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Synthesis of 2H-benzo[b][1,4]oxazin-3(4H)-one linked 1,2,3-triazole hybrids and their in-vitro anti-bacterial screening.

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ABSTRACT- A series of 1,4-benzoxaine linked 1,2,3-triazoles(4a-4k) are synthesized using copper(I) catalyzed 3+2 cycloaddition reaction in good yields. All the compounds were screened for their *in vitro* anti-bacterial activity against both gram positive and gram negative bacteria.

KEY WORDS - 1,4- Benzoxazine, 1,2,3-triazole and anti-bacterial activity.

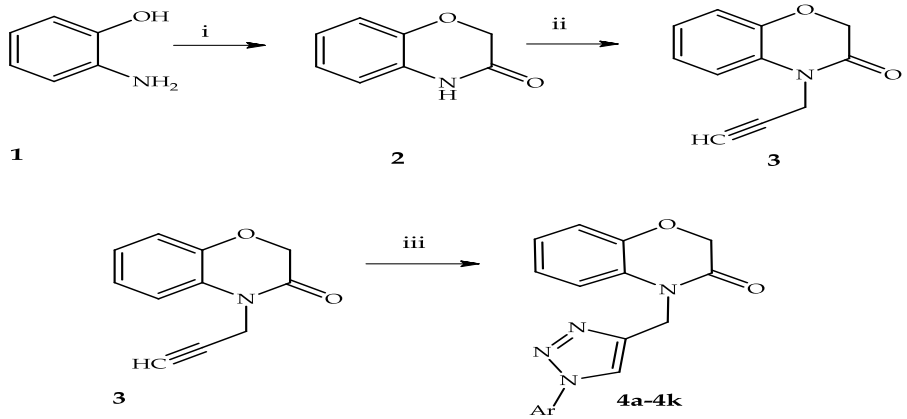
INTRODUCTION

The 1,4-oxazinones have gained more attention due to their biological importance. For example, a large number of 1,4-oxazinones have been incorporated into a wide variety of therapeutically interesting drug candidates posses- sing antibacterial [1], anticancer [2], anticonvulsant [3] and antithromobotic activities [4]. They are also known as 5-HT6 receptor antagonists [5], bladder-selective potassium channel openers [6]. Some substituted [1,4]-oxazines are also related to blocking the TXA2 receptor and activatethe PGI2 receptor [7]. At the same time the chemistry of 1,2,3- triazole derivatives have received attention not only in organic chemistry but also in medicinal chemistry due to their easy synthesis by click chemistry bearing attractive features, as well as numerous biological activities such as antibacterial [8], H1-antihistamine [9], anti-HIV [10] activities.

By taking the biological importance of both pharmacophores we designed the scheme to combine both to enhance the biological applications.

RESULTS AND DISCUSSIONS

The cyclization of 2-aminophenol (**1**) with 2-chloroacetyl chloride in the presence of $NaHCO_3$ in dry THF afforded the corresponding 2H-benzo[b][1,4]oxazin-3(4H)-one (**2**) in good yield. The target intermediate 4-(prop-2-yn-1-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**3**) was prepared by treating 2H-benzo[b][1,4]oxazin-3(4H)-one with 3-bromoprop-1-yne in the presence of Cs_2CO_3 in acetone. The key step of the synthesis, *i.e.,* 1,3-dipolar cyclo addition of terminal alkyne **3** with differentaryl azides using a catalytic amount of copper iodide at roomtemperature, afforded the corresponding 1,4-di-substituted1,2,3-triazoles (**4a–4k**) in good to excellent (scheme-1). The structures of all the synthesized compounds confirmed by spectral data analysis.



Ar: **4a** = 3,5-dichloro phenyl (75%) **4b** = 3,5-dimethyl phenyl (72%) **4c** = 4-methoxy phenyl (80%) **4d** = 3-chloro phenyl (79%) **4e** = 4-butyl phenyl (80%) **4f** = 4-chloro-3,5-dimethoxy phenyl (68%) **4g** = 4-fluoro phenyl (74%) **4h** = 3-(trifluoromethyl)phenyl (75%) **4i** = 4-bromo phenyl (68%) **4j** = napthyl (68%) **4k**= 3-nitro phenyl (80%)

Scheme 1: Reagents and conditions - i)Chloroacetyl chloride, $NaHCO_3$, TEBA, THF, reflux, 12 h; ii) Propargyl bromide, Cs_2CO_3, Acetone, RT, 1 h; iii) Aryl azide, CuI, THF, RT, 8-10 h.

BIOLOGICAL ACTIVITY

The compounds 4a-4k were evaluated for bactericidal activity against freshly prepared standard cultures of Gram-positive *Bacillus Sphaericus* and *Staphylococcus Epidermidis* and Gram-negative *KlebsiellaPneumoniae* and *Escherichia Coli* species using the agar well diffusion method. The results are given in the table below.

