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Docking analysis and synthesis some new substituted n-(6-chloro-3-cyano-4-phenyl-4H-chromen-2-yl)-2-(4-chloro-phenoxy)-acetamide as impending antimicrobial agents

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Abstract

In recent year heterocyclic compounds analogues and derivatives have attracted strong interest due to their useful biological and pharmacological properties. Oxadiazole derivates play vital role in biological field such as anti-microbial, anti-viral, anti-tubercular, anti-inflammatory and anti-convulsant activity.

Keywords: 1,3,4- Oxadiazole, Docking, Antimicrobial Activity.

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1. Introduction

Antimicrobial use is known to have been common practice for at least 2000 years. Ancient Egyptians and ancient Greeks used specific molds and plant extracts to treat infection. [1]

In the 19th century, microbiologists such as Louis Pasteur and Jules Francois Joubert observed antagonism between some bacteria and discussed the merits of controlling these interactions in medicine.[2] In 1928, Alexander Fleming became the first to discover a natural antimicrobial fungus known as *Penicillium rubens* and named the extracted substance penicillin which in 1942 was successfully used to treat a *Streptococcus* infection.[3]

An antimicrobial is an agent that kills microorganisms or stops their growth. [4] Antimicrobial medicines can be grouped according to the microorganisms they act primarily against. For example, antibiotics are used against bacteria and antifungals are used against fungi. They can also be classified according to their function. Agents that kill microbes are called microbicidal, while those that merely inhibit their growth are called biostatic. The use of antimicrobial medicines to treat infection is known as antimicrobial chemotherapy, while the use of antimicrobial medicines to prevent infection is known as antimicrobial prophylaxis.

Antibacterials are used to treat bacterial infections. The drug toxicity to humans and other animals from antibacterials is generally considered low. [5] Prolonged use of certain antibacterials can decrease the number of gut flora, which may have a negative impact on health. Consumption of probiotics and reasonable eating can help to replace destroyed gut flora. Stool transplants may be considered for patients who are having difficulty recovering from prolonged antibiotic treatment, as for recurrent *Clostridium difficile* infections.[5,6]

The discovery, development and use of antibacterials during the 20th century have reduced mortality from bacterial infections. The antibiotic era began with the pneumatic application of nitroglycerine drugs, followed by a "golden" period of discovery from about 1945 to 1970, when a number of structurally diverse and highly effective agents were discovered and developed.

Since 1980 the introduction of new antimicrobial agents for clinical use has declined, in part because of the enormous expense of developing and testing new drugs.[7] In parallel there has been an alarming increase in antimicrobial resistance of bacteria, fungi, parasites and some viruses to multiple existing agents.[8]

Antibacterials are among the most commonly used drugs and among the drugs commonly misused by physicians, for example, in viral respiratory tract infections. As a consequence of widespread and injudicious use of antibacterials, there has been an accelerated emergence of antibiotic-resistant pathogens, resulting in a serious threat to global public health. The resistance problem demands that a renewed effort be made to seek antibacterial agents effective against pathogenic bacteria resistant to current antibacterials. Possible strategies towards this objective include increased sampling from diverse environments and application of metagenomics to identify bioactive compounds produced by currently unknown and uncultured microorganisms as well as the development of small-molecule libraries customized for bacterial targets.[9]

2. Experimental Protocol

2.1 Chemistry

All the chemicals and solvents, purchased from Sigma-Aldrich (India), and S. D. Fine, Himedia (India), were used without further purification. Thin layer chromatography analyses of compounds were performed on silica gel G coated Aluminum foils. The solutions of compounds were applied as a spot on the aluminum foils about 2 cm above from the lower edge. The mobile phases were preferred according to the polarity of compounds (Ethyl acetate: hexane).

The melting points of synthesized compounds were decisive by using open capillary melting point apparatus. FT-IR spectra (KBr) were recorded on a Thermo-Scientific (Nicole 6700) spectrophotometer. The ^{1}H-NMR spectra were reported on Joel and Bruker 400 MHz High-Resolution NMR spectrometer using TMS as an internal standard. Chemical shifts were reported in ppm (δ) and signals were described as singlet (s), doublet (d), triplet (t) and multiple (m). The mass spectra were recorded via Direct-infusion on a Waters Micro-Mass ZQ 2000 mass spectrophotometer and data were acquired with electrospray ionization (ESI) source.

