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Regioselective synthesis and biological evaluation of novel bis(2-chloroquinolines)

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Abstract Reaction of substituted 2,4-dichloroquinolines with bisphenol A in the presence of K_2CO_3 leads to novel bis(2-chloroquinolines) with high regioselectivity. All the synthesized compounds were characterized by use of spectral data. Preliminary evaluation of in-vitro antibacterial activity against a variety of Gram-positive and Gram-negative organisms was also conducted.

Keywords Bis(2-chloroquinolines) · 2,4-Dichloroquinolines · Bisphenol A · Anti-bacterial activity

Introduction

Synthesis of the quinoline ring system is of major interest in the chemistry of fused five and six-membered heterocycles, because it has many applications in pharmaceuticals [1] and occurs widely in alkaloids, therapeutics, and synthetic analogues with interesting activity [2–4], and because quinoline compounds have antimalarial [5], antiasthmatic [6], and anti-inflammatory [7] activity and function as inhibitors of platelet-derived growth factor receptor tyrosine kinase (PDGF-RTK) [8]. Some quinoline derivatives, their salts, and esters are used in the prophylaxis or treatment of arthritis, cardiovascular diseases, diabetes, renal failure, and, particularly, eating disorders and obesity [9]. 2,4-Disubstituted quinolines with additional substituents at positions 5 and 8 have anthelmintic properties and are also found to be active against drug-resistant nematodes [10, 11]. Similarly bisphenol A (BPA) is widely used as a

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reagent for producing epoxy resins and other polymers [12]. Although it has been widely used for production of plastic products [13], it is regarded as an estrogenic endocrine-disrupting chemical and affects steroid hormone production in rat ovarian theca-interstitial and granulosa cells [14, 15]. Bisphenol A has structural resemblance to thyroid hormone (TH), and acts as a TH agonist or antagonist by affecting the release of thyrotropin (TSH) [16].

This prompted us to perform work in which one of the chlorine atoms in 2,4-dichloroquinolines is selectively replaced, under controlled temperature conditions, by the BPA moiety, which was chosen on the basis of our continuing interest in quinolines [17–19], particularly synthesis of novel substituted quinoline heterocycles [20], by exploiting the regioselectivity of 2,4-dichloroquinolines. Although regioselective nucleophilic substitution of 2,4-dichloroquinoline with 4-methoxybenzylalcohol in the presence of sodium hydride [21] is known, it is not cost effective because of use of catalyst 15-crown-5. Likewise, reaction of 2,4-dichloroquinoline with sodium methoxide gave 2,4-dimethoxyquinoline without any selectivity [22]. Powdered K_2CO_3 was therefore used as an effective catalyst to achieve regioselective synthesis of 2,4-dichloroquinolines under controlled temperature conditions.

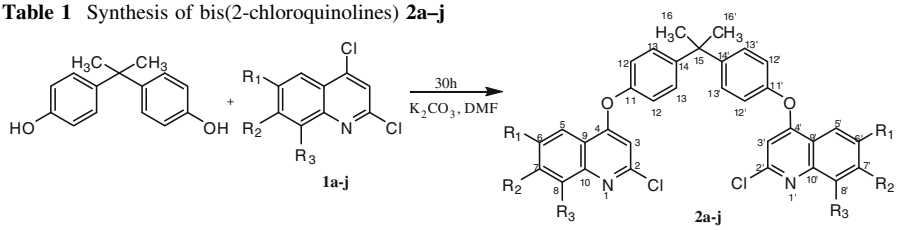
Results and discussion

2,4-Dichloroquinolines **1a–j** were synthesized, in accordance with our earlier report [23], by treating malonic acid and different substituted anilines with excess phosphorus oxychloride. The target molecules **2a–j** were synthesized in 66–81 % yield by reaction of BPA and 2,4-dichloroquinolines **1a–j** catalyzed by powdered K_2CO_3 in DMF (Table 1). All the synthesized compounds were characterized by use of spectral data.

