IJMPR 2023, 7(6), 85-89

International Journal of Modern Pharmaceutical Research

www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article

SJIF Impact Factor: 5.273

AN EFFICIENT BIO ACTIVE SYNTHESIS OF N-SUBSTITUTED ACRIDINE ANALOGOUS

L. Rama Lakshmi, B. Pryanka and Dr. N. Krishna Rao*

PRISM PG & DG College (Affiliated to Andhra University), Visakhapatnam, India.

Received on: 11/04/2023
Revised on: 01/05/2023
Accepted on: 21/05/2023

***Corresponding Author**
Dr. N. Krishna Rao
PRISM PG & DG College (Affiliated to Andhra University), Visakhapatnam, India.

ABSTRACT

The highly versatile and an efficient synthesis of N-alkyl derivatives of acridine 10-benzyl-9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione is by obtained from 9-(4-bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione with substituted (bromomethyl) benzene which is also three component cyclocondensation of 1,2-dicarbonyl compounds like dimedone, bromo benzaldehyde and ammonium chloride in the presence KIO_4 solvent free condition. All the compounds were confirmed by advanced spectroscopic data (1H NMR, 13C NMR& LCMS) and the structural determination of the novel derivations was calculated by elemental analysis. In the present study, ten hybridized imidazoles derivatives were synthesized via cyclo condensation and evaluated for their invitro antimicrobial activity.

KEYWORDS: Dimedone, bromobenzalehyde, KIO_4, 10-benzyl-9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione,9-(4-bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione, Anti-microbial activites.

INTRODUCTION

Multicomponent reactions were encouraged an outstanding status in synthetic organic and medicinal chemistry for their high degree of atom economy and application in the diversity oriented convergent synthesis of complex organic moiety from simple and readily available substrates in a single vessel. Acridine and its derivatives are important structural motifs possessing antimalarial, antiviral, and antiallergic properties,[1–3] acridines act as potent drugs for antitumor activity both in vitro and in vivo against a range of murine and human tumors.[4] They are also found to act as fluorescent molecular probes for monitoring polymerization processes.[5] and are used as -type semiconductors and in the electroluminescent devices. Recently fluorinated acridones are reported to possess anticancer activity.[6–9] There are a few reports in the literature on the three-component Hantzsch-type condensation of aromatic aldehydes, anilines, and dimedone via traditional heating in organic solvents.[10,11] under microwave irradiation,[12] and in ionic liquids.[13] The main drawbacks of these methods are the inability to synthesize profuse quantity of acridines using substituted anilines containing electron withdrawing groups.[14] Further, the reactions are carried out in refluxing organic solvents, which require higher temperature and longer hours for completion.[10,15] and unusual breaking of C–N bond takes place under certain reaction conditions as noticed in a few cases.[16] Hence, the exploration of a simple, efficient, and green method for the synthesis of acridines using electron-deficient amines and electron-deficient aldehydes is of current interest. In continuation with our work on one-pot multicomponent reactions under sonic condition.[17–19] we, herein, report the synthesis of a series of acridines by a one-pot four-component reaction as shown in Schemes 1.

2. METHODS

2.1. Materials and Instruments

All starting materials such as reagents, solvents and chemicals were commercial products were procured from Sigma Aldrich and were used without further purification except liquid aldehydes and benzyl bromide which were distilled before use. Melting points were measured on Agarwal thermometer make melting point apparatus. 1HNMR and 13CNMR spectra were obtained on 400 MHz and 100 MHz Bruker Avance instruments in $CDCl_3$ using TMS as a standard. Mass spectra were recorded using ESI-Q TOF instrument. Yields refer to yield of the isolated products.