The synthetic routes of compounds (A1-4) are shown in the Figure 2. The chemical structure of the synthesized derivatives was analyzed and confirmed on the basis of spectral data. The formation of ^{4}H chromenderivatives was supported by the presence of amide stretching (3500-3200 cm-1 and 1600-1400cm-1), and appeared NH around δ = 9.5 to 8.0 in ^{1}H NMR spectra. Further mass spectra were used to confirm the assigned structure of compounds.

2.2 Synthesis

2.2.1 Synthesis of C1 to C4

In a 50 mL of RB flask, a mixture of substituted aromatic aldehyde (0.02 mol), malononitrile (0.02 mol), and a catalytic amount of 2-aminopyridine (5 mol %) in ethanol (10 mL) was allowed to stir for few minutes, P-Chlorophenol (0. 2mol) was added and refluxed with stirring for the time completion of the reaction as evidenced by TLC. The reaction mixture was allowed to cool resulting in crystalline solids.

2.2.2 Synthesis of B1 to B4 from C1 to C4

A mixture of the compound (C1to C4)(0.01mol), and 2-chloroacetyl chloride (0.01mol), and (TEA**)** triethylaminein DMF (dimethylformamide 10 mL) was stirred at 0-5°C for 16 hrs. Later, reaction was monitored by TLC. Solid compound separated from the reaction mixture.

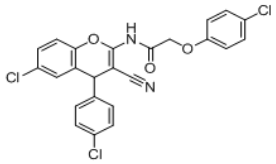
2.2.3 Synthesis of A1 to A4 from B1 to B4

A mixture of compounds (B1to B4) (0.01mol) and P-chlorophenol (0.01mol) and K_2CO_3 in acetonitril was refluxed for 6 hrs. The cooled mixture was filtered and recrystallized from DMSO/alcohol.

2.3 Characterization of synthesized compounds

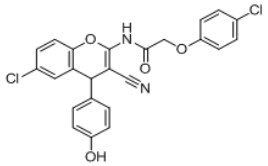
2.3.1 N-[6-Chloro-4-(4-chloro-phenyl)-3-cyano-4H-chromen-2-yl]-2-(4-chloro-phenoxy)-acetamide (A1)

^{1}H NMR (DMSO-d_6) δ ppm: 8.82 (s, 1H, NH), 8.25 (s, 1H, Ar-H), 7.98-7.94 (d, 4H, Ar-H), 7.68-7.63 (d, 2H, Ar-H), 7.17-7.14(d, 4H, Ar-H), 4.09 (s, H, -CH), 3.50 (s, 2H, -CH_2). IR (KBr) ν_{max}= 619.0 (C-Cl), 1120.2 (C-O-C), 2160.4(CN), 3313.4 (NH), 1594.2 (C=O), 1440.0 (CH_2), 3013.1(Ar-C-H), 1512.6 (Ar-C=C). MS (ESI) m/z (%): 486.4 (22.0) $[M+H]^{+}$.



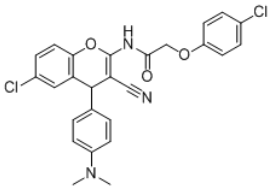
2.3.2 N-[6-Chloro-3-cyano-4-(4-hydroxy-phenyl)-4H-chromen-2-yl]-2-(4-chloro-phenoxy)-acetamide (A2)

^{1}H NMR (DMSO-d_6) δ ppm: 8.87 (s, 1H, NH), 8.72 (s, 1H, Ar-H), 7.91-7.87 (d, 4H, Ar-H), 7.72-7.70 (d, 2H, Ar-H),7.32-7.21(d, 4H, Ar-H), 5.34(s,1H,OH)3.94 (s, H, -CH),3.82 (s, 2H, -CH_2). IR (KBr) ν_{max}= 3429.4(OH), 737.5(C-Cl), 1090.2(C-O-C), 2161.5(CN), 3561.5(NH), 1561.5(C=O), 1414.0 (CH_2), 2832.1(Ar-C-H), 1561.5(Ar-C=C). MS (ESI) m/z (%): 468.6 (32.0) $[M+H]^{+}$.



