SYNTHESIS, CHARACTERIZATION, AND ANTICANCER ACTIVITY OF SOME NOVEL ACRIDINE DERIVATIVES

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ABSTRACT

Objective: The objective of the study was to synthesize and evaluate the anticancer activity of some novel acridine derivatives.

Methods: The present works involve condensation of acridine and various 2, 4-Thiazolidine-2,4-dione derivatives (2a–2h) with chloroacetyl chloride to give a novel acridine derivatives (5a–5l), respectively.

Results: All the newly synthesized molecules (5a–5l) were characterized by FTIR, H-NMR, and mass spectral analysis along with physical data. The biological potentials of the new synthesized compounds are evaluated for their in vitro anticancer activity by MTT assay.

Conclusion: The synthesized compounds 5a, 5f, and 5h exhibited good anticancer activity against MCF-7 and SKVO3 cancer cell lines at a concentration of 0.5 mg/mL.

Keywords: Acridine, 2, 4-Thiazolidinedione, Substituted aldehydes, Chloroacetyl chloride, Anticancer activity, MCF-7, SKVO3 cells.

INTRODUCTION

Acridine was first isolated by Carl Grabe and Heinrich Caro in Germany in 1870 from high boiling fraction of coal tar [1]. The antimicrobial property [2] of acridine was discovered Ehrlich and Benda in 1917. Bemthausen reported the primary synthesis of acridine, in which diphenylamine was reacted with benzilic acid using zinc chloride and high temperatures. The synthesis of acridine and its derivatives has attracted considerable attention from untreated and medicinal chemists for many natural life, as a number of natural source have been report to have this heterocyclic nucleus. Chemically, acridine is also known by the names of dibenzo pyridine, 2,3,5,6-dibenzo pyridine, and 10-aza anthracene. It has an irritating odor and crystallizes in colorless to light yellow needles with melting point of 110°C and boiling point of 346°C. Acridine is a class of heterocyclic compounds which merit special attention because it belongs to a group of substances with activity in medicinal chemistry. This try cyclic nucleus derivatives are associated with anti-inflammatory [3,4], antitumor activity [5], antitubercular [7,8], antiparasitic [9], antimalarial [10,11], antiviral [12,13], and fungicidal activities [14]. The basic in nature of pyridine, quinoline, and acridine is more or less similar compounds which possess no benzene ring, one benzene ring, and two benzene rings, respectively. Acridone is one of the heterocyclic compounds with a tricyclic ring having nitrogen at 10th position and keto group at 9th positions with the formula C18H14N2. Acridines are substituted derivative of the parent ring. It is a planar molecule so as to be structurally related to anthracene by means of one of the central CH groups replaced by nitrogen.

In view of the facts mentioned above and the wide applications of acridine molecule and its derivatives in medicinal chemistry, an attempt has been made to synthesize novel 3-(2-(9-oxoacridin-10(9H)-yl) acetyl) 5-(benzylidene) thiazolidine-2,4-dione moiety as new anticancer agents.

METHODS

The synthesized compound was screened for sterile and anticancer activities. Fourier transform IR spectrometer (model Shimadzu 8700) in the range of 400–4000 cm⁻¹ using KBr pellets and values are report in cm⁻¹ and the spectra were interpreted. H-NMR spectra were recorded on DPX-200 MHz NMR spectrometer using DMSO-d₆ and the spectra were interpreted. Mass spectra were record on mass spectrophotometer (model Shimadzu) by LC–MS and the spectra were interpreted. Pre-coated silica gel G plates were used to monitor the progress of reaction as well as to check the purity of the compound: n-Hexane: ethyl acetate (7:3) [15-17].

General procedures

Step 1: Preparation of N-phenyl anthracitic acid

In a 500 ml round-bottomed flask are placed a combination of o-Chlorobenzoic acid (20 g, 0.128 mol), Aniline (11.8 ml, 0.128 mol) and Copper metallic (0.5 g). To this solution 100 ml of amyl alcohol was added with constant stirring. To this mixture, dry potassium carbonate (20 g) was slowly added with stirring and the reaction mixture was allowed to reflux for 6 h in a light liquid paraffin oil bath at 135–140°C. Then the amyl alcohol was removed by using steam distillation and combination poured into two 2 L of hot water and acidified with targeted hydrochloric acid, boiled in the presence of activated charcoal, and filtered. On acidification of the filtrates with concentrated hydrochloric acid, light yellowish precipitate was obtained, which was washed with hot water. The crude acid was recrystallized from aqueous methanol to give a light yellow solid.

Step 2: Preparation of acridin-9-one

N-Phenyl anthranilic acid (18 g, 0.084 mol) was taken in a 500 ml of round bottom flask to which polyphosphoric acid (180 g, 0.532 mol) was added, shaken well, and refluxed on a water bath at 100°C for 3 h. Appearance of yellow color indicated the completion of reaction. Then, it was poured into 2 L of hot water and made alkaline by 25% ammonia solution. The yellow precipitate formed was filtered, washed with hot water, and collected. The crude acid 9-(10H)-one was recrystallized from acetic acid.
Step 3: General procedure for thiazolidine-2,4-dione

The equimolar quantity (1:1) of chloroacetic acid (56.4 g, 0.6 mol) in 60 ml of irrigate be added to the answer of thiourea (45.6 g, 0.6 mol) in 60 ml of water. The mixture be enthused for 15 min and precipitates were obtain after cooling. After that 60 ml of concentrated hydrochloric acid was added slowly by using a dropping funnel. Once the mixture got transformed to solution shape, it was refluxed for 8–10 h at 100–110°C. On cooling, the contents of the flask solidified to a come together of white needles. The manufactured goods were filtered and washed with water to take away traces of hydrochloric acid and dried. It was purified by recrystallization as of ethyl alcohol. Yield: 85%; m.p.: 123–125°C.

