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RESEARCH ARTICLE

NOVEL SYNTHESIS OF ANTI-CANCER ACTIVE ARYL SUBSTITUTED ACRIDINEDIONE DERIVATIVES BY ONEPOT

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ABSTRACT

Nearly twenty four acridinedione derivatives are prepared by thermal method using P_2O_5 / ethanol catalyst. The same compounds are prepared by solvent free green approach involves the exposure of neat reactants to microwave irradiation of three component reaction of dimedone, aromatic aldehydes and amines in a stoichiometric ratio 2:1:1 for few minutes afforded the formation of stable acridinedione derivatives in an excellent yield (80-95%). The structure of all the products has been characterized by IR, ^{1}H, ^{13}C NMR and mass spectral studies. The percentage of yield and purity is compared and found to be excellent in greener method and this method is found to be environmental friendly.

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INTRODUCTION

Microwave irradiation can be used as a facile and general method for the construction of a wide variety of acridine derivatives. Multi-component reactions (MCRs) are a promising and vital field of chemistry because the synthesis of complicated molecules can be achieved in a very fast, efficient and time saving manner without the isolation of any intermediate. These reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single step. In recent years, the discovery of MCRs has become an increasingly active area of research yielding novel chemical scaffolds for drug discovery. Thus the development of new multicomponent reaction is a popular area of research in current organic chemistry (Menendez, 2006). In the past decade there have been tremendous development in three and four component reactions and great efforts continue to be made to develop new MCRs (Bagley, 2002; Bertozzi, 2002; Huma, 2002). It is well documented that the acridinediones are of great importance both in organic synthesis and in biological chemistry (Murugan, 1998; Thull, 1994). Synthetic methods for these compounds have been developed to a great extent, including conventional thermal reactions (Martin, 1993; Rajanarendran, 2011), microwave irradiation reaction (Tu, 2004; HVA, 2005) by using catalysts P_2O_5 and Amberolite[7]. Acridinedione derivatives have a wide spectrum of biological activities such as antibacterial, antimalarial, anticancer and mutagenic properties. Acridine

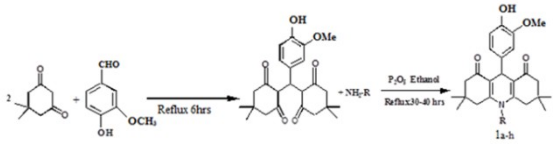
systems have attracted considerable attention due to their potential pharmacological activity and there are many industrial applications for acridines (Albert, 1996; Ramamurthy, 1996; Ramamurthy, 1998). A three-component Hantzsch-type condensation of different anilines with dimedone and benzaldehye leads to the formation of a unique acridine derivative with an unusual breaking of a C-N bond. The reaction was also carried out employing rapid microwave or conventional heating and sonication as alternative energy source[9]. Because of its biological activity and applications, our interest is to synthesize new acridinedione derivatives. The interaction between microorganism with plants and animals are natural and constant.

Many chemicals kill or prevent the growth of microorganisms. Such chemicals have been called antimicrobial agents[16]. Concentration and contact time are critical factors that determine the effectiveness of an antimicrobial agent against a particular microorganism. Microorganisms vary in their sensitivity to particular antimicrobial agents. Many antimicrobial agents block active metabolism and prevent the organism generating the macro molecular constituents needed for reproduction. The important of heterocyclic chemistry in biological system as well as in chemotherapy is well established[6, 10, 11, 17]. Acridines the earliest known antibiotics[1, 2, 8] are toxic towards bacteria and particularly towards malarial parasites due to their ability to inhibit DNA and RNA synthesis. In continuation of our interest in the synthesis of biologically active acridinediones, it was considered worthwhile to evaluate antimicrobial activity of some new acridinediones.

