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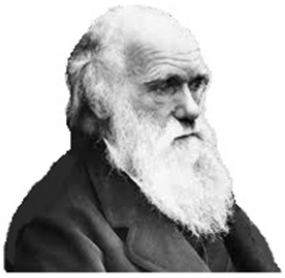

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Synthesis, spectral analysis and antimicrobial activity of 2(1H)-quinolinone tethered 1,3,5-triazine derivatives

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ABSTRACT

A series of novel quinolinone containing 1,3,5-triazine derivatives have been synthesized, characterized and screened for antimicrobial activity. 7-((4-((3-fluoro-4-morpholinophenyl)amino)-6-(arylamino)-1,3,5-triazin-2-yl)oxy)-3,4-dihydroquinolin-2(1H)-one derivatives were prepared by condensation of 7-((4-chloro-6-((3-fluoro-4-morpholinophenyl)amino)-1,3,5-triazin-2-yl)oxy)-3,4-dihydroquinolin-2(1H)-one with differently substituted aniline derivatives. The designed compounds were confirmed via IR, ^{1}H NMR, Mass spectral data. The synthesized compounds checked for their antimicrobial activity using gram-positive bacteria, gram-negative bacteria and fungi against standard drugs.

Keywords: 3-4-dihydro-2(1H)-quinolinone, 1-3-5-triazine, Antibacterial Activity, Anti-fungal Activity

1. INTRODUCTION

Recent synthetic research majorly focuses on the development of potentially active heterocyclic [1] compounds, which are simple to synthesize with good yield and will possessing good pharmacological activity [2]. For such aim, most common choice of heterocycles are of

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nitrogen possessing heterocycles such as derivatives of quinoline [3] and 1,3,5-triazine[4]. 3,4-dihydro-2(1H)-quinolinone (C_9H_9NO) [5] and 2,4,6-trichloro-1,3,5-triazine ($C_3Cl_3N_3$) [6] represent two significant compounds in the realm of organic chemistry, each offering distinct properties and applications that contribute to a wide array of scientific and industrial advancements.

2,4,6-trichloro-1,3,5-triazine, a derivative of triazine, is characterized by its high reactivity due to the presence of three chlorine atoms, which can be easily replaced by various nucleophiles. This property makes it a valuable intermediate in the synthesis of herbicides [7], dyes [8], resins [9, 10], and other chemical products. Its role in facilitating chlorination, amination, and esterification processes underscores its importance in both academic research and industrial applications. On the other hand, 3,4-dihydro-2(1H)-quinolinone, an important lactam, serves as a key building block in the synthesis of quinoline and quinolinone derivatives[11]. These derivatives are prominent in pharmaceuticals [12], known for their broad spectrum of biological activities including antibacterial [13], antifungal [14], anti-inflammatory [15], anticancer [16, 17], antimalarial [18], analgesic properties. The versatility of 3,4-dihydro-2(1H)-quinolinone in forming heterocyclic compounds enhances its significance in medicinal chemistry and drug development.

This paper aims to provide a comprehensive exploration of the chemical properties, synthesis methods, and applications of 7-((4-((3-fluoro-4-morpholinophenyl)amino)-6-(arylamino)-1,3,5-triazin-2-yl)oxy)-3,4-dihydroquinolin-2(1H)-one derivatives. Furthermore, the paper will discuss the potential synergies between 3,4-dihydro-2(1H)-quinolinone and 2,4,6-trichloro-1,3,5-triazine in the creation of new organic frameworks, highlighting their relevance in both current practices and future innovations in chemistry science.

Through a detailed analysis, we will underscore the significance of 2,4,6-trichloro-1,3,5-triazine and 3,4-dihydro-2(1H)-quinolinone in modern chemistry, illustrating how their unique properties and versatile applications pave the way for ongoing research and industrial progress.

2. MATERIALS AND METHODS

All the chemicals were purchased from Loba chemie and SRL are of AR grade and used without purification. Melting points were determined using open glass capillaries method. To check the advancement of reaction, thin-layer chromatography was performed using a 0.2 mm pre-coated silica gel plate and visualization have been done using Shimadzu UV spectrophotometer (254 nm and 365 nm). For the determination of NMR spectra, Bruker Advance II (400 MHz) spectrometer were used by employing solvent DMSO-d^6. All chemical shifts are expressed as δ ppm with respect to downfield from the signal of tetramethylsilane (TMS), which used as an internal standard. The FT-IR spectra were recorded in Bruker Alpha II IR spectroscope. GC-MS QP-2010 mass spectrometer was used for mass spectroscopy data.