Step 4: General procedure for the synthesis of 5-substituted-1,3-thiazolidine-2,4-dione (4a-4h)

A combination of 2,4-thiazolidinedione 1 (1.17 g, 0.01 mol), substitute benzaldehyde (0.01 mol), glacial acetic acid (25 mL), and fused sodium acetate (0.18 g) be refluxed for 1 h with occasional shaking. Cool, then, the reaction mixture be cooled to room temperature and it was poured in water (250 mL), the product obtained was filtered, wash with water, alcohol, and ether and was recrystallized with glacial acetic acid.

Step 5: 3-(2-(9-oxoacridin-10(9H)-yl) acetyl)-5-(benzylidene) thiazolidine-2,4-dione

A mixture of acridone (0.01 mol), 5-substituted-1,3-thiazolidine-2,4-dione (0.01 mol), and chloroacetyl chloride (0.01 mol) in DMF (30 ml) was refluxed for 3–4 h. Progress of reaction was monitor by TLC using n-Hexane: acetone (7:3). After the completion of response, the content was added to cold water. The solid product was obtained and filtered, dried, and purified by crystallization from ethanol (Table 1).
Novel acridine derivatives (5a–5l) were evaluated for cytotoxicity and anticancer activities. The structures of all the newly synthesized compounds were characterized as 5a–5l on the basis of satisfactory analytical and spectral data including IR, LC-MASS, and H-NMR data. The synthesized compounds were screened for antimicrobial activity against human breast cancer cells (MCF7) and human ovarian cancer cells (SKVO3) with chloroacetyl chloride to give a novel acridine derivatives (5a–5l), respectively. The synthesized compounds were screened for antimicrobial activity with different concentrations of test compound in labeled wells in 96 plates. After 48 h, discard the drug solution and add the fresh media with MTT solution (0.5 mg/ml) be added to each well and plates were incubated at 37°C for 3 h. At the end of incubation time, precipitates are formed as a result of the decrease in cell growth by 50% values is generated from the dose-response curves for each cell line by with origin software.

% Inhibition = \frac{(Control - Treatment)}{(Control)} \times 100

RESULTS AND DISCUSSION

The present work involves the reaction between condensation of acridine and various 2,4-Thiazolidine-2,4-dione derivatives (2a-2h) with chloroaetyl chloride to give a novel acridine derivatives (5a–5l), respectively. The synthesized compounds were screened for antimicrobial and anticancer activities. The structures of all the newly synthesized compounds were characterized as 5a–5l on the basis of satisfactory analytical and spectral data including IR, LC-MASS, and 1H-NMR data.

Anticancer activity

Novel acridine derivatives (5a–5l) were evaluated for cytotoxicity against human breast cancer cells (MCF7) and human ovarian cancer cells (SKVO3). Cell viability was evaluated by the MTT assay with three independent experiments with six concentrations of compounds in triplicates. Cells were trypsinized and perform the trypsin blue assay to know viable cells in cell suspension. Cells were counted by hemocytometer and seeded at density of 5.0 × 10^4 cells/well in 100 μl media in 96-well plate culture medium and incubated overnight at 37°C. After incubation, take off the old media and add fresh media 100 μl with different concentrations of test compound in labeled wells in 96 plates. After 48 h, discard the drug solution and add the fresh medici with MTT solution (0.5 mg/ml) be added to each well and plates were incubated at 37°C for 3 h. At the end of incubation time, precipitates are formed as a result of the decrease of the MTT salt to chromophore Formosan crystals by the cells with metabolically active mitochondria. The optical density of solubilized crystals in MTT was measured at 570 nm on a microplate reader.

The percentage growth inhibition was calculated using the following formula and concentration of test drug essential to slow down cell growth by 50% values is generated from the dose-response curves for each cell line by with origin software.
carcinoma cell lines (SKVO3) using MTT assay, with doxorubicin as standard. Results (Table 2) proposed that both MCF7 and SKVO3 cell lines were susceptible to the evaluated compounds. Compounds 5a-5l showed IC\textsubscript{50} values in the range of 17.98–72.72 \(\mu\)M against MCF7 cell line and 18.8–49.15 \(\mu\)M against SKVO3 cell line. Compounds 5a, 5f, 5g, and 5h showed good activity against both the cell lines, whereas remaining all other compounds showed moderate activity against both cell lines (Fig. 1). Whereas, remaining all other compounds showed moderate activity against both cell lines. Compounds 5a and 5h having dimethyl amine group and nitro substitution, respectively, at 4\textsuperscript{th} position. Electron releasing nature of these atoms may be the possible reason for good activity.

CONCLUSION

The objective of the present work was to synthesize, purify, characterize, and evaluate the biological action of newly synthesized structural analogs of acridine derivatives containing thiazolidine moieties. The yield of the synthesized compounds was found to be in the range from 66 to 84\%.

In conclusion, the present study highlights the importