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OPTIMIZATION STUDY AND ANTIMICROBIAL ACTIVITY OF HEXAHYDROACRIDINE-1,8(2*H*,5*H*)-DIONE: A PROMISING COMPOUND FOR NOVEL THERAPEUTICS

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ABSTRACT:
Hexahydroacridine-1,8-dione is a chemical compound that has gained significant attention in medicinal chemistry and drug discovery research. This versatile building block offers a unique molecular structure that serves as a valuable precursor for the synthesis of diverse chemical scaffolds. In this research paper, we explore the synthesis and potential applications of hexahydroacridine-1,8-dione derivatives in the development of novel therapeutic agents. We develop into its pharmacological activities, including antibacterial and antifungal activity. The synthetic derivatives were confirmed using IR, 1H NMR, 13CNMR, mass spectra, and elemental analysis. The use of water as a solvent that is believed to be reasonably environmentally beneficial.

KEYWORDS: Hexahydroacridine-1,8-dione, Morpholine, One pot multi-component reaction, Optimization study, aqueous condition, green chemistry, Antibacterial and Antifungal activity.

INTRODUCTION:

Multicomponent reactions (MCRs) have emerged as highly efficient and powerful synthetic strategies in the field of organic chemistry, enabling the rapid and simultaneous assembly of multiple reactants into complex molecular architectures [1]. These innovative reactions have revolutionized synthetic methodologies by providing streamlined approaches to access diverse chemical structures with exceptional atom and step economy. Through the convergence of multiple components within a single reaction vessel, MCRs offer a remarkable platform for constructing complex molecules and generating diverse compound libraries in a time- and cost-effective manner [2].

Traditionally, organic synthesis heavily relied on sequential transformations, often involving the isolation and purification of intermediates, leading to prolonged reaction times and increased complexity [3]. In stark contrast, MCRs present a conceptually distinct approach by bringing together two or more starting materials in a single step, thereby accelerating synthesis and simplifying the purification process [4]. This unique strategy has garnered significant

attention from academia and industry alike, resulting in the development of numerous MCR methodologies over the past few decades.

Hexahydroacridine-1,8-dione, also known as hexahydro-1,8-acridinedione, is a chemical compound that has gained considerable interest in the field of medicinal chemistry and drug discovery. Its distinctive molecular structure and versatile properties make it an intriguing building block for synthesizing diverse chemical scaffolds, thereby holding immense potential for the development of novel therapeutic agents.

Extensive research has been dedicated to organic and synthetic acridine scaffold compounds due to their wide range of biological and physical characteristics [5-9]. Acridine compounds have garnered particular attention as potential anti-tumor [10-13], anti-bacterial [14], anti-malarial [15], and anti-inflammatory agents [16]. Notably, acridinediones have demonstrated promising anti-malarial and anti-tumor activities [17-19]. Furthermore, derivatives of hexahydroacridine-1,8-dione have been found to exhibit significant qualities such as high fluorescence efficiency [20]. Consequently, organic chemists continue to show great interest in the synthesis and structural modification of hydroacridinone derivatives. It has also been observed that introducing substituted groups to the nitrogen atom of hexahydroacridine-1,8-diones enhances their fluorescence activity [21-22].

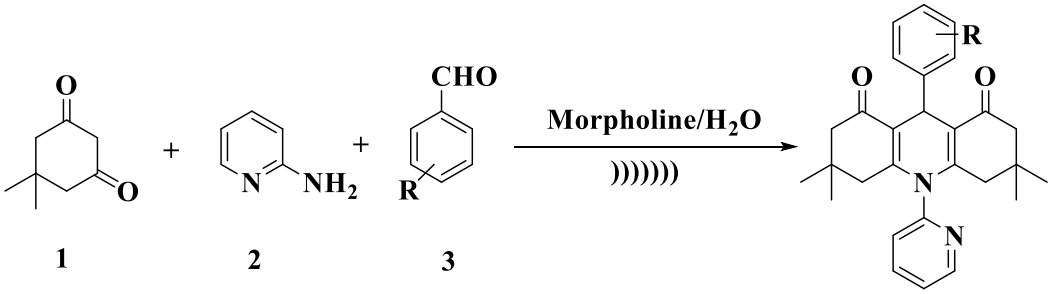
In summary, hexahydroacridine-1,8-dione represents a captivating compound with immense potential in the fields of medicinal chemistry and materials science. Its unique molecular structure, coupled with its pharmacological activities and applicability in organic electronics, positions it as a compelling target for exploration and utilization across various scientific disciplines. In this study, we have undertaken the synthesis of hexahydroacridine-1,8-dione derivatives, focusing on optimizing reaction conditions, and conducting thorough evaluations of their pharmaceutical activities, including antibacterial and antifungal properties. By systematically exploring the structure-activity relationships of these derivatives, we aim to contribute to the development of novel compounds with enhanced therapeutic potential and broaden our understanding of the pharmacological properties associated with hexahydroacridine-1,8-dione-based scaffolds.

EXPERIMENTAL:

We used solvents and reagents that could be purchased commercially. All of the chemicals and solvents required for the synthesis were provided by Merk Ltd., S D Fine Chemicals Ltd., and LOBA Chemie. Here, the open end capillary technique is used to determine each melting point without making any corrections. TLC plates used for monitoring the completion of reaction were purchased from Merk (TLC silica gel 60 F254). The IR spectral data were measured using Bruker FT-IR alpha-t (ATR).Using TMS as an internal standard, the 1H NMR and 13C NMR spectra were captured at 400 MHz and 100 MHz on the Bruker Avance instrument, respectively. Shimadzu mass spectrometer was utilized for the mass spectral analysis. The Perkin-Elmer 2400 CHN analyser was used to do the elemental analysis.

General procedure for 3,3,6,6-tetramethyl-9-aryl-10-(pyridine-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione

A mixture of dimedone (20 mmol), 2-amino pyridine (10 mmol) and substituted aromatic aldehyde (10 mmol) in water (10–15 mL) with morpholine (5 mmol) as a catalyst was treated with ultrasound (33 kHz) at room temperature (30 °C). The mobile phase was *n*-hexane/ethyl acetate (60 : 40 v/v) and TLC was employed to detect reaction completion. The final product was filtered, washed with water (5 mL), dried, and recrystallised from ethanol.



1 **2** **3** **4a-h**

Where R = -H
= 3-OH
= 4-OH
= 2-OH
= 3-Cl
= 4-Cl
= 4-NO_2
= 4-$N(CH_3)_2$

ANALYTICAL DISCUSSION:

Synthesis of 3,3,6,6-tetramethyl-9-phenyl-10-(pyridine-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (4a)

White solid (80% yield), m.p. 102°C. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.00-8.50 (m, 9H, Ar), 4.80 (s, 1H, *CH), 1.90 (s, 4H, CH_2), 1.55 (s, 4H, CH_2), 1.02 (s, 12H, CH_3). ^{13}C NMR (100 MHz, DMSO-d6) δ 194.0, 148.2, 147.8, 146.5, 141.0, 139.7, 128.6, 125.7, 123.9, 117.6, 111.4, 51.5, 44.6, 32.9, 30.4, 25.4; IR: 3000, 2985, 1750, 1660, 1485. MS (m/z): 426.56. Anal cald for $C_{28}H_{30}N_2O_2$: C, 78.84; H, 7.09; N, 6.57. Found: C, 77.54; H, 6.28; N, 6.23.

Synthesis of 9-(3-hydroxyphenyl)-3,3,6,6-tetramethyl-10-(pyridine-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (4b)

Off white solid (75% yield), m.p. 118°C. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.29 (s, 1H, OH), 6.87-8.00 (m, 8H, ArH), 4.55 (s, 1H, CH), 2.05 (s, 4H, CH_2), 1.78 (s, 4H, CH_2), 1.02 (s, 12H, CH_3). ^{13}C NMR (100 MHz, DMSO-d6) δ 199.2, 155.3, 149.2, 147.3, 146.9, 143.2, 138.5, 130.6, 123.6, 122.6, 117.6, 114.9, 112.3, 110.6, 51.3, 44.4, 33.9, 27.3; IR: 3550, 2950, 1745, 1665, 1444. MS (m/z):442.56. Anal cald for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 75.45; H, 6.78; N, 6.22.

Synthesis of 9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-10-(pyridine-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (4c)

White solid (85% yield), m.p. 125°C. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.00 (s, 1H, OH), 6.74-8.20 (m, 8H, ArH), 4.75 (s, 1H, CH), 2.22 (s, 4H, CH_2), 1.45 (s, 4H, CH_2), 1.00 (s, 12H, CH_3). ^{13}C NMR (100 MHz, DMSO-d6) δ 197.5, 152.8, 148.8, 147.9, 146.3, 144.5, 139.7, 130.6, 125.8, 121.1, 117.7, 115.8, 113.7, 109.3, 52.4, 43.5, 30.6, 26.4; IR: 3545, 2995, 1756, 1648, 1430. MS (m/z):442.56. Anal cald for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 75.22; H, 6.67; N, 6.19.

Synthesis of 9-(2-hydroxyphenyl)-3,3,6,6-tetramethyl-10-(pyridine-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (4d)

White solid (78% yield), m.p. 133°C. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.70 (s, 1H, OH), 6.57-7.89 (m, 8H, ArH), 4.57 (s, 1H, CH), 2.45 (s, 4H, CH_2), 1.73 (s, 4H, CH_2), 1.06 (s, 12H, CH_3). ^{13}C NMR (100 MHz, DMSO-d6) δ 198.4, 150.7, 147.9, 146.5, 145.7, 143.6, 139.1, 130.8, 126.7, 123.2, 117.6, 114.1, 113.7, 110.8, 54.3, 44.9, 32.6, 25.8; IR: 3559, 2956, 1748, 1653,

1422. MS (m/z):442.56. Anal cald for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 75.84; H, 6.72; N, 6.27.

Synthesis of 9-(3-chlorophenyl)-3,3,6,6-tetramethyl-10-(pyridine-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (4e)

Light yellow solid (73% yield), m.p. 155°C. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.00-8.64 (m, 8H, ArH), 4.85 (s, 1H, CH), 2.09 (s, 4H, CH_2), 1.75 (s, 4H, CH_2), 1.08 (s, 12H, CH_3). ^{13}C NMR (100 MHz, DMSO-d6) δ 194.2, 148.6, 146.7, 143.8, 138.6, 134.9, 128.5, 125.7, 124.6, 118.9, 115.7, 108.3, 55.9, 43.7, 32.5, 25.6; IR: 2987, 1736, 1654, 1432. MS (m/z): 461.00. Anal cald for $C_{28}H_{29}ClN_2O_2$: C, 72.95; H, 6.34; N, 6.08. Found: C, 72.58; H, 6.28; N, 5.57.

Synthesis of 9-(4-chlorophenyl)-3,3,6,6-tetramethyl-10-(pyridine-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (4f)

Light yellow solid (76% yield), m.p. 168°C. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.30-8.47 (m, 8H, ArH), 4.73 (s, 1H, CH), 2.54 (s, 4H, CH_2), 1.84 (s, 4H, CH_2), 1.03 (s, 12H, CH_3). ^{13}C NMR (100 MHz, DMSO-d6) δ 196.3, 148.1, 147.6, 146.2, 142.7, 138.4, 131.5, 130.6, 128.3, 117.6, 110.8, 56.7, 44.5, 33.9, 26.6; IR: 2990, 1765, 1629, 1418. MS (m/z): 461.00. Anal cald for $C_{28}H_{29}ClN_2O_2$: C, 72.95; H, 6.34; N, 6.08. Found: C, 72.69; H, 6.21; N, 6.03.

Synthesis of 3,3,6,6-tetramethyl-9-(4-nitrophenyl)-10-(pyridine-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (4g)

Yellow solid (77% yield), m.p. 203°C. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.00-8.17 (m, 8H, ArH), 4.69 (s, 1H, CH), 2.56 (s, 4H, CH_2), 1.95 (s, 4H, CH_2), 1.08 (s, 12H, CH_3). ^{13}C NMR (100 MHz, DMSO-d6) δ 196.6, 150.8, 148.9, 147.2, 146.7, 144.6, 138.9, 127.4, 117.3, 111.5, 52.9, 36.3, 31.0, 26.8; IR: 2980, 1784, 1632, 1420. MS (m/z): 471.56. Anal cald for $C_{28}H_{29}N_3O_4$: C, 71.32; H, 6.20; N, 8.91. Found: C, 71.20; H, 6.00; N, 8.45.

Synthesis of 9-(4-(dimethylamino)phenyl)-3,3,6,6-tetramethyl-10-(pyridine-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (4h)

Yellow solid (80% yield), m.p. 215°C. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.52-8.00 (m, 8H, ArH), 4.95 (s, 1H, CH), 3.00 (s, 6H, CH_3), 2.08 (s, 4H, CH_2), 1.83 (s, 4H, CH_2), 1.00 (s, 12H, CH_3). ^{13}C NMR (100 MHz, DMSO-d6) δ 197.3, 148.7, 148.3, 146.8, 145.2, 144.9, 139.5, 126.4, 123.8, 118.6, 111.1, 50.6, 45.8, 41.7, 35.5, 32.4, 28.0. MS (m/z): 469.63. Anal cald for $C_{30}H_{35}N_3O_2$: C, 76.73; H, 7.51; N, 8.95. Found: C, 76.55; H, 7.23; N, 8.74.

RESULT AND DISCUSSION:

Comparison of solvents

The formation of titled derivatives was synthesized using Dimedone, 2-amino pyridine and different substituted aldehyde in 2:1:1 stoichiometric ratio. Morpholine is used as a catalyst and water is used as a green solvent. To determine the ideal solvent, a reaction was created as a model, and it is shown in Table No. 1.

Table 1: The use of different solvents for the reaction of dimedone 1, 2-amino pyridine 2 and 4-hydroxy benzaldehyde to afford 9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-10-(pyridine-2-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (4c)

No.	Solvent	Time(min)	Yield%
1	Solvent free	10	None
2	Water	04	85
3	Ethanol	07	76
4	Methanol	08	70
5	Acetone	10	60
6	n-Hexane	19	-
7	Toluene	20	-

Table 2. **Effect of amount of catalyst in the synthesis of the product 4c**

No.	**Amount of morpholine**	**Time(min)**	**Yield %**
1	Trace	02	Trace
2	5	04	85
3	10	06	80
4	15	07	73
5	20	08	69
6	25	08	65
7	30	08	61

Table 3. Effect of time in the synthesis of the product 4c

No.	Solvent	Time(min)	Yield%
1	Water	04	85
2	Water	05	79
3	Water	10	74
4	Water	15	68
5	Water	20	62

Table 4. Effect of temperature in the synthesis of the product 4c

No.	Solvent	Temperature(˚C)	Time(min)	Yield%
1	Water	30	04	85
2	Water	40	06	81
3	Water	50	06	76
4	Water	60	07	71
5	water	70	08	66

PHARMACOLOGY:

Antibacterial activity

Gram-positive bacteria *Bacillus subtilis* and gram-negative bacteria *Escherichia coli* were used for antimicrobial activity testing of the newly synthesized compounds 4a-h at different concentrations, with chloramphenicol used as a standard drug for comparison of antibacterial activity of the synthesised novel compounds. In comparison to the standard drug chloramphenicol, only three derivatives (4c (4-OH), 4f (4-Cl) and 4g (4-NO_2) demonstrated very good activity against gram positive bacteria *Bacillus subtilis* at concentrations of 1000, 500, and 250 µg/ml. Other derivatives performed good against gram-positive bacteria when compared to the standard, as shown in Table 5.

The novel synthesised compounds were tested against gram-negative bacteria *Escherichia coli* at different concentrations of 1000, 500, 250 µg/ml, and only three compounds (4c (4-OH), 4f (4-Cl) and 4g (4-NO_2) were found to have good activity against gram-negative bacteria *Escherichia coli* when compared to standard drug. Other derivatives performed good against gram negative bacteria when compared to the standard, as shown in Table 5.

Antifungal activity

The newly synthesized compounds were tested for antifungal activity against *Aspergillus niger* at concentrations of 1000, 500, 250 µg/ml. Fluconazole was used as a control drug to compare and assess the antifungal activity of the synthesized compounds. At different concentrations, compounds (4c (4-OH), 4f (4-Cl) and 4g (4-NO_2) demonstrated excellent activity

when compared to the standard drug. Othe derivatives performed good against the standard drug fluconazole reported in Table 5.

SAR study-Structure Activity Relationship

SAR studies revealed that the presence of an electron-withdrawing group on the benzene ring increased antimicrobial activity, while the presence of electron releasing atoms or groups decreased activity. Specifically compounds with a nitro group, hydroxy group and chloro group in position 4 of the benzene ring significantly increased potency against different panel of microbial strains. The use of electron withdrawing group on the benzene ring in basic structures was worthy. Compounds bearing 4-OH,4-Cl and 4-NO_2 exhibited more pronounced activity.

Table: 5 Zone of Inhibition (ZOI) Values of Newly Synthesized Compounds 4_{a-h}

-R (Derivatives)	**Zone of Inhibition (mm)**								
	B. subtilis **(Gram-positive bacteria)**			***E. coli*** **(Gram-negative bacteria)**			***A.niger*** **(Fungi)**		
	1000 *µg/ml*	**500 *µg/ml***	**250 *µg/ml***	**1000 *µg/ml***	**500 *µg/ml***	**250 *µg/ml***	**1000 *µg/ml***	**500 *µg/ml***	**250 *µg/ml***
4a	19	16	12	19	17	14	18	13	10
4b	20	15	13	18	17	14	18	15	12
4c	**23**	**17**	**14**	**21**	**18**	**14**	**20**	**14**	**10**
4d	18	14	12	17	15	12	14	11	9
4e	17	15	-	16	10	-	11	9	-
4f	**23**	**18**	**15**	**15**	**13**	**11**	**20**	**15**	**13**
4g	**22**	**16**	**15**	**16**	**14**	**11**	**21**	**15**	**13**
4h	15	12	10	14	11	9	13	10	9
Fluconazole							**22**	**22**	**21**
Chloramphenicol	**30**	**28**	**27**	**30**	**28**	**27**			

CONCLUSION:

We created a green method for the one-pot multicomponent reaction using water as a green solvent to create hexahydroacridine-1,8-dione derivatives. This technology has the advantages of higher product yields, quicker reaction times, and simplicity of setup. Finally, the green approach produces a high yield in a short time. This result showed that optimization studies, which offer data on a variety of solvents, time, temperature, and base quantity, among other things, were successful. Finally, we determine that utilising water as a solvent delivers the greatest results in this procedure.

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