2. 1. Experimental Section

2. 1. 1. Synthesis of 4,6-dichloro-N-(3-fluoro-4-morpholinophenyl)-1,3,5-triazine-2-amine(3)

2,4,6-Trichloro-1,3,5-triazine **1** (100 mmol) and 3-fluoro-4-morpholinoaniline **2** (120 mmol) were mixed in a conical flask, containing 25 mL of DMF as the solvent, maintaining

the temperature between 0-5 °C. The reaction mixture was left for stirring, and base was added to ensure the pH remained above 7. Reaction progress was monitored using TLC. After continuous stirring of 2 h, reaction mass was poured into crushed ice. The resulting solid was filtered, washed with water, dried, and recrystallized from ethanol to get the desired compound **3** with yield: 60%, M.P.: 188-190 °C.

2. 1. 2. Synthesis of 7-((4-chloro-6-((3-fluoro-4-morpholinophenyl)amino)-1,3,5-triazin-2-yl)oxy)-3,4-dihydroquinolin-2(1H)-one(5)

4,6-Dichloro-N-(3-fluoro-4-morpholinophenyl)-1,3,5-triazine-2-amine **3** (100 mmol) and 7-hydroxy-3,4-dihydro-2(1H)-quinolinone **4** (100 mmol) were allowed to dissolve in solvent 1,4-dioxane in the catalytic presence of K_2CO_3. Further, reaction mixture was stirred for 14 h at room temperature and completion of the reaction was checked using TLC. The reaction mixture was then poured into crushed ice, and the resulting solid was filtered, dried, and recrystallized from ethanol to get compound **6** with 64% yield. M.P.: 210-212 °C.

2. 1. 3. General Synthesis of 7-((4-((3-fluoro-4-morpholinophenyl)amino)-6-(arylamino)-1,3,5-triazin-2-yl)oxy)-3,4-dihydroquinolin-2(1H)-one derivatives (8a-8j)

7-((4-chloro-6-((3-fluoro-4-morpholinophenyl)amino)-1,3,5-triazin-2-yl)oxy)-3,4-dihydroquinolin-2(1H)-one **(5)** (100 mmol) and Various substituted aniline derivatives (120 mmol) **(6a-6j)** were added to RBF containing tetrahydrofuran (THF), and resulting reaction mixture was refluxed at a temperature of 90-100 °C for overnight. After completion of reaction, reaction mass was allowed to cool and solvent was removed. It was treated with base and poured into ice-cold water to precipitate the solid product. Solid crude product was filtered, dried, and recrystallized using methanol with yield range of 47-72 %.

Spectral Data Analysis

7-((4-((3-fluoro-4-morpholinophenyl)amino)-6-(phenylamino)-1,3,5-triazin-2-yl)oxy)-3,4-dihydroquinolin-2(1H)-one (8a), IR (KBr) cm^{-1}: 3422, 2961, 2854, 1678, 1604, 1496, 1580, 1509, 1434, 1352, 1301, 1253, 1047, 873, 808, 692. ^{1}H NMR (DMSO-d^6) δ ppm: 2.892-2.926 (t, 4H), 3.568 (s, 4H), 3.730 (s, 4H), 6.706-6.795 (m, 3H), 7.016 (s, 1H), 7.217-7.237 (m, 5H), 7.606 (s, 2H), 9.813 (s, 1H), 10.180 (s, 1H). MS: m/z; 527.10

7-((4-((3-fluoro-4-morpholinophenyl)amino)-6-(o-tolylamino)-1,3,5-triazin-2-yl)oxy)-3,4-dihydroquinolin-2(1H)-one (8b): ^{1}H NMR (DMSO-d^6) δ ppm: 1.225 (s, 3H), 2.489-2.498 (t, 4H), 2.876-2.897 (s, 4H), 3.697-3.706 (s, 4H), 6.606-6.675 (m, 2H), 6.752-6.783 (m, 2H), 7.128-7.320 (m, 4H), 7.352-7.682 (m, 2H), 10.137 (s, 1H), 10.176 (s, 1H). MS: m/z; 541.40

7-((4-((2-chlorophenyl)amino)-6-((3-fluoro-4-morpholinophenyl)amino)-1,3,5-triazin-2-yl)oxy)-3,4-dihydroquinolin-2(1H)-one (8e), ^{1}H NMR (DMSO-d^6) δ ppm: 2.330-2.672 (t, 4H), 2.832-2.949 (s, 4H), 3.706-3.815 (s, 4H), 6.637-6.809 (m, 3H), 6.939-6.967 (m, 3H), 7.112-7.322 (m, 2H), 7.327-7.360 (m, 2H), 10.197 (s, 1H), 10.268 (s, 1H). MS: m/z; 563.10

