activity

INTRODUCTION

Click chemistry represents an ideal set of near perfect reactions (Nordell, P. *et, al.;* 2007 [1]). In recent years, click chemistry has emerged as a fast and powerful approach to the synthesis of novel compounds with desired properties. Among the various click reactions capable of producing wide range of functional organic molecules, the copper catalyzed [3+2] azide and alkyne cycloaddition (CuAAC) resulting in the formation of 1,2,3-triazoles has drawn considerable attention as an archetypical example of click chemistry (Barraja, p. *et al.*; 2006 [2]). [CuAAC] is particularly useful for the synthesis of a variety of molecules ranging from enzyme inhibitors to molecular materials [3].

1, 2, 3-Triazoles are important class of target molecules due to their interesting biological properties such as anti-allergic[4] anti-bacterial [5] and anti-HIV activity[6] some of these classes of drug molecules are now available in the market or in the final stage of clinical trials [7] additionally, due to the resemblance in physiochemical properties such as planarity, dipole moment, Ca distance and H-bond acceptor properties (of the lone pairs in nitrogen atoms), 1,2,3-triazoles are considered as peptide bond isosteres (Caturla, *et, al*.; 2003 [8]). In addition to this, 1,2,3-triazole ring is highly chemically stable under hydrolytic as well as reductive and oxidative conditions. Consequently, amide-to-triazole substitutions are now common in drug-like molecules whose amide bonds are known to be crucial for biological activity [9]. A recent trend in this field is the synthesis.

Quinolines have been the interest of research for many years as a large number of natural products contain these heterocyclic and they are found in numerous commercial products including pharmaceuticals, fragrances and dyes (Levy. S. et, al.;1994 [10]). Quinoline alkaloids such as quinine, chloroquine, mefloquine and amodiaquine are used as efficient drugs for the treatment of malaria (Wenekebach, *et,al.*;1923 [11]). The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmaceutical properties. Quinolines possess interesting physiological properties such as phthalide isoquinoline alkaloids play interesting roles such as noscapine, a non-narcotic cough cure and (þ)-biculine, an effective antagonist of an inhibitory neurotransmitter g-aminobutyric acid (GABA) (Bilker, O. *et, al;* 1998] [12]). Quinoline derivatives, protoberbines and 8-oxoberbines are known to possess biological properties such as antileukemic, Antitumor and anticancer activities (Chen, Y.*et al.*; 2000 [13]). The potent antitumor agents dynamicin A and Virantmycin are important natural products containing the quinoline core [14]. Compounds containing quinoline are most widely used as antimalarials [15] antibacterial [16] antifungal [17] and anticancer agents[18], antioxidant[19] additionally, quinoline derivatives find use in the synthesis of fungicides, virucides, biocides, alkaloids, rubber chemicals and flavoring agents[20].

Methodology

Compounds synthesis

The azide compounds (6a) (1.0 equiv) and substituted alkynes (a-k) (1.1 equiv) were dissolved in THF/H2O (9:1). To this solution $CuSO_4.5H_2O$ (0.05 equiv) and sodium ascorbate (0.40 equiv) were added. The reaction mixture was stirred for 11-12 h at room temperature. After completion of reaction, reaction mixture was poured on crushed ice. The solid obtained was extracted with EtOAc (2*50 ml). The organic extract was washed with water and brine. The solvent was removed under reduced pressure to afford crude product (7a-k), which was purified by column chromatography on silica gel by MeOH:CH_2Cl_2(2:8) as an eluent to obtain pure compounds(7a-k).

Antimicrobial activity

All these compounds were also evaluated for their antimicrobial activity. The compounds were dissolved in dimethyl sulfoxide (DMSO) with required concentrations for bioassay. Antimicrobial activity was evaluated by screening of the compounds by standard method i.e. agar cup plate [22] method against a panel of human pathogenic microorganisms: Gram positive, *B. subtilis* NCIM 2250, Gram negative, *E. coli* ATCC 25922 were used for the antibacterial assay, while for the antifungal assay, *C. albicans* MTCC 277 and *A. niger* NCIM 545 were used for antifungal assay. NA (Nutrient agar) was used as the culture media for antibacterial activity and PDA (Potato Dextrose agar) and YPD (yeast peptone dextrose) agar were used as the culture media for antifungal activity. The commercial antibiotics such as streptomycin and griseofluvin in DMSO served as reference standards to compare inhibition of growth. The plate containing bacterial organism were incubated at 37^{0}C and plates containing fungal organism were incubated at 30^{0}C for 48 h. The zone of inhibition was calculated by measuring the diameter of zone