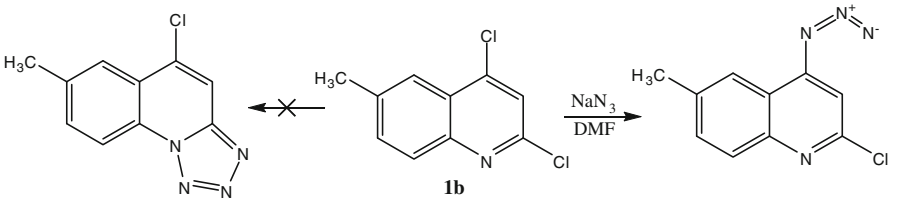
Substitution of quinoline at C4 is known to be favored in reactions with powdered K_2CO_3 as catalyst. It was also evident from the literature that use of an acid catalyst in absolute ethanol alone can bring about regioselectivity at C2, and that base-catalyzed reactions will be driven toward C4 [24]. This is also confirmed by similar reactions; for example, reaction of 4-chlorobenzenethiol with 2,4-dichloroquinoline at room temperature in the presence of triethylamine as mild base also leads to the 4-substituted rather than 2-substituted product [25]. To understand the regioselectivity better, the azidation reaction of 2,4-dichloro-6-methylquinoline (**1b**) was also investigated to check its behavior in nucleophilic substitution at both the α and γ positions (Scheme 1).

Reaction of 2,4-dichloro-6-methylquinoline (**1b**) with sodium azide in the molar ratio 1:1, in DMF, led regioselectively to 4-azido-2-chloro-6-methylquinoline [26], the structural conformation of which was determined by single-crystal X-ray diffraction; this also is indicative of the reactivity of C4 in 2,4-dichloroquinolines. This result is also confirmed by literature reports of kinetic studies which indicate that the γ-chloro atom of dichloroquinolines is approximately twice as reactive towards nucleophiles and predominantly an addition–elimination process occurred [27, 28] The LC–MS spectrum of the crude sample **2b** is also indicative of the formation of mono regio-isomeric product, and hence substitution at C4 was expected to occur

Table 1 Synthesis of bis(2-chloroquinolines) **2a–j**

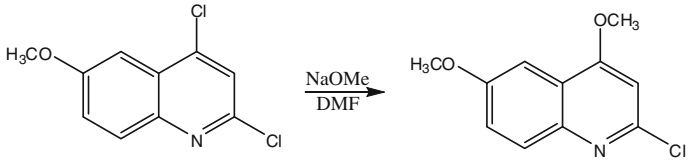


Compound	R_1	R_2	R_3	Yield (%)	M.p. (°C)
2a	–H	–H	–H	79	216
2b	$-CH_3$	–H	–H	81	222
2c	–H	$-CH_3$	–H	77	194
2d	–H	–H	$-CH_3$	79	202
2e	$-OCH_3$	–H	–H	82	212
2f	–H	–H	$-OCH_3$	76	278
2g	–Br	–H	–H	72	146
2h	–F	–Cl	–H	66	254
2i	$-CH_3$	–H	$-CH_3$	69	242
2j	4,4′-(4,4′-(propane-2,2-diyl)bis(4,1-phenylene) bis(oxy)bis(2-chlorobenzo[*h*] quinoline)			71	122



Scheme 1 Synthesis of 4-azido-2-chloro-6-methylquinoline

under the basic conditions used in this work. Better results were obtained with powdered K_2CO_3 than with the granular form, because the larger surface area enables maximum reactivity of 2,4-dichloroquinoline with BPA. A simple monomeric 2-chloro-4,6-dimethoxyquinoline (**2k**) was also synthesized by treating 2,4-dichloro-6-methoxyquinoline (**1e**) with sodium methoxide in the presence of K_2CO_3 in DMF (Scheme 2).



Scheme 2 Synthesis of 2-chloro-4,6-dimethoxyquinoline (**2k**)

Results (Table 2) from evaluation of in-vitro antibacterial activity against a variety of Gram-positive and Gram-negative organisms revealed that most of the derivatives had mild to good activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, and *Pseudomonas aeruginosa*. Compounds **2b**, **2d**, **2j**, and **2k** had high MIC values (MIC = 750–1,000 μg/mL) and the other compounds had moderate MIC values (MIC = 500–750 μg/mL) except for **2h**, for which the MIC was low (MIC = 250–500 μg/mL).

Experimental

Materials were purchased from Sigma–Aldrich and Merck and were used without additional purification. All reactions were monitored by thin-layer chromatography (TLC). Melting points were recorded on an Elchem digital melting-point apparatus in open capillaries and are uncorrected. Infrared (IR) spectra were recorded at room temperature from 4,000 cm^{-1} as KBr pellets at a resolution of 4 cm^{-1}, by use of an Avatar 330 equipped with DTGS detector. Most of the vibrational bands of the IR spectrum were identified by comparison with those available in literature. ^{1}H NMR spectroscopy of ~0.03 M solutions in $CDCl_3$, with TMS as internal reference, was performed with a Bruker Avance-200 MHz instrument at room temperature, using X-WIN NMR version 1.3 cn drx software. The accuracy of the ^{1}H shifts is believed to be 0.02 ppm. The coupling constants *J* are in Hertz. Mass spectra were obtained by use of ESI mass spectrometry.

General procedure for synthesis of bis(2-chloroquinolines) **2a–j**

A mixture of substituted 2,4-dichloroquinoline (**1a–j**) (1 mol), powdered K_2CO_3 (1 mol), and BPA (0.5 mol) in DMF was stirred at 80 °C for 30 h. Progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into a beaker containing ice-cold water and stirred well. The solid which separated was filtered to dryness and purified by column chromatography on silica gel (60–120 mesh) with pet. ether–ethyl acetate 8:2 as eluent. This afforded the white solid products **2a–j** in the pure form. The products were characterized by IR, NMR, and mass spectrometry. The spectral data for compounds **2a–j** are given below.

4,4′-(4,4′-(propane-2,2-diyl)bis(4,1-phenylene)bis(oxy)bis(2-chloroquinoline) (**2a**)

IR (KBr), *v*, cm^{-1}: 3057, 2966, 1617, 1579, 1497, 1416, 1363, 1313, 1233, 1213, 1174, 1143, 1070, 1014, 920, 855, 763. ^{1}H NMR (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.81 (s, 6H, H-16, 16′); 6.56 (s, 2H, H-3, 3′); 7.16 (d, $J = 10.0$, 4H, H-13, 13′); 7.42 (d, $J = 10.0$, 4H, H-12, 12′); 7.59 (t, $J = 8.0$, 2H, H-6, 6′); 7.78 (t, $J = 8.0$, 2H, H-7, 7′); 8.00 (d, $J = 8.0$, 2H, H-8, 8′); 8.32 (d, $J = 8.0$, 2H, H-5, 5′). ESI–MS *m/z*: 551.36 [M + 1]. Anal. calcd for $C_{33}H_{24}Cl_2N_2O_2$, %: C, 71.87; H, 4.39; N, 5.08; Found: C, 71.79; H, 4.52; N, 4.98.

4,4′-(4,4′-(propane-2,2-diyl)bis(4,1-phenylene)bis(oxy)bis(2-chloro-6-methylquinoline) (**2b**)

IR (KBr), *v*, cm^{-1}: 3050, 2962, 2920, 1566, 1501, 1433, 1320, 1299, 1217, 1167, 1097, 1066, 1013, 930, 837. ^{1}H NMR (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.80 (s, 6H, H-16, 16′); 2.56 (s, 6H, –CH_3 at 6, 6′); 6.53 (s, 2H, H-3, 3′); 7.14 (d, 4H, $J = 8.0$, H-13, 13′); 7.40 (d, 4H, $J = 8.0$, H-12, 12′); 7.60 (dd, $J = 8.0$, 2H, H-7, 7′); 7.89 (d, $J = 8.0$, 2H, H-8, 8′); 8.08 (s, 2H, H-5, 5′). ESI–MS *m/z*: 579 [M + 1]. Anal. calcd for $C_{35}H_{28}Cl_2N_2O_2$, %: C, 72.54; H, 4.87; N, 4.83; Found: C, 72.39; H, 4.90; N, 4.90.