2.2.1.GeneralProcedure9-(4-Bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro acridine-1,8(2H,5H)-dione

A mixture of 4-bromobenzaldehydes (1mmole), dimedone (2mmole) and Ammonium chloride (1.5mmole) and freshly prepared catalytic amount of KIO_4 in ethanol was taken in four neck 50mL RB flask. When the solution becomes clear, was added and the reaction mixture was refluxed for 3-4 hours. The reaction

was checked by TLC (5:5, ethyl acetate: n-hexane) after the completion of reaction. The reaction mixture was poured into crushed ice. The solution was neutralized with aqueous solution of sodium bi carbonate and product was extracted using ethyl acetate, the combined organic layer was washed using water and organic layer seperated. The organic layer was dried on anhydrous sodium sulphate and the solvent was removed under reduced pressure with using vacuum pump to get the solid product. All the titled compounds were recrystallized from ethanol.

Characterizationof9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahy droacridine-1,8(2H,5H)-dione

Paleredsolid,yields-91%.IR(KBr,$cm^{-1)}$:3293,2980,1666,16021HNMR(400Mz,$CDCl_3$)ppm :9.458(s,1H,NH),7.541-7.287 (m,4H,Ar-H),4.345(s,1H,-CH),3.985(s,1H,-CH-),2.162(s,2H,-CH_2), 1.653(s,2H,-CH_2),1.112(s,3H,CH_3), 0.987 (s,3H,-CH3);13CNMR(100MHz,$CDCl_3$)ppm: 196.85,146.08, 140.56,132.45,127.65, 124.48,119.05,116.87, 111.73 ,55.46,51.24,40.38,32.84. 28.09, 27.65.LCMS (m/z):429.04(M+2). Molecularformule: $C_{25}H_{31}NBrO_2$; Elemental Analaysis: CalculatedC-64.49, H-6.12, N-3.27. Obtained: C-64.40, H-6.10, N-3.35.

2.2.2.Geneneralprocedurerof10-benzyl-9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,6, 7,9,10-hexahydroacridine-1,8(2H,5H)-dione derivatives

A mixture 9-(4-bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dioneand substituted (bromomethyl)benzene is dissolved in triethylamine and methylene dichloride which is taken in four neck 50mL RB flask. When the solution becomes clear, was added and the reaction mixture was refluxed for 5 hours. The reaction was monitored by TLC (3:7, ethyl acetate: n-hexane) after the completion of reaction. The reaction mixture was poured into crushed ice. The solution was neutralized with aqueous solution of sodium bi carbonate and product was extracted using ethyl acetate, the combined organic layer was washed using water and organic layer separated. The organic layer was dried on anhydrous sodium sulphate and the solvent was removed under reduced pressure with using vacuum pump to get the solid product. All the titled compounds were recrystallized from ethanol.

1.10-benzyl-9-(4-bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione

Palebrownsolidyield-88%,m.p 261-263^0C.1HNMR(400Mz,$CDCl_3$)ppm:7.810-7.713 (m,2H,Ar-H),7.345-7.273 (m,7H,Ar-H),4.435(s,1H,-CH-),.135(s,2H,-CH_2-),2.045(s,,2H,-CH_2-),1.528 (s,2H,-CH_2-),0.964(s,3H,-OCH_3),0.905 (s,3H-OCH_3).^{13}CNMR (100MHz, $CDCl_3$) ppm:195.76, 160.17, 140.38, 134.29, 130.04, 129.74, 127.15, 126.09, 124.74, 120.15, 112.09, 50.05, 42.16, 31.99, 30.24, 28.06, 27.85 .LCMS(m/z): 519.23(M+2). Molecular formulae: $C_{30}H_{32}BrNO_2$, .Elemental Analysis: Calculated C-69.50.,H-6.22,N-2.70. Obtained: C-69.41, H-6.20, N-2.79.