of inhibition for bacterial and fungal growth around the well or cup. Averages of three independent determinations were recorded. The minimum inhibitory concentration (MIC) of the samples by cup plate method on NA for bacteria and YPDA for *C. albicans* and PDA for *A. niger* plates containing the following concentrations (mg/mL): 0 (control), 1, 2, 3, 5, 10, 15, 20, 30 and 40. Agars were molted and poured in Petri dishes according to Clinical and Laboratory Standards Institute (CLSI, M2-A5 January 2007). The plates were incubated at 37^{0}C, examined after 24 h and incubated further for 72 h, where necessary. The MIC was defined as the lowest and their antimicrobial activities have been evaluated. was tested through agar diffusin method against human pathogenic fungal at *Aspergillus niger*. The antifungal result revealed that the compounds 3a ,3d ,3f , 3e and 3h shown good antifungal activity as compared with standard drug *Griseofluvin*, while remaining compounds showed moderate antifungal activity and antibacterial results revealed that the compounds 7b, 7c, 7f and 7h have shown significant activity as compared with standard drug *streptomycin*, while as remaining compounds showed moderate antifungal activity.

RESULT AND DISCUSSION

Chemistry

Compound 6a: Yield :93 % , mp:170-172^{0}C: IR , (KBr) cm^{-1}: 3008 , 2107, 1635, 1579, 1295, 1216, 1161, 1022 , 817 ; ^{1}HNMR (300 MHz,$CDCl_3$): δ 7.310 (s, 1H) , 7.359 (d, 1H) , 7.488 (t, 1H) , 6.910 (s, 1H) , 7.113 (s, 1H), 3.950 (s, 3H) , 3.728(s, 3H) , 2.519 (s, 3H); MS: m/e 404 (M+1)

Compound 7a: Yield: 90%, mp: 185-187^{0}C: IR (KBr) cm^{-1}: 3010 , 1609, 1448, 1244, 1123, 1088, 1062 ; ^{1}H NMR(300 MHz,$CDCl_3$): δ 6.788(s, 1H) , 7.319 (d, 1H) , 7.493(t, 1H) , 6.990 (d , 1H) , 7.113 (s , 1H) , 8.121(s, 1H, triazole), 3.979(s,3H) , 3.877(s,3H) , 2.681(s,3H) , 7.965(d,2H) , 7.401(d,1H) , 7.501(t,2H) ; MS: m/e 506 (M+1) .

Compound 7b: Yield: 92%, mp: 192-194^{0}C, : IR(kBr cm^{-1}) ; 2960, 1605, 1520, 1281,1281,1091 cm^{-1} ^{1}HNMR (300 MHz,CDCl3): δ 6.749(s, 1H), 7.319 (d, 1H), 7.493(t, 1H), 6.990 (d, 1H), 8.027(s, 1H),8.741 (s, 1H, triazole), 3.979 (s,3H), 3.877 (s,3H), 2.641 (s,3H), 4.971 (s,2H).

Compound7c: Yield:89%, mp:190-192^{o}C: IR (KBr) cm^{-1}: 2979, 1711, 1505, 1439, 1204, 1001: ^{1}HNMR (300 MHz,CDCl3): δ 6.796(s, 1H), 7.296 (d, 1H), 7.402 (t, 1H), 6.959 (d, 1H), 7.108 (s,1H), 8.037 (s, 1H), 8.761(s, 1H) , 3.497 (s,1H) , 4.973 (s, 2H) , 2.667(s,3H), 3.857 (s,3H): MS: m/e 460 (M+1).

Compound 7d: Yield:87%, mp:184-186^{0}C: IR(KBr) cm^{-1}: 2979, 1607, 1449, 1221, 1031; ^{1}HNMR (300 MHz,CDCl3): δ 7.261(s, 1H), 7.420 (d, 1H), 7.401(t, 1H), 7.382 (d, 1H),7.110(s,1H), 8.037(s, 1H),8.761(s, 1H, triazole), 4.975 (s,1H), 7.315 (s,1H), 6.770 (s,1H), 6.960(s,2H), 6.979 (d,2H), 3.934 (s,3H), 2.668 (s,3H), 3.880 (s,3H).