MATERIALS AND METHODS

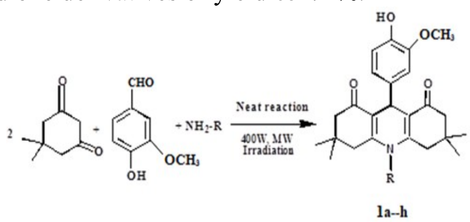
All the melting points are uncorrected; IR spectra were recorded on FTIR – 8300 shimadzu spectrometer. ^{1}H NMR spectra were recorded on Jeol- FXQ (90 MHz), Jeol GSX (400 MHz) and DPX 200 (200 MHz). Mass spectra were recorded on Jeol- JMS- DX 303hf.

Synthesis of 9-Aryl substituted acridinedione derivatives 1a-h



Scheme 1. Thermal method

Two equivalents of dimedone with benzaldehyde were refluxed for 6 hours the tetra ketone compound is obtained. The structure of the tetra ketone is identified by ^{1}H NMR studies. This tetra ketone compound is refluxed with amine substituents for 30-40 hours in thermal condition in presence of P_2O_5 and excess ethanol. It gives the substituted acridinedione derivatives of yield 65-72%.



Neat reaction: Hantzsh condensation of dimedone, benzaldehyde and substituents (2:1:1) in a solvent free conditions (neat reaction) is treated on microwave irradiation for 10 minutes afforded the formation of the orange solid mass of acridinedione derivative of an excellent yield (85-92%). Various substituted acridinediones were prepared and reported below.

RESULTS AND DISCUSSION

Chemical and pharmaceutical industries are facing constraints regarding environmental aspects and saving energy. To overcome such problems in organic synthesis, the microwave (MW) irradiation as a source of energy is used.

Table 1. Amine Substituents (R) used for the synthesis of acridinedione derivatives

Compounds	R
1a	$NHCOCH_2NH_2$
1b	$NHCOCH(CH_3)NH_2$
1c	$NHCOC\ H(CH_2C_6H_5)NH_2$
1d	$NHCOCH(NH_2)(CH_2)_3NHC(NH_2)_2$
1e	$NHCOCH(NH_2)CH_2(OH)$
1f	$NHCOCH(NH_2)CH_2CH(CH_3)_2$
1g	$NHCOCH(NH_2)CH_2CH_2CH_3$
1h	$NH(CO(NH_2)CH_2S)_2$

In this study we use an excellent synthetic method for new decahydroacridine-1,8-dione derivatives 1a-h through three component condensation reactions by microwave technique. The employed amines exhibit an excellent substrate for synthesis of acridinediones under our reaction conditions.

Characterization 2, 2’-(benzylidene) bisdimedone: ^{1}H NMR: δ 1.98, 2.56 (Gem dimethyl, 2d), 2.35 (1, 3, 7, 8, CH_2,m), 6.9 – 7.8 (Ar-H, m), ^{13} C-NMR: δ 28.5, 31.0, 33.6, 40.39(aliphatic carbons), 112.2, 155.8 (olefinic carbons), 114.1, 122.5, 129.7, 131.6, 136.8 (aryl carbons), 196.7 (ketocarbonyl)

10-Glycine- (3-methoxy-4-hydroxy)-9-Phenyl-3,3,6,6-tetramethy l-3, 4, 6,7, 9, 10- hexahydro-1,8-(2H,5H)-acridinedione: (1a): Hantzsh condensation of two equivalents of dimedone (3.08g, 0.022m) with glycine hydrazide (1g, 0.011m), 4-hydroxy-3-methoxy benzaldehyde (1.67g, 0.011m) in solvent free condition, is treated on microwave irradiation for 3 minutes. The formation of yellow solid confirm acridinedione derivative **(**1a**),** in an excellent yield.^{1}H NMR = δ 0.98-1.10 (gem dimethyl), 2.14-2.25 (d, 4H, C2&C4), 2.46 (m, -CH), 3.12 ($-OCH_3$), 4.74 (s, $CH-NH_2$), 7.08-7.29 (m, Ar-H).^{13}C NMR = δ 27.35, 29.31, 31.85, 32.24, 40.89, 50.76 (aliphatic carbons), 115.69 (olefinic carbon), 126.40, 128.08, 128.40, 144.11 (aryl carbons), 162.29 (amide carbon), 196.47 (keto carbon). IR: 1520, 1665, 1703, 3307 cm^{-1}. Mass: m/z=468, 467.

10- Alanine- (4-hydroxy-3-methoxy)-9- Phenyl-3,3,6,6-tetramethyl- 3, 4, 6, 7, 9, 10-hexahydro-1,8-(2H,5H)-acridinedione: (1b): The microwave irradiation of two equivalents of dimedone (2.71g, 0.019m) with alanine hydrazide (1g, 0.009m), 4-hydroxy-3-methoxy benzaldehyde (1.47g, 0.009m) in solvent free condition, is treated for 3 minutes. The formation of orange solid confirm acridinedione derivative **(**1b**),** in an excellent yield.^{1}H NMR = δ 1.0-1.10 (gem dimethyl), 2.16-2.27 (d, 4H, C2&C4), 2.45 (m, -CH), 3.89 (s, OCH_3), 4.65 (s, $CH-NH_2$), 6.58-7.26 (m, Ar-H).^{13}C NMR = δ 27.30, 28.27, 28.34, 29.34, 30.97, 31.33, 32.24, 40.88, 50.78, 54.15, 55.91, 57.35 (aliphatic carbons), 115.83 (olefinic carbon), 120.04, 136.47, 144.02, 145.90 (aryl carbon), 162.18 (amide carbon), 196.76 (keto carbonyl). IR: 1520, 1665, 1703, 3307 cm^{-1}. Mass: m/z= 482, 481.

(4-hydroxy-3-methoxy)-9-Phenyl-10-phenylalanine-3, 3, 6, 6-tetramethyl- 3, 4, 6, 7, 9, 10-hexahydro-1,8-(2H,5H)-acridinedione: (1c): Hantzsh condensation of two equivalents of dimedone (1.4g, 0.010m) with phenyl alaninehydrazide (1g, 0.005m), 4-hydroxy-3-methoxy benzaldehyde (0.76g, 0.005m) in solvent free condition, is treated on microwave irradiation for 4 minutes. The formation of yellow solid confirm acridinedione derivative **(**1c**),** in an excellent yield.^{1}H NMR = δ 0.98-1.168 (gem dimethyl), 2.14-2.25 (d, 4H, C2&C4), 2.46 (m, -CH), 3.08 (s, OCH_3), 4.74 (s, $CH-NH_2$), 7.09-7.53 (m, Ar-H).^{13}C NMR = δ 27.37, 28.15, 29.33, 31.86, 32.93, 40.93, 50.77 (aliphatic carbons), 115.70 (olefinic carbon), 126.42, 128.09, 128.41, 128.49, 128.94, 129.06, 129.52, 129.81, 130.16, 133.57, 144.10 (aryl carbons), 162.33 (amide carbon), 196.53 (keto carbonyl). IR: 1520, 1665, 1703, 3307 cm^{-1}. Mass: m/z= 558, 557.

10-Arginine-(4-hydroxy-3-methoxy)-9-Phenyl-3, 3, 6, 6-tetramethyl-3, 4, 6, 7, 9, 10-hexahydro-1,8-(2H,5H)-acridinedione: (1d): The microwave irradiation of two equivalents of dimedone (1.4g, 0.010m) with arginine hydrazide (1g, 0.005m), 4-hydroxy-3-methoxy benzaldehyde (0.76g, 0.005m) in solvent free condition, is treated for 3 minutes. The formation of reddish orange solid confirm acridinedione derivative (1d), in an excellent yield.^{1}H NMR = δ 1.0-1.10 (gem dimethyl), 2.17-2.21 (d, 4H, C2&C4), 2.46 (m, -CH), 3.88 (s, OCH_3), 4.65 (s, CH-NH_2), 6.5-7.30 (m Ar-H).^{13}C NMR = δ 27.28, 29.34, 30.97, 31.26, 32.19, 40.88, 50.80, 55.95 (aliphatic carbons), 115.79 (olefinic carbon), 120.13, 136.34, 144.15, 146.09 (aryl carbons), 162.16 (amide carbon), 196.65(keto carbon). IR: 1520, 1665, 1703, 3307 cm^{-1}. Mass: m/z= 568, 567.