2.9-(4-bromophenyl)-10-(4-hydroxybenzyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro acridine-1,8(2H,5H)-dione

Pale Yellow solid yield-90%, m.p 269-271 0C.1HNMR (400Mz,CDCl3)ppm:8.842(s,1H,-OH), 7.804-7.715(m,2H,Ar-H), 7.328-7.294(m,4H,Ar-H), 7.125-6.964 (m,4H,Ar-H), 4.416(s,1H,-CH-) 2.156(s,2H,-CH_2-), 1.615 (s,2H,-CH_2-),0.956(s,3H,-CH_3-),0.845(s,3H,-CH_2-).13CNMR (100MHz,CDCl3)ppm:195.09, 159.74, 150.01, 141.56, 129.35, 129.06, 128.92, 128.54, 121.65, 119.48, 51.66, 40.26, 31.86, 28.09, 27.66.LCMS(m/z): 535.09(M+2). Molecular formulae: C30H32NO3Br .Elemental Analysis: Calculated C-67.42.,H-6.03,N-2.62. Obtained: C-67.34, H-6.01, N-2.71.

3.9-(4-bromophenyl)-10-(4-methoxybenzyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro acridine-1,8(2H,5H)-dione

White solid yield-91%,.1HNMR(400Mz,$CDCl_3$)ppm: 7.806-7.092(m,2H,Ar-H), 7.313-7.284 (m,2H,Ar-H), 7.145-6.645(m,4H,Ar-H), 4.567(s,1H,-CH-), 4.196 (s,2H,-CH_2-), 3.664(s,3H,-OCH_3),1.965(s,2H,-CH_2-), 0.946 (s,3H,-CH_3), 0.894(s,3H,-CH_3-).13CNMR (100MHz, $CDCl_3$) ppm:195.27, 158.45, 151.66, 141.08, 130.56, 129.87, 129.04, 128.76, 12765, 121.58, 110.55, 50.44, 41. 40.72, 32.67, 30.95, 28.07, 27.68.LCMS (m/z): 549.67(M+2). Molecular formulae: $C_{31}H_{34}Br\ NO_3$ .Elemental Analysis: Calculated C-67.88.,H-6.25,N-2.58. Obtained: C-67.82, H-6.23, N-2.67.

4.**9-(4-bromophenyl)-3,3,6,6-tetramethyl-10-(4-methylbenzyl)-3,4,6,7,9,10-hexahydro acridine-1,8(2H,5H)-dione**

White solid yield-92%, m.p-246-248 0C.1HNMR (400Mz,$CDCl_3$)ppm: 7.816-7.729(m,2H,Ar-H), 7.315-7.289(m,2H,Ar-H), 7.120-6.982(m,4H,Ar-H), 4.565 (m,2H,-CH-), 4.096(s,2H,-CH_2), 1.984(s,2H,-OCH_2), 1.635 (s,2H,-CH_2),0.973(s,3H,-CH3-),0.884 (s,3H,-CH_3). 13CNMR (100MHz, CDCl3)ppm: 194.38, 159.84, 140.45, 132.47, 131.04, 130.45, 128.94, 128.45, 110.39, 50.28, 41.36, 40.26, 30.56, 28.12, 27.88. LCMS(m/z): 533.27(M+2). Molecular formulae: $C_{31}H_{34}NBrO_2$ .Elemental Analysis: Calculated C-69.92.,H-6.44,N-2.63. Obtained: C-69.85, H-6.43, N-2.70.

5.**9-(4-bromophenyl)-3,3,6,6-tetramethyl-10-(4-nitrobenzyl)-3,4,6,7,9,10-hexahydro acridine-1,8(2H,5H)-dione**