Table: The *in vitro* antibacterial activity of the compounds 4a-4k. zone of inhibition (diameter in millimeter)

Compound	*Bacillus sphaericus*	*Staphylococcus epidermidis*	*Klebsiella pneumoniae*	*Escherichia coli*
4a	*14*	*12*	*14*	*10*
4b	*15*	*14*	*16*	*11*
4c	*11*	*10*	*12*	*14*
4d	*08*	*10*	*16*	*07*
4e	*12*	*12*	*08*	*16*
4f	*13*	*11*	*10*	*12*
4g	*12*	*13*	*11*	*13*
4h	*10*	*14*	*14*	*11*
4i	*09*	*08*	*15*	*12*
4j	*18*	*06*	*10*	*16*
4k				
Penicillin-G	*23*	*19*	*-*	*-*
Streptomycin	*-*	*-*	*25*	*25*
DMSO	*0*	*0*	*0*	*0*

CONLUSION

The compounds (4a-4k) synthesized by Cu(I) catalyzed 1,3-dipolar cycloaddition. Among all, the compounds 4a, 4b and 4j were exhibited promising *in vitro* anti-bacterial activity over a series of *Gram-positive Bacillus Sphaericus and Staphylococcus Epidermidis and Gram-negative KlebsiellaPneumoniae and Escherichia Coli species when* compared with the commercial standard drugs Penicillin-G and Streptomycin.

SPECTRAL DATA

4-((1-(3,5-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**4a**)-^{1}H NMR (500MHz, CDCl3): δ 8.063 (s, 1H, triazole), 7.660 (s, 2H, Ar), 7.354–7.523 (m, 3H, Ar), 7.104–7.223 (m, 2H, Ar), 5.214 (s, 2H, N–CH2), 4.626 (s, 2H, O–CH2): ^{13}C NMR (125 MHz, dimethyl sulfoxide (DMSO)): δ 163.6, 145.7, 143.6, 136.8, 131.2, 127.9, 125.2, 123.9, 122.1, 119.3, 117.3, 116.6, 114.8, 67.0, 36.2.

4-((1-(3,5-dimethylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (**4b**)-^{1}H NMR (500 MHz, CDCl3): δ 8.529 (brs, 1H, triazole),7.653 (brs, 1H), 7.469 (brs, 3H, Ar), 7.384 (s, 1H, Ar), 7.307 (brs, 1H, Ar), 7.182 (brs, 1H, Ar), 5.357 (brs, 2H, N–CH2), 4.767 (s, 2H, O–CH2), 2.507 (s, 6H, Ar–CH3), ^{13}C NMR (125MHz, DMSO): δ 163.7, 145.7, 143.1, 139.3, 136.3, 129.9, 127.9, 125.2, 121.5, 119.2, 117.5, 117.3, 114.8, 67.0, 36.3, 20.7.

4-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (4c)-^{1}H NMR (500 MHz, CDCl3): δ 7.965 (s, 1H, triazole), 7.599 (d, J=8.8 Hz, 2H, Ar), 7.519 (d, J=8.6Hz, 1H, Ar), 7.112–7.221 (m, 3H, Ar), 7.002 (d, J=8.8Hz, 2H, Ar), 5.220 (s, 2H, N–CH2), 4.631 (s, 2H, O–CH2), 3.859 (s, 3H, O–CH3).^{13}C NMR (125MHz, DMSO): δ 163.7, 159.2, 145.7, 143.0, 129.8, 127.9, 125.2, 121.6, 119.2, 117.4, 114.7, 67.0, 55.5, 36.2.

4-((1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (4d)-^{1}H NMR (500 MHz, CDCl3): δ 8.061 (s, 1H, triazole), 7.764 (brs, 1H, Ar), 7.621 (d, J=7.3Hz, 1H, Ar), 7.389–7.526 (m, 3H, Ar), 7.174 (m, 2H, Ar), 5.227 (s, 2H, N–CH2), 4.638 (s, 2H, O–CH2): ^{13}C NMR (125MHz, DMSO): δ 163.6, 145.7, 143.5, 137.4, 134.1, 131.5, 128.4, 127.8, 125.2, 121.9, 119.6, 119.2, 118.5, 117.3, 114.8, 67.0, 36.2.

4-((1-(4-butylphenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (4e)-^{1}H NMR (500MHz, CDCl3): δ 8.322 (s, 1H, triazole), 7.567–7.801 (m, 3H, Ar) 7.366–7.493 (m, 3H, Ar), 7.268–7.362 (m, 2H, Ar), 5.348 (s, 2H, N–CH2), 4.757 (s, 2H, O–CH2), 2.785 (t, J=7.7Hz, 2H, Ar–CH2–CH2–CH2–CH3), 1.653–1.808 (m, 2H, Ar–CH2CH2–CH2–CH3), 1.404–1.562 (m, 2H, Ar–CH2– CH2–CH2–CH3), 1.056 (t, J=7.3Hz, 3H, Ar–CH2– CH2–CH2–CH3): ^{13}C NMR (125MHz, DMSO): δ 163.7, 145.7,143.1,134.3,129.5,127.9,125.2,121.6,119.8,119.2, 117.4, 114.8, 67.0, 36.2, 34.1, 32.8, 21.6, 13.6.