4,4′-(4,4′-(propane-2,2-diyl)bis(4,1-phenylene)bis(oxy)bis(2-chloro-7-methylquinoline) (**2c**)

IR (KBr), *v*, cm^{-1}: 2968, 2930, 1625, 1578, 1496, 1420, 1374, 1339, 1299, 1212, 1173, 1136, 1074, 1015, 916, 855, 831, 768. ^{1}H NMR (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.80 (s, 6H, H-16, 16′); 2.57 (s, 3H, –CH_3 at 7); 2.92 (s, 3H –CH_3 at 7′); 6.50 (s, 1H, H-3); 6.55 (s, 1H, H-3′); 7.09–7.16 (m, 4H, $J = 8.0$, H-13,13′); 7.30-7.42 (m, 6H); 7.55-7.63 (m, 1H); 7.82 (t, $J = 9.0$, 2H, H-6, 6′); 8.19 (d, $J = 8.0$, 1H). ESI–MS *m/z*: 579.16 [M + 1]. Anal. calcd for $C_{35}H_{28}Cl_2N_2O_2$, %: C, 72.54; H, 4.87; N, 4.83; Found: C, 73.28; H, 4.83; N, 4.80.

4,4′-(4,4′-(propane-2,2-diyl)bis(4,1-phenylene)bis(oxy)bis(2-chloro-8-methylquinoline) (**2d**)

IR (KBr), *v*, cm^{-1}: 2967, 2920, 1612, 1578, 1496, 1445, 1402, 1322, 1300, 1227, 1210, 1168, 1108, 1015, 942, 882, 838, 761. ^{1}H NMR (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.80 (s, 6H, H-16, 16′); 2.77 (s, 6H, –CH_3 at 8, 8′); 6.56 (s, 2H, H-3, 3′); 7.14 (d, $J = 10.0$, 4H, H-13, 13′); 7.40 (d, $J = 10.0$, 4H, H-12, 12′); 7.46–7.50 (m, 2H, H-6, 6′); 7.62 (d, 2H, $J = 8.0$, H-7, 7′); 8.16 (d, $J = 8.0$, 2H, H-5, 5′). ESI–MS *m/z*: 579.20 [M + 1]. Anal. calcd for $C_{35}H_{28}Cl_2N_2O_2$, %: C, 72.54; H, 4.87; N, 4.83; Found: C, 72.56; H, 4.71; N, 4.88.

4,4′-(4,4′-(propane-2,2-diyl)bis(4,1-phenylene)bis(oxy)bis(2-chloro-6-methoxyquinoline) (**2e**)

IR (KBr), *v*, cm^{-1}: 2965, 2924, 1577, 1499, 1227, 1170, 1098, 1027, 916, 827. ^{1}H NMR (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.81 (s, 6H, H-16, 16′); 3.95 (s, 6H, –OCH_3 at 6, 6′); 6.55 (s, 2H, H-3, 3′); 7.16 (d, $J = 10.0$, 4H, H-13, 13′); 7.39–7.43 (m, 6H, H-12, 12′, 7, 7′); 7.54 (s, 2H, H-5, 5′); 7.91 (d, 2H, $J = 10.0$, H-8, 8′). ESI–MS *m/z*: 611 [M + 1]. Anal. calcd for $C_{35}H_{28}Cl_2N_2O_4$, %: C, 68.74; H, 4.62; N, 4.58; Found: C, 68.80; H, 4.66; N, 4.47.

4,4′-(4,4′-(propane-2,2-diyl)bis(4,1-phenylene)bis(oxy)bis(2-chloro-8-methoxyquinoline) (**2f**)

IR (KBr), *v*, cm^{-1}: 3036, 2970, 1614, 1573, 1495, 1405, 1326, 1308, 1265, 1211, 1171, 1105, 1062, 1014, 951, 840, 748. ^{1}H NMR (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.80 (s, 6H, H-16,16′); 4.08 (s, 6H, –OCH_3 at 8, 8′); 6.59 (s, 2H, H-3, 3′); 7.14 (d, $J = 8.0$, 6H, H-13, 13′, 7, 7′); 7.4 (d, $J = 8.0$, 4H, H-12, 12′); 7.51 (t, 2H, $J = 9.0$, H-6, 6′); 7.87 (d, 2H, $J = 8.0$, H-5, 5′). ESI–MS *m/z*: 611.37 [M + 1]. Anal. calcd for $C_{35}H_{28}Cl_2N_2O_4$, %: C, 68.74; H, 4.62; N, 4.58; Found: C, 68.56; H, 4.72; N, 4.49.