Pale Red solid yield-89%, m.p-269-271 0C.1HNMR (400Mz,$CDCl_3$)ppm: 8.126-8.065(m,2H,Ar-H), 7.810.-7.626(m,4H,Ar-H), 7.326-7.296(m,2H,Ar-H), 4.567 (s,2H,-CH2-), 4.145(s,2H,-CH_2-),1.946(s,2H,-CH_2-), 1.674 (s,2H,-CH_2-), 0.967(s,3H,-CH_3-),0.874(s,3H,-CH_3-). 13CNMR (100MHz,$CDCl_3$)ppm: 195.67, 162.74, 141.76, 140.12, 138.68, 129.42, 128.74, 128.072, 128.32, 128.15, 121.76, 112.96, 52.64, 43.35, 40.15, 31.36, 28.09, 27.64 .LCMS(m/z): 564.25(M+2). Molecular

formulae: $C_{30}H_{31}N_3O_4$ Br .Elemental Analysis: Calculated C-63.95.,H-5.35,N-4.97. Obtained: C-63.86, H-5.33, N-5.08.

3. Biological Activity

3.1. Anti- Bacterial Activity

In vitro anti-bacterial activities of newly tested compounds are screened against four pathogenic bacteria strains. The results of the bacterial activity were examined for the compounds. The gram negative bacteria were examined Escherichia Coli Pseudomonas aeruginosa. The gram positive bacteria screened were S-aureas and Bacillus .The target compound's a solvent the streptomycin 10 µglml discs were used as a standard. The rest of the compounds were found to be moderate active against the tested micro- organism.

3.2.Anti- Fungal Activity

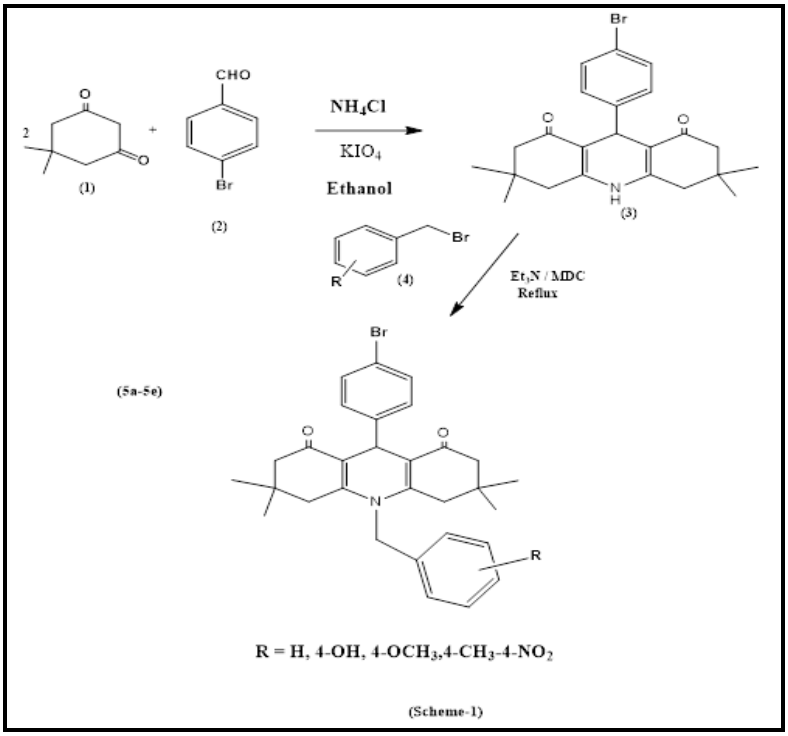
Anti- fungal activities of newly tested compounds were examined by disc diffusion method against the organism of AspergillusNiger and Candida albicans. The target compounds were used at the various concentration and average value and using DMSO as a solvent. The standard drug was used as ketoconazole 50 µglml against both organisms.

4. RESULT AND DISCUSSION

4.1. Chemistry

To a mixture of 3-nitro benzaldehyde (2mmol), dimedone (4mmol) and ammonium chloride (3mmol) and KIO_4 (4mmol) was added in 50ml round bottom flask and was stirred at 70^oC. This reaction is considered as model reaction. The progress of the reaction was monitored by TLC. After completion of the reaction the reaction mixture was cooled to room temperature and water (5 ml) was added, solid separated was filtered and product was obtained. It was characterized by IR, 1H NMR, 13C-NMR and mass.

All newly synthesized compounds can be synthesized under at RT condition. These target derivatives were obtained. The advantages of these catalysts can be used to accelerate the rate of reaction and reaction is completed maximum two hours. The rate of reaction enhanced by using these catalysts KIO_4. We used various substituted benzyl bromide electron releasing group of benzyl bromide and electron attracting group of benzyl bromide. The main focus of this process is cost effectiveness of catalyst, easy work-up and purification of products by non-chromatographic methods, good to excellent yields and very short time reactions.



(Scheme-1)

4.2. Biological Activity

All the titled compounds were examined by anti-bacterial activity as well as antifungal. Activity. The electron withdrawing group of compounds and electron releasing group compounds exhibited various potent activities. Therefore, electron withdrawing group of compounds exhibited low biological potent activity compared with electron releasing groups.The compound which possess electron donating group showed well to excellent activity as shown in Table-I.

Table-I: Antimicrobial activity screening activity synthesized scaffold.

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substill	A. Niger	C. albicans
4a	05	07	08	08	07	08
4b	13	12	14	16	09	08
4c	19	20	15	18	14	12
4d	18	20	20	19	15	16
4e	21	20	20	21	15	16
4f	10	11	07	08	09	08
streptomycin	25	25	22	22	NA	NA
Ketoconazole	NA	NA	NA	NA	20	20
DMSO	---	----	---	---	---	---

5. CONCLUSION

The reaction condition carried at 70^0C condition for all the newly titled derivatives. The yields of the titled compounds were obtained from 85-92%. This compound possesses electron releasing group acquired maximum highest yield than that of the compound possesses electron attracting group. The rates of the reaction of the titled derivatives are improved by using catalystKIO_4. All the derivatives are examined by anti- microbial activity against gram(+Ve), gram(-Ve) and fungal. Otherwise the compounds having electron releasing group which showed excellent potent active than that of the electron attracting group**.**

6. ACKNOWLEDGEMENTS

Authors are very thankful to PRISM PG&DG College and they were for providing all the necessary facilities.