4-((1-(4-chloro-3,5-dimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo [b][1,4] oxazin- 3(4H)-one (4f)-^{1}H NMR (500MHz, CDCl3): δ 8.225 (s, 1H, triazole), 7.542 (d, J=8.4Hz, 1H, Ar) 7.453 (brs, 1H, Ar), 7.062–7.248 (m, 4H, Ar), 5.241 (s, 2H, N–CH2), 4.630 (s, 2H, O–CH2), 3.904 (s, 3H, –OCH3), 3.848(s, 3H, –OCH3): ^{13}C NMR (125MHz, DMSO): δ 163.7, 148.5, 145.8, 145.3, 141.9, 127.9, 125.7, 125.2, 124.4, 122.3, 119.3, 117.5, 115.1, 114.8, 110.1, 67.0, 56.9, 56.7, 35.9 .

4-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (4g)1H NMR (500 MHz, CDCl3): δ 8.049 (s, 1H, triazole), 7.557–7.784 (m, 4H, Ar), 7.485 (d, J=8.6Hz, 1H, Ar), 7.110–7.242 (m, 3H, Ar), 5.220 (s, 2H, N–CH2), 4.638 (s, 2H, O–CH2): 13C NMR (125MHz, DMSO): δ 163.7, 148.4, 145.7, 143.7, 137.0, 131.4, 127.8, 125.9, 125.2, 123.1, 122.2, 119.3, 117.3, 114.8, 114.6, 67.0, 36.2.

4-((1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol- 4-yl)methyl)-2H-benzo[b][1,4] oxazin-3(4H)-one (4h)1H NMR (500 MHz, CDCl3): δ 8.125 (s, 1H, triazole), 7.999 (s, 1H, Ar), 7.943 (d, J=7.9Hz, 1H, Ar), 7.643–7.740 (m, 3H, Ar),7.484 (d, J=8.6Hz, 2H, Ar), 7.192 (dd, J=2.1, 6.5Hz, 1H, Ar), 7.143 (d, J=2.1Hz, 1H, Ar), 5.240 (s, 2H, N–CH2), 4.642 (s, 2H, O–CH2): 13C NMR (125MHz, DMSO): δ 163.6, 145.7, 143.6, 136.8, 131.2, 130.6, 130.3, 129.9, 127.9, 125.2, 124.8, 123.9, 122.1, 119.3, 117.3, 116.6, 114.8, 67.0, 36.2.

4-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (4i)1H NMR (500 MHz, CDCl3): δ 8.052 (s, 1H, triazole), 7.549–7.820 (m, 4H, Ar) 7.484 (d, J=8.6Hz, 1H, Ar), 7.091–7.251 (m, 3H, Ar), 5.213 (s, 2H, N–CH2), 4.652 (s, 2H, O–CH2): 13C NMR (125MHz, DMSO)δ163.7, 148.5, 145.8, 145.3, 141.9, 127.9, 125.7, 125.2, 124.4, 122.3, 119.3, 117.5, 115.1, 114.8, 110.1, 67.0, 56.9, 56.7, 36.3.

4-((1-(naphthalen-1-yl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (4j)1H NMR (500 MHz, CDCl3): δ 7.928–8.324 (m, 1H-triazole and 2H-Ar, 3H), 7.526–7.806 (m, 6H, Ar), 7.200–7.419 (m, 3H, Ar), 5.420 (s, 2H, N–CH2), 4.743 (s, 2H, O–CH2): 13C NMR (125MHz, DMSO): δ 163.7, 145.8, 142.3, 133.5, 133.0, 128.3, 128.0,127.9, 127.8, 127.0, 126.3, 123.8, 121.8, 119.3, 117.5, 114.8, 67.1, 36.2;

4-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (4k)1H NMR (500 MHz, CDCl3): δ 8.591 (s, 1H, triazole), 8.314 (d, J=7.7Hz, 1H, Ar), 8.086–8.258 (m, 3H, Ar), 7.751 (t, J=8.1Hz, 1H, Ar), 7.470 (d, J=8.4Hz, 1H, Ar), 7.089–7.235 (m, 2H, Ar), 5.253 (s, 2H, N–CH2), 4.651 (s, 2H, O–CH2): 13C NMR (125 MHz, DMSO): δ 163.7, 148.4, 145.7, 143.7, 137.0, 131.4, 127.8, 125.9, 125.2, 123.1, 122.2, 119.3, 117.3, 114.8, 114.6, 67.0, 36.2

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