Table 1. Characteristic physical data of 7-((4-chloro-6-((3-fluoro-4-morpholinoaryl)amino)-1,3,5-triazin-2-yl)oxy)-3,4-dihydroquinolin-2(1H)-one derivatives **(8a-8j)**

Code	-R	M.F.	M.W.	M.P (°C)	% Yield
8a	4-H	$C_{28}H_{26}FN_7O_3$	527.10	276-278	72
8b	2-CH_3	$C_{29}H_{28}FN_7O_3$	541.40	278-280	47
8c	4-CH_3	$C_{29}H_{28}FN_7O_3$	541.40	>300	38
8d	4-OCH_3	$C_{29}H_{28}FN_7O_4$	557.60	282-284	54
8e	2-Cl	$C_{28}H_{25}ClFN_7O_3$	563.10	>300	52
8f	3-Cl	$C_{28}H_{25}ClFN_7O_3$	563.10	240	56
8g	4-Cl	$C_{28}H_{25}ClFN_7O_3$	563.10	>300	67
8h	3-Br	$C_{28}H_{25}BrFN_7O_3$	606.46	>300	49
8i	4-F	$C_{28}H_{25}F_2N_7O_3$	545.55	272-274	60
8j	2-NO_2	$C_{28}H_{25}FN_8O_5$	572.56	>300	52

2. 2. Reaction Scheme

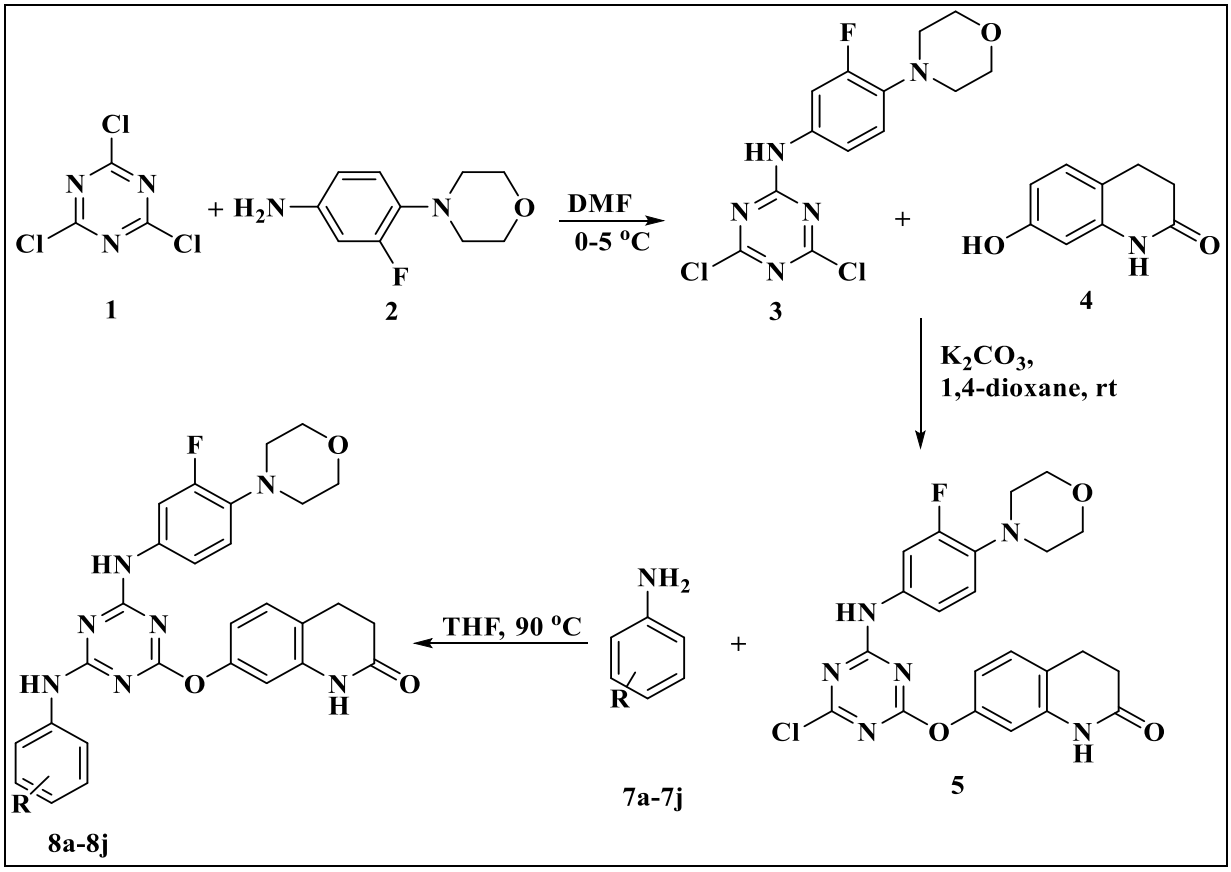

Figure 1. Reaction scheme for the synthesis of 7-((4-((3-fluoro-4-morpholinophenyl)amino)-6-(arylamino)-1,3,5-triazin-2-yl)oxy)-3,4-dihydroquinolin-2(1H)-one derivatives **(8a-8j)**

3. RESULTS AND DISCUSSION

3. 1. Antimicrobial Activity

Table 2. Antimicrobial activity data of 7-((4-((3-fluoro-4-morpholinophenyl)amino)-6-(phenylamino)-1,3,5-triazin-2-yl)oxy)-3,4-dihydroquinolin-2(1H)-one derivatives **(8a-8j)**

Compounds	Antibacterial MIC (µg/mL)				Antifungal MIC (µg/mL)	
	B. subtilis	***S. aureus***	***E. coli***	***P. aeruginosa***	***C. albicans***	***A. niger***
Streptomycin			**50**	**50**		
Ampicillin	**100**	**100**				
Nystatin					**100**	**100**
8a	1000	1000	**500**	1000	1000	**500**
8b	1000	1000	1000	1000	1000	**500**
8c	1000	1000	1000	1000	1000	1000
8d	1000	1000	**500**	1000	1000	1000
8e	**500**	1000	1000	1000	**500**	1000
8f	**500**	1000	1000	1000	**500**	1000
8g	1000	1000	1000	1000	1000	1000
8h	1000	1000	1000	1000	1000	1000
8i	1000	1000	1000	1000	1000	1000
8j	1000	1000	1000	1000	1000	1000

Table 3. Compounds (8a-8j) showing antibacterial & antifungal activity compared with known standard drugs

Compounds	Antibacterial activity				Antifungal Activity	
	Gram positive bacteria		Gram negative bacteria		Fungus	
	B. subtilis	***S. aureus***	***E. coli***	***P. aeruginosa***	***C. albicans***	***A. niger***
8a-8j	8e, 8f	-	8a,8d	-	8e,8f	8a,8b
Activity of Known Standard Drugs:						
Streptomycin	-	-	50	50	-	-
Ampicillin	100	100	-	-	-	-
Nystatin	-	-	-	-	100	100

All the synthesized compounds were tested for antimicrobial activity [20] using Agar well diffusion method [20] to determine the zone of inhibition. The sample concentration was maintained at 100 µg/ml, while the standard drug concentration was set at 50 µg/ml, with DMSO used as the solvent. The antibacterial activity was evaluated against Gram-positive bacteria, including *Bacillus subtilis* and *Staphylococcus aureus*, and Gram-negative bacteria, such as *Proteus vulgaris* and *Pseudomonas aeruginosa*. The antifungal activity was assessed using the fungus *Aspergillus niger* and *Candila albicans*. Streptomycin served as the standard drug for gram negative bacteria antibacterial activity, Ampicillin for gram positive bacteria and nystatin was used as the standard for antifungal activity. The results of the antimicrobial activity study, indicated by the zone of inhibition (clearance of bacterial and fungal colonies), are presented in Table no.2 and 3.

4. CONCLUSION

In the present study, we have successfully synthesized and characterized 7-((4-((3-fluoro-4-morpholinophenyl)amino)-6-(phenylamino)-1,3,5-triazin-2-yl)oxy)-3,4-dihydroquinolin-2(1H)-one derivatives **(8a-8j)** using 7-((4-chloro-6-((3-fluoro-4-morpholinoaryl)amino)-1,3,5-triazin-2-yl)oxy)-3,4-dihydroquinolin-2(1H)-one derivatives **(5)** with various aniline derivatives **(7a-7j)**. All designed compounds were subjected to antimicrobial activity study using various gram positive, gram negative bacteria and fungi against the standard drug streptomycin, ampicillin as an anti-bacterial agent, while nystatin as an anti-fungal agent respectively. The results of antimicrobial activity of these derivatives shows moderate activity of compounds **8a, 8d, 8e** and **8f** against bacterial strains, while **8a, 8b, 8e,** and **8f** of the being moderately active against fungi.

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