7. REFERENCES

1. J. Zhu, H. Bienayme, Multicomponent Reactions, Wiley, Weinheim, 2005.
2. J. Safari, Z. Zarnegar, M. Heydarian, Practical, ecofriendly,and highly efficient synthesis of 2-amino-4H-chromenes usinnanocrystalline MgO as a reusable heterogeneous catalyst in aqueous media, J. Taibah Univ. Sci., 2013; 7: 17–25.
3. M.M. Heravi, K. Bakhtiari, V. Zadsirjan, F.F. Bamoharram,O.M. Heravi, Aqua mediated synthesis of substituted 2-amino4H-chromenes catalyzed by green and reusable Preyssleheteropolyacid, Bioorg. Med. Chem. Lett., 2007; 17: 4262–4265.
4. Korolkovas, Y. Takahata, Quantitativestructure–activity relationships of 1,4-dihydropyridine calciumchannel antagonists (nifedipine analogues): a quantum chemical/classical approach, J. Pharm. Sci., 1994; 83: 1110–1115.
5. H. Tanabe, S. Tasaka, H. Ohmori, N. Gomi, Y. Sasaki, T. Machida,M. Iino, A. Kiue, S. Naito, M. Kuwano, Newly synthesizedihydropyridine derivatives as modulators of P-glycoproteinmediated multidrug resistance, Bioorg. Med. Chem, 1994; 6(1998): 2219–2227.
6. S. Tasaka, H. Ohmori, N. Gomi, M. Iino, T. Machida, A. KiueS. Naito, M. Kuwano, Synthesis and structure–activity analysis of novel dihydropyridine derivatives to overcome multidruresistance, Bioorg. Med. Chem. Lett., 2001; 11: 275–277.
7. S. Girault, P. Grellier, A. Berecibar, L. Maes, E. Mouray, PLemiere, M. Debreu, E. Davioud-Charvet, C. Sergheraet, Antimalarial, antitrypanosomal, and antileishmanial activities ancytotoxicity of bis(9-amino-6-chloro-2-methoxyacridines): influence of the linker, J. Med. Chem, 2000; 43: 2646–2654.
8. S.A. Gamega, J.A. Spicer, G.J. Atwell, G.J. Finlay, B.C. Baguley, W.A. Deny, Structure–activity relationships for substitutebis(acridine-4-carboxamides): a new class of anti-cancer agents, J. Med. Chem, 1999; 42: 2383–2393.
9. D.G. Carole, D.M. Michel, C. Julien, D. Florence, N. Anna,J. Séverine, D. Gérard, T.D. Pierre, G. Jean-Pierre, Synthesisand antileishmanial activities of 4,5-di-substituted acridines acompared to their 4-mono-substituted homologues, Bioorg. MedChem, 2005; 13: 5560–5568.
10. P. Yang, Q. Yang, X. Qian, L. Tong, X. Li, Isoquino[4,5-bc]acridines: design, synthesis and evaluation of DNA binding,anti-tumor and DNA photo-damaging ability,J. Photochem. Photobiol. B, 2006; 84: 221–226.
11. I. Antonini, P. Polucci, L.R. Kelland, E. Menta, N. Pescalli, SMartelli, 2,3-Dihydro-1H,7H-pyrimido[5,6,1-de]acridine-1,3,7trione derivatives, a class of cytotoxic agents active omultidrug-resistant cell lines: synthesis, biological evaluationand structure–activity relationships, J. Med. Chem, 1999; 42: 2535–2541.
12. M.G. Gunduz, A.E. Dogan, R. Simsek, K. Erol, C. Safak, Substituted 9-aryl-1,8-acridinedione derivatives and their effects onpotassium channels, Med. Chem. Res., 2009; 18: 317–325.
13. M. Alvala, S. Bhatnagar, A. Ravi, V.U. Jeankumar, T.H.Manjashetty, P. Yogeeswari, D Sriram, Novel acridinedionederivatives: design, synthesis SIRT1 enzyme and tumor cell growth inhibition studies, Bioorg. Med. Chem. Lett., 2012; 22: 3256–3260.

14. A. Jamalian, R. Miri, O. Firuzi, M. Amini, A.A. MoosaviMovahedi, A. Shafiee, Synthesis, cytotoxicity and calciuantagonist activity of novel imidazolyl derivatives of 1,8acridinediones, J. Iranian Chem. Soc., 2011; 8: 983–991.
15. P. Shanmugasundaram, P. Murugan, V.T. Ramakrishnan, N. Srividya, P. Ramamurthy, Synthesis of acridinedione derivatives oflaser dyes, Heteroatom. Chem, 1996; 7: 17–22.
16. N. Srividya, P. Ramamurthy, P. Shanmugasundaram, V.T.Ramakrishnan, Synthesis, characterization, and electrochemistry of some acridine-1,8-dione dye, J. Org. Chem, 1996; 61: 5083–5089.
17. C. Selvaraju, P. Ramamurthy, Excited-state behavior andphotoionization of 1,8-acridinrdione dyes in micelles – comparison with NADH oxidation, Chem. Eur. J., 2004; 10: 2253–2262.
18. R. Velu, E.J.P. Malar, V.T. Ramakrishnan, P. Ramamurthy, Acridinedione-functionalized gold nanoparticles and model forthe binding of 1,3-dithiol linked acridinedione on gold clusters, Tetrahedron Lett., 2010; 51: 5680–5685.
19. R. Velu, V.T. Ramakrishnan, P. Ramamurthy, Selective fluorideion recognition by a thiourea based receptor linked acridinedionefunctionalized gold nanoparticles, J. Photochem. Photobiol. A: Chem, 2011; 217: 313–320.