4,4′-(4,4′-(propane-2,2-diyl)bis(4,1-phenylene)bis(oxy)bis(2-chloro-6-bromoquinoline) (**2g**)

IR (KBr), *v*, cm^{-1}: 2967, 1575, 1490, 1435, 1390, 1318, 1224, 1172, 1077, 1015, 924, 868, 827. ^{1}H NMR (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.81 (s, 6H, H-16, 16′); 6.57 (s, 2H, H-3, 3′); 7.14 (d, $J = 8.0$, 4H, H-13, 13′); 7.42 (d, $J = 10.0$, 4H, H-12, 12′); 7.85 (bs, 4H, H-7, 7′, 8, 8′); 8.48 (s, 2H, H-5, 5′). ESI–MS *m/z*: 708 [M+2], 709 [M+3], 710 [M+4]. Anal. calcd for $C_{33}H_{22}Br_2Cl_2N_2O_2$, %: C, 55.88; H, 3.13; N, 3.95; Found: C, 55.73; H, 3.16; N, 3.88.

4,4′-(4,4′-(propane-2,2-diyl)bis(4,1-phenylene)bis(oxy)bis(2,7-dichloro-6-fluoroquinoline) (**2h**)

IR (KBr), *v*, cm^{-1}: 3062, 2969, 1575, 1498, 1448, 1324, 1213, 1171, 1116, 1070, 1015, 932, 827. ^{1}H NMR (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.81 (s, 6H, H-16, 16′); 6.57 (s, 1H, H-3); 6.68 (s, 1H, H-3′); 7.14 (d, $J = 8.0$, 4H, H-13, 13′); 7.42 (d, $J = 10.0$, 4H, H-12, 12′); 7.59 (t, $J = 9.0$, 1H, H-5); 7.89–8.09 (m, 3H, H-5′, 7, 7′). ESI–MS *m/z*: 656 [M+2], 657 [M+3]. Anal. calcd for $C_{33}H_{20}Cl_4F_2N_2O_2$, %: C, 60.39; H, 3.07; N, 4.27; Found: C, 60.26; H, 3.11; N, 4.33.

4,4′-(4,4′-(propane-2,2-diyl)bis(4,1-phenylene)bis(oxy)bis(2-chloro-6,8-dimethylquinoline) (**2i**)

IR (KBr), *v*, cm^{-1}: 3058, 2967, 2919, 1578, 1495, 1448, 1319, 1235, 1172, 1100, 1015, 942, 893, 858. ^{1}H NMR (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.80 (s, 6H, H-16, 16′); 2.52 (s, 6H, –CH_3 at 6, 6′); 2.74 (s, 6H, –CH_3 at 8, 8′); 6.54 (s, 2H, H-3, 3′); 7.13 (d, $J = 8.0$, 4H, H-13, 13′); 7.40 (d, 4H, $J = 10.0$, H-12, 12′); 7.47 (s, 2H, H-7, 7′); 7.94 (s, 2H, H-5, 5′). ESI–MS *m/z*: 607.52 [M + 1]. Anal. calcd for $C_{37}H_{32}Cl_2N_2O_2$, %: C, 73.14; H, 5.31; N, 4.61; Found: C, 73.39; H, 5.37; N, 4.52.

4,4′-(4,4′-(propane-2,2-diyl)bis(4,1-phenylene)bis(oxy)bis(2-chlorobenzo[*h*]quinoline) (**2j**)

IR (KBr), *v*, cm^{-1}: 3051, 2967, 1621, 1580, 1491, 1440, 1399, 1316, 1258, 1214, 1174, 1108, 1015, 956, 825, 756. ^{1}H NMR (200 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.83

(s, 6H, H-16, 16′); 6.76 (s, 2H, H-3, 3′); 7.18 (d, $J = 8.0$, H-13, 13′; 7.43 (d, $J = 8.0$, 4H, H-12, 12′); 7.72–7.94 (m, 8H); 8.21 (d, $J = 10.0$, 2H); 9.20–9.24 (m, 2H). ESI–MS *m/z*: 651 [M + 1]. Anal. calcd for $C_{41}H_{28}Cl_2N_2O_2$, %: C, 75.58; H, 4.33; N, 4.30; Found: C, 76.36; H, 4.26; N, 4.23.

2-chloro-4,6-dimethoxyquinoline (**2k**)

IR (KBr), *v*, cm^{-1}: 3089, 2921, 2849, 1572, 1494, 1275, 1094, 1027, 829, 786. ^1H NMR (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.93 (s, 3H, -OCH_3 at C-4); 4.05 (s, 3H, -OCH_3 at C-6); 6.71 (s, 1H, H-3); 7.35 (d, $J = 9.0$, 1H, H-7); 7.38 (s, 1H, H-5); 7.85 (d, $J = 9.0$, 1H, H-8). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 55.6 (–OCH_3 at C-6); 56.1 (–OCH_3 at C-4); 100.1 (C-5); 101.2 (C-3); 121.1 (C-9); 122.0 (C-7); 129.4 (C-8); 143.9 (C-10); 149.0 (C-2); 157.6 (C-6); 162.5 (C-4). ESI–MS *m/z*: 224 [M + 1]. Anal. calcd for $C_{35}H_{28}Cl_2N_2O_4$, %: C, 59.07; H, 4.51; N, 6.26; Found: C, 58.98; H, 4.57; N, 6.21.

Antibacterial activity

In-vitro evaluation of the antibacterial activity of compounds **2a–k**

The broth microdilution method [29] with Mueller–Hinton agar medium was used in a preliminary study of the antibacterial activity of synthesized compounds **2a–k** with standard pathological bacterial strains *E. coli* ATCC 25922, *P. aeruginosa* ATCC 25619, *S. aureus* ATCC 25923, and *B. subtilis* ATCC 29212. The antibacterial activity of the test compounds was compared with that of ciprofloxacin. Twofold serial dilutions of the test compounds and reference drugs were prepared in Mueller–Hinton broth. Test compounds and the standard drug ciprofloxacin were dissolved in dimethylsulfoxide (DMSO, 1 mL) and the solution was diluted with distilled water (9 mL). Further progressive serial dilutions were performed to obtain the required concentrations from 250 to 1,000 μg/mL. Petri dishes were inoculated with 5×10^4 colony-forming units (cfu)/mL and incubated at 37 °C for 24 h. The minimum inhibitory concentration (MIC) was the lowest concentration of the tested compound that resulted in no visible growth on the plate. To ensure that the solvent had no effect on bacterial growth, a control was performed with the test medium supplemented with DMSO at the same dilutions as used in the experiments. The results of the study are listed in Table 2.

Conclusion

We have described the highly regioselective synthesis of novel bis(2-chloroquinolines) by reaction of 2,4-dichloroquinolines with BPA catalyzed by powdered K_2CO_3 in DMF. Substitution at C4 of the quinoline is known to be favored, and substitution at C2 was zero during the course of the reaction. The azidation reaction of 2,4-dichloro-6-methylquinoline (**1b**) was also investigated to check its behavior

Table 2 In-vitro antibacterial activity (MIC, μg/mL) of bis(2-chloroquinolines) **2a–k**

Compound	*S. aureus*	*B. subtilis*	*Acaule*	*P. aeruginosa*
2a	500	500	500	500
2b	1,000	1,000	1,000	1,000
2c	750	750	750	750
2d	1,000	1,000	1,000	1,000
2e	250	500	500	250
2f	250	500	500	500
2g	500	500	500	500
2h	250	250	500	250
2i	500	750	750	750
2j	1,000	1,000	1,000	750
2k	750	1,000	1,000	1,000
Ciprofloxacin	12.5	12.5	12.5	12.5

in nucleophilic substitution with significant γ-attack. Preliminary evaluation of the in-vitro antibacterial activity (MIC μg/mL) of all the synthesized compounds revealed mild to moderate activity against the organisms tested.

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