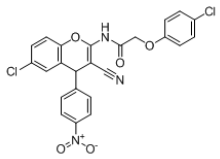
2.3.4 N-[6-Chloro-3-cyano-4-(4-dimethylamino-phenyl)-4H-chromen-2-yl]-2-(4chloro-phenoxy) acetamide (A3)

^{1}H NMR (DMSO-d_6) δ ppm: 9.40 (s, 1H, NH), 8.88 (s, 1H, Ar-H), 8.39-8.34 (d, 2H, Ar-H), 8.11-8.09 (d, 2H, Ar-H),7.93-7.90(d, 2H, Ar-H), 7.44-7.39(d,4H,Ar-H),4.87 (s, H, -CH),4.11 (s, 2H, -CH_2), 3.83(s,6H,CH_3). IR (KBr) ν_{max}= 697.1(C-Cl), 1068.7(C-O-C), 2192.7(CN), 3265.2(NH), 1509.4(C=O), 1459.3 (CH_3), 1406.3 (CH_2)3091.4(Ar-C-H), 1589.5(Ar-C=C). MS (ESI) m/z (%): 495.8 (34.0) $[M+H]^+$.

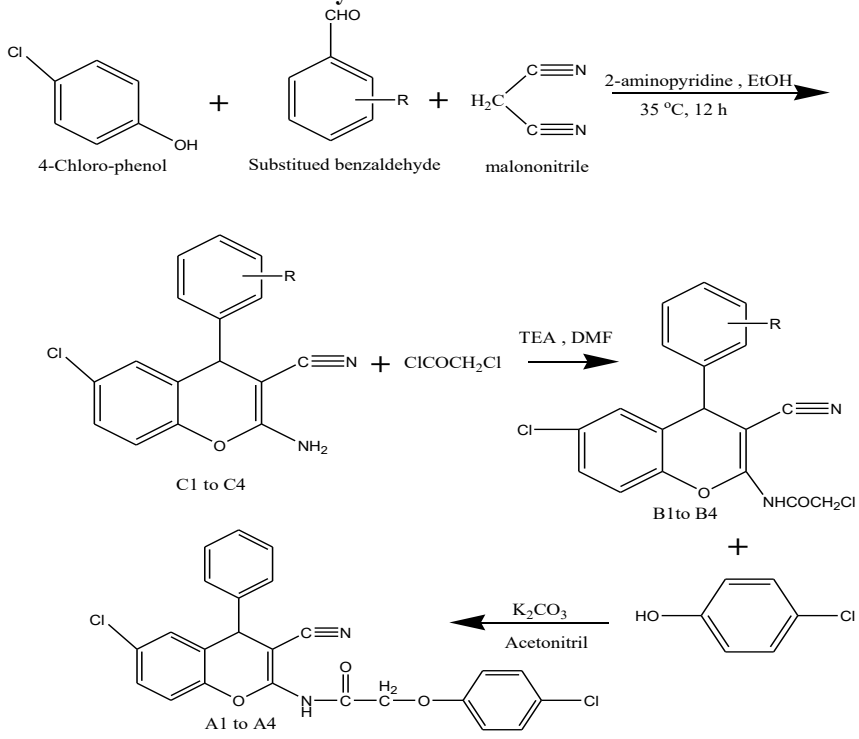


2.3.5 N-[6-Chloro-3-cyano-4-(4-nitro-phenyl)-4H-chromen-2-yl]-2-(4-chloro-phenoxy)-acetamide (A4)

^{1}H NMR (DMSO-d_6) δ ppm: 8.84 (s, 1H, NH), 8.04-8.01 (d, 4H, Ar-H), 7.09(s, 1H, Ar-H), 7.45-7.40 (d, 4H, Ar-H),7.93-7.90(d, 2H, Ar-H), 7.04-7.01(d,2H,Ar-H),4.14 (s, H, -CH),3.44 (s, 2H, -CH_2). IR (KBr) ν_{max}= 727.8(C-Cl), 1601.8(NO_2) 1067.0(C-O-C), 2132.2(CN), 3280.7(NH), 1527.5(C=O), 1436.9 (CH_2), 3089.9(Ar-C-H), 1569.1(Ar-C=C). MS (ESI) m/z (%): 497.2 (16.0) $[M+H]^+$.



Synthetic Scheme 1



Substitued *N*-(6-Chloro-3-cyano-4-phenyl-4*H*-chromen-2-yl)-2-(4-chloro-phenoxy)-acetamide

R = Cl , OH , $N(CH_3)_2$, NO_2

2.4 Molecular Docking

2.4.1 Docking Studies

Docking study of designing compound was performed with *E. coli* (PDB: 1LXC) receptor. Active site domain was recognized of protein with the assist of online server where the ligand showed the best configuration. Later, Grid was set according to an active site sequence of amino acid. Their binding affinity (kcal/mol) and H-bonds were determined (Table 2) through docking studies. Docking images of compounds with the target receptor was shown in Figure.3.13. Compound A3 exhibited good binding properties with (*E. coli*) (1LXC) receptor along with hydrogen bond, π-bond with binding affinity (more than -6.0 kcal/mol, respectively). Moreover, Compounds A1, A2 and A4 also so the similar binding with (*E. coli*) (PDB: 1LXC). as is shown in Table 2. Hence, this observation could be attributed as potential antimicrobial with (*E. coli*) (PDB: 1LXC) facilitator mode of action.

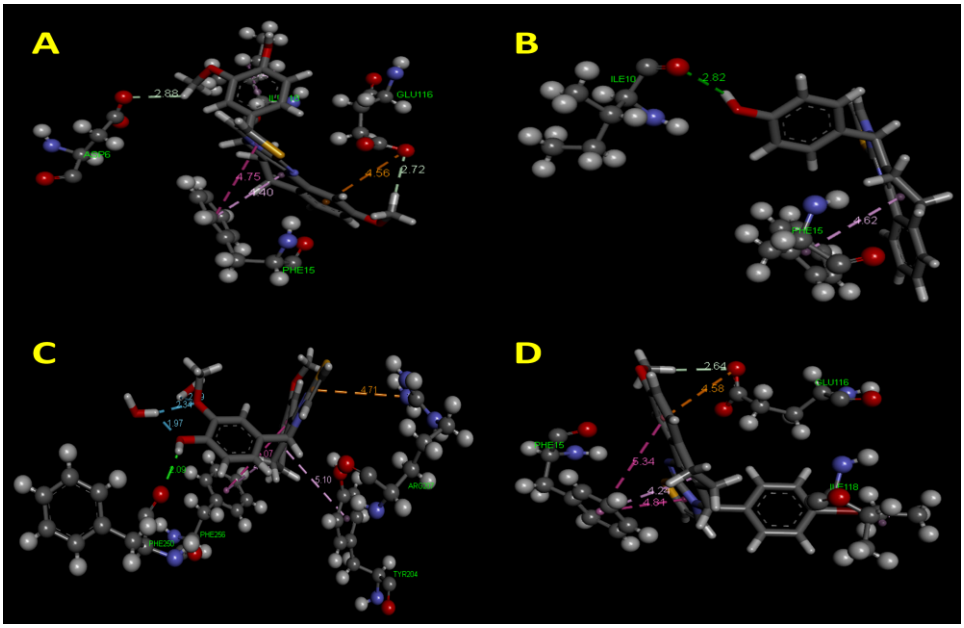


Figure 1: Binding interaction of compounds A1 (A), A2(B), A3(C) and A4(D) with (*E. coli*) (1LXC) receptor

2.4.2 Antibacterial Evaluation:

Antimicrobial results are expressed as zone of inhibition (mm) test drug compared with zone of inhibition (mm) of standard drug**.** The compounds A3 showed the better zone of inhibition against both gram positive and negative bacterial media which is shown in Table 2. Other compound of this series showed 50% inhibition of zone compared with standard drug. Higher doses 200 mg/ml were shown higher effectiveness against the bacterial culture media both gram positive and gram negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli.*).

3. Result and Discussion

The present studies reported 4 new substituted 1,3,4-Oxadiazole and their structure were established on the basis of spectral studies and elemental analysis. Auto dock…….. molecular docking software has been used for descriptor calculation. Biological activity of all compound were performed by using Cup plate method in which MTCC-1688 (gram+ve) and MTCC-521(gram-ve).

Table 1: Physical data of all the compounds

S. No.	Molecular Formula (M.W.)	Melting point(°C)	%Yield	R_f Value
A1	$C_{24}H_{15}Cl_3N_2O_3$ (485.75)	161-166	85	0.55
A2	$C_{24}H_{16}Cl_2N_2O_4$ (467.30)	170-174	65	0.36
A3	$C_{26}H_{21}Cl_2N_3O_3$ (494.37)	181-185	77	0.61
A4	$C_{24}H_{15}Cl_2N_3O_5$ (496.30)	175-179	80	0.51

3.1 Binding Site analysis:

The experimental analysis of binding site shows that ASN A 43 ARG A 44 CYS A 47 MET A 48 PRO A 153 PRO A 154 CYS A 36 CYS A 37 ASN A 39 PRO A 40 TYR A 130 GLY A 135 and LEU A 152 could be the catalytic site residue present in the structure of 1LXC proteins.

Table 2: Docking affinity of titled compounds with assigned (*E. coli*) (1LXC) proteins

Ligands	Receptors	Binding affinity [kcal/mol]	Amino acids involved in interaction	H-bonds	π-bonds
A1	(*E. coli*) (1LXC).	-5.2	ASN A 43 ARG A 44 CYS A 47 MET A 48 PRO A 153 PRO A 154 CYS A 36 CYS A 37 ASN A 39 PRO A 40 TYR A 130 GLY A 135 LEU A 152	1	2
A2	(*E. coli*) (1LXC).	-6.5	ASN A 153 PRO A 154 VAL A 43 ARG A 44 CYS A 47 MET A 48 TYR A 130 GLY A 135 LEU A 152 PRO A PRO A 40 CYS A 41 GLN A 42	1	2
A3	(*E. coli*) (1LXC).	-7.8	CYS A 47 ASN A 34 CYS A 36 CYS A 37 ASN A 39 MET A 48 TYR A 130 PRO A 40 CYS A 41 GLN A 42 ASN A 43 ARG A 44 GLY A 135 LEU A 152 PRO A 153 PRO A 154	2	3
A4	(*E. coli*) (1LXC).	-6.3	GLN A 42 ASN A 43 ARG A 44 CYS A 47 ASN A 34 CYS A 36 CYS A 37 ASN A 39 MET A 48 TYR A 130 GLY A 135 LEU A 152 PRO A 153 PRO A 154 PRO A 40 CYS A 41	3	1

3.2 Antimicrobial screening result:

The compounds A3 showed the better zone of inhibition against both gram positive and negative bacterial media which is shown in Table 3 and represent by figure 1.

Table 3: Antimicrobial screening by Cup-plate method Zone of inhibition (nm)

Compounds	Zone of inhibition (mm)			
	MTCC-1688 (gram+ve)		MTCC-521(gram-ve)	
	100µg/ml	200µg/ml	100µg/ml	200µg/ml
A1	04	07	06	08
A2	07	09	04	07
A3	09	10	08	11
A4	06	09	07	10
Std. Ampicillin	12	18	11	16
Control.	-	-	-	-

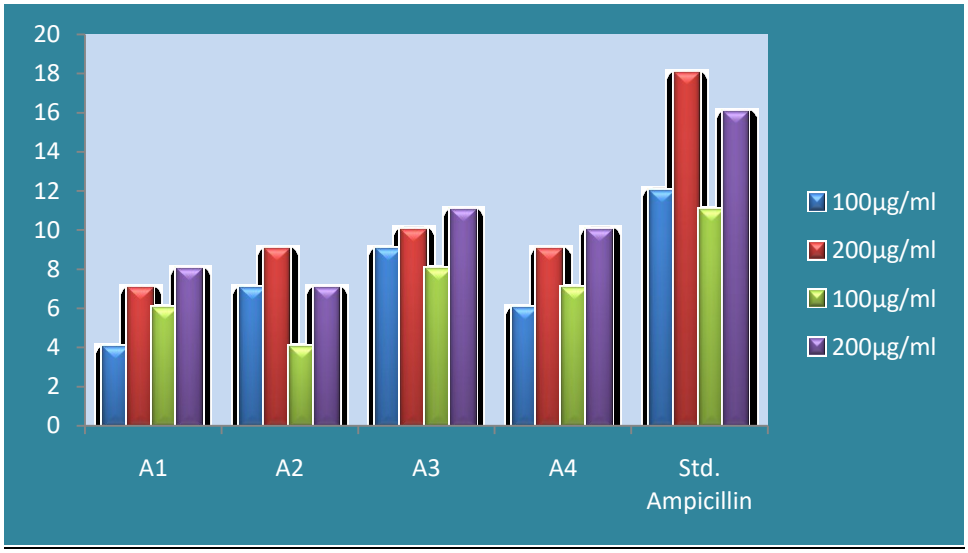


Figure 1: Antimicrobial screening by Cup-plate method Zone of inhibition (nm)

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