Table 2. Comparison of Thermal and Microwave method (Yield and reaction time of acridinedione derivatives)

Compound	R	Thermal method (Hrs.)	Yield %	Micro wave method (min)	Yield %	Melting point ^{0}C
1a	$NHCOCH_2NH_2$	35	65	3	91	208-210
1b	$NHCOCH(CH_3)NH_2$	34	56	4	92	180-182
1c	$NHCOC\ H(CH_2C_6H_5)NH_2$	37	62	3	89	175-177
1d	$NHCOCH(NH_2)(CH_2)_3NHC(NH_2)_2$	31	60	5	88	184-186
1e	$NHCOCH(NH_2)CH_2(OH)$	30	70	6	92	198-200
1f	$NHCOCH(NH_2)CH_2CH(CH_3)_2$	39	65	5	90	213-215
1g	$NHCOCH(NH_2)CH_2CH_2CH_3$	35	69	4	91	167-169
1h	$NH(CO(NH_2)CH_2S)_2$	32	68	6	92	192-195

Table 3. Antimicrobial activity of the synthesized 9-Aryl Acridinedione compounds

Compound	Conc. (µ.g/well) In DMF	Zone of inhibition in mm*					
		Antibacterial activity				Antifungal activity	
		P. aeruginosa	*E. coli*	*S. pyogenes*	*S. aureus*	*C. albicans*	*A.flavus*
1a	600	8	10	11	8	9	9
1b	600	10	8	10	9	8	10
1c	600	9	10	9	7	7	8
1d	600	11	9	9	10	9	7
1e	600	12	8	8	11	8	9
1f	600	9	10	10	9	7	11
1g	600	8	11	7	12	9	9
1h	600	10	9	11	8	7	8
Gentamycin	600	18	17	17	17	-	-
Ketaconozole	600	-	-	-	-	17	19
*Diameter of well (bore size) – 6mm							

(4-hydroxy- 3- methoxy)- 9-Phenyl-10-serine-3, 3, 6, 6-tetramethyl-3, 4, 6, 7, 9, 10- hexahydro-1,8-(2H,5H)-acridinedione: (1e): The microwave irradiation of two equivalents of dimedone (2.24g, 0.016m) with serine hydrazide (1g, 0.008m), 4-hydroxy-3-methoxy benzaldehyde (1.21g, 0.008m) in solvent free condition, is treated for 5 minutes. The formation of pale red solid confirm acridinedione derivative **(1e),** in an excellent yield.^{1}H NMR = δ 1.0-1.10 (gem dimethyl), 2.20-2.26 (d, 4H, C2&C4), 2.46 (m, -CH), 3.87 (s, OCH_3), 4.66 (s, CH-NH_2), 6.58-6.98 (m, Ar-H). ^{13}C NMR = δ 27.34, 29.39, 31.31, 32.21, 40.94, 50.84, 56.01 (aliphatic carbons), 115.82 (olefinic carbon), 120.14, 136.39, 144.11, 146.01 (aryl carbons), 162.22 (amide carbon), 196.74 (keto carbon). IR: 1520, 1665, 1703, 3307 cm^{-1}. Mass: m/z= 498, 497.

(4-hydroxy-3- methoxy)- 10-leucine-9- Phenyl-3,3,6,6-tetramethyl- 3, 4, 6, 7, 9, 10- hexahydro-1,8-(2H,5H)-acridinedione: (1f): Hantzsh condensation of two equivalents of dimedone (1.4g, 0.01m) with leucine hydrazide (1g, 0.005m), 4-hydroxy-3-methoxy benzaldehyde (1.03g, 0.005m) in solvent free condition, is treated on microwave irradiation for 6 minutes. The formation of yellow solid confirm acridinedione derivative (**1f**), in an excellent yield.^{1}H NMR = δ 1.0-1.10 (gem dimethyl), 2.15-2.26 (d, 4H, C2&C4), 2.46 (m, CH), 3.88 (s, OCH3), 4.65 (s, CH-NH2), 6.57-7.29(m, Ar-H).^{13}C NMR = δ 27.27, 29.33, 31.28, 32.21, 39.65, 39.86, 40.07, 40.28, 40.49, 40.85, 50.77, 55.90 (aliphatic carbons), 115.79 (olefinic carbon), 120.08, 136.38, 144.09, 146.02 (aryl carbons), 162.17 (amide carbon), 196.71 (keto carbonyl). IR: 1520, 1665, 1703, 3307 cm^{-1}. Mass: m/z= 524, 523.

(4-hydroxy-3-methoxy)-9-Phenyl- 3, 3, 6, 6- tetramethyl-3, 4, 6, 7, 9, 10- hexahydro-1,8-(2H,5H)-10-valine acridinedione: (1g): Hantzsh condensation of two equivalents of dimedone (2.12g, 0.015m) with valinehydrazide (1g, 0.0076m), 4-hydroxy-3-methoxy benzaldehyde (1.15g, 0.0076m) in solvent free condition, is treated on microwave irradiation for 4 minutes. The formation of reddish yellow solid confirm acridinedione derivative (**1g**), in an excellent yield.^{1}H NMR = δ 1.0-1.10 (gem dimethyl), 2.16-2.26 (d, 4H, C2&C4), 2.45 (m, -CH), 3.89 (s, OCH_3), 4.66 (s, CH-NH_2), 6.56- 7.26 (m, Ar-H).^{13}C NMR = δ 27.31, 28.27, 29.35, 31.33, 32.24, 40.88, 50.79, 54.16, 55.92, 57.34 (aliphatic carbons), 115.83 (olefinic carbon), 120.03, 136.49, 144.01, 145.87 (aryl carbons), 162.14 (amide carbon), 196.70 (keto carbonyl). Mass: m/z= 510, 509.

10-Cystine-(4-hydroxy-3-methoxy)-9- phenyl-3, 3, 6, 6-tetramethyl-3, 4,6, 7, 9, 10-hexahydro-1, 8-(2H,5H)-acridinedione: **(1h):** The microwave irradiation of two equivalents of dimedone (1.0g, 0.008m) with cystinehydrazide (1g, 0.004m), 4-hydroxy-3-methoxy benzaldehyde (0.60g, 0.004m) in solvent free condition, is treated for 6 minutes. The formation of pale orange solid confirm acridinedione derivative (**1h**), in an excellent yield.^{1}H NMR = δ 1.0-1.10 (gem dimethyl), 2.16-2.22 (d, 4H, C2&C4), 2.45 (m, -CH), 3.96 (s, OCH_3), 4.65 (s, CH-NH_2), 6.56-7.26 (m, Ar-H).^{13}C NMR = δ 27.31, 28.28, 28.40, 29.35, 30.97, 31.34, 32.24, 40.89, 50.79, 54.15, 55.93, 56.16, 57.35 (aliphatic carbons), 115.83 (olefinic carbons), 120.04, 136.47, 144.02, 145.90 (aryl carbons), 162.19 (amide carbon), 196.77 (keto carbonyl). IR:

1520, 1665, 1703, 3307 cm^{-1}. Mass: m/z= 616, 615. Biological studies of 9 -Aryl acridinedione derivatives: Antibacterial activity testing is done by well diffusion method. The nutrient agar medium is used, and the solvent is Chloroform of concentration ranging from 50 and 100µL. The acridinedione derivatives were screened *in vitro* for their potency against bacterial strains such as *S. aureus, E. coli, P. aeruginosa,* and *S. pyogenes*and fungal strains such as *C. albicans*and *A. flavus*. The *in vitro* activities of the test compounds were studied using agar plates containing Sabourauds dextrose broth for fungi and in Nutrient broth (Himedia, Mumbai) for bacteria. Three fixed concentrations of the test compounds were tested against each microbial species. The antibacterial and antifungal potencies of the test compounds were compared with gentamycin (bacteria) and ketaconozole (fungi). The relative antimicrobial potencies of test compounds are expressed as the area of zone of inhibition and summarized in Table 3. A clear distinction between the in vitro antibacterial and antifungal activity profiles of the acridinedione derivatives (1a-h) is that all the derivatives display very good antibacterial and antifungal activity.

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