Compound 3e: Yield:86%,mp:186-188^{0}C: IR(KBr) cm^{-1}: 2980, 1604, 1449, 1255, 1034; ^{1}HNMR (300 MHz,CDCl3): δ 7.260 (s, 1H), 7.411 (d, 1H), 7.392 (t, 1H), 7.373 (d, 1H), 7.090 (s,1H), 8.080 (s , 1H), 8.875 (s, 1H, triazole), 5.629 (s,2H), 6.967 (d,2H), 7.050 (d,2H), 7.289 (t,1H), 3.866 (s,3H), 2.642 (s,3H), 3.561 (s,3H).

Compound 7f: Yield:87%, mp:1198-200^{0}C: IR,(KBr) cm^{-1}: 2987, 1711,1603, 1449, 1242, 1034; ^{1}HNMR (300 MHz,CDCl3): δ 7.310 (s, 1H), 7.359 (d, 1H), 7.488 (t, 1H), 7.026 (d, 1H), 6.910 (s,1H), 7.113 (s, 1H), 3.950 (s, 1H), 2.519 (s,2H), 3.725 (s,3H), 8.158 (s, 1H, triazole), 3.953 (s,2H), 6.997(d,2H), 6.917(d,2H), 7.245 (d,1H), 7.515(t,2H), 7.782 (d,1H), 2.560(t,2H), 2.501(quintet, 2H), 1.684 (sextet, 2H), 1.229 (t,3H).

Compound 7g: Yield:90%, mp: 183-185^{0}C: IR, KBr) cm^{-1}: 3401, 2989, 1604, 1505, 1439, 1204, 1001; ^{1}HNMR (300 MHz,CDCl3): δ 6.796 (s, 1H), 7.296 (d, 1H), 7.402(t, 1H), 6.959 (d, 1H), 7.108 (s,1H), 8.037 (s, 1H), 8.761(s, 1H, triazole), 8.137 (s,2H), 4.973 (s,2H), 2.667 (s,3H), 3.857 (s,3H).

Compound 7j: Yield: 80%, mp:187-189^{0}C: IR (KBr) cm^{-1}: 2987, 1603, 1449, 1242, 1034cm-1:^{1}HNMR (300 MHz,CDCl3): δ 7.262(s, 1H) , 7.411 (d, 1H) , 7.392(t, 1H) , 7.373 (d, 1H) , 6.711(s,1H) , 7.020

(s, 1H), 7.262 (s, 1H, triazole), 4.057 (s,2H), 6.967 (d,2H), 7.050 (d,2H), 4.016 (s,3H), 2.628 (s,3H), 3.761(s, 3H).

DISCUSSION

Chemistry

The completion of the reaction was monitored by TLC. The synthesized compounds were characterized by IR, ^{1}H NMR, and Mass spectroscopy. IR spectra of azide showed characteristic band at near region 2107 cm^{-1} due to (–N_3) stretching vibrations. IR spectrum in azido and alkyne peak are disappeared to confirmed 1, 2, 3-triazole formation, of compounds (7a-7k). These assignments are in agreement with those observed by several research groups. In the 1H NMR spectra of compounds 7a and 7g the 1, 2, 3-triazole proton appeared at ð 8.037-8.121 respectively as singlet. These values confirmed the formation of desired 1, 2, 3-triazole quionoline derivatives .These newly synthesized compounds are also confirmed by mass spectral analysis.

Biological evaluation

All these newly synthesized 1, 2, 3-triazole quinoline derivatives were evaluated for their antioxidant activity, the superoxide scavenging assay was performed by the reported method and OH radicals scavenging activity was demonstrated with Fenton reaction method are shown in Table 1. The antioxidant (H_2O_2 radical scavenger) result reveals that compounds 7h and 7k showed excellent activity whereas the compounds 7a, 7b, 7c, 7d and 7f showed significant activity after comparing with ascorbic acid.

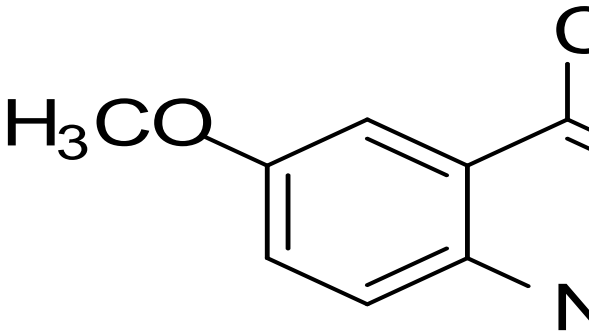
The new series of quinoline derivatives were synthesized by using 1, 3 dipolar cycloaddition reaction and identified as antioxidant and antimicrobial agents. The reaction was clean and the products were obtained in excellent yields without formation of any detectable side products. Among the synthesized compounds, compounds 7a, 7c, 7e, 7h and 7k showed significant activities in both antibacterial and antifungal screening when compared with standard drug *streptomycin* and *griseofluvin* respectively.

Table 1: Antioxidant and antimicrobial activity of quinoline derivatives (7a-k)

	Antioxidant activity		Antimicrobial activity			
Entry	**H_2O_2 (%)**	**OH (%)**	**A. N. ZI [a](MIC)[b]**	**C.A. ZI(MIC)**	**E.C. ZI(MIC)**	**B.S. ZI(MIC)**
7a	37.28	24.65	**15±0.1 (10)**	**16.4±0 (15)**	14.8±0.1 (20)	14.8±0.1 (20)
7b	13.15	39.06	14.1±0.1(15)	13.7±0.1 (15)	**15.4±0.2 (20)**	12.8±0.1 (15)
7c	17.10	28.83	13.5±0 (15)	14.9±0 (15)	14.8±0.2 (20)	**16.3±0.1 (20)**
7d	11.40	28.83	**14.1±0.1 (15)**	14.5±0.1=(15)	14.6±0.1 (15)	14.6±0.1 (15)
7e	17.54	39.53	14.2±0 (20)	**16.5±0.1 (15)**	13.6±0.1 (15)	13.6±0.1 (20)
7f	39.03	**46.04**	14.2±0 (20)	14.3±0.1 (15)	**16.3±0.1 (15)**	14.7±0 (15)
7g	12.07	45.58	13.9±0.1(30)	16±0.1(15)	14.8±0.2 (15)	12..8±0.2 (15)
7h	**86.40**	**53.34**	**17.5±0.1 (20)**	14.8±0.1 (15)	**15.8±0.1 (15)**	**15.3±0.2 (15)**
7i	30.26	33.95	n.t.	n.t.	n.t.	n.t.
7k	**69.29**	37.20	n.t.	n.t.	n.t.	n.t.
Ascorbic Acid	54.29	49.18	n.t.	n.t.	n.t.	n.t.
Streptomycin	n.t.	n.t.	n.t.	n.t.	16.6±0.2(5)	16.2±0.2(5)
Griseofluvin	n.t.	n.t.	17.0±0.3 (5)	16.8±0.2 (5)	n.t.	n.t.

Bold values indicate better results. a. Zone of inhibition in mm. b. Minimum inhibitory concentration in mg/mL. c. n. t. not tested.

Scheme 1: Synthesis of 1, 2, 3-triazol-1-yl quinoline derivatives (7a-k)



Scheme 1. Reagents and conditions :(i) SO_2Cl_2 , acetic acid 60-65^{0}C (ii) N-methyl pyrrolidine, 65-70^{0}C, acetic acid , quenching , KNO_3 , H_2SO_4 (iii)DMF, K_2CO_3 , 105-110^{0}C.(iv) $SNCl_2$, HCl, temp-0-5^{0}C. (v) H_2SO_4 , $NaNO_2$, water, NaN_3, 0^{o}C – r.t. - 3h , 90% (vi) $CuSO_4.5H_2O$, Sodium ascorbate , R (substituted alkynes (3a-k), THF.H_2O , r.t.-10-12h.

CONCLUSIONS

Hence, it can be concluded that, the importance of such work lies in the possibility that the new compounds might be more efficacious drugs against bacteria, fungi, oxidant activity which could be helpful in designing more potent antibacterial, antifungal and antioxidant agents for therapeutic use. Further studies in relation to cytotoxicity and ADME are warranted for the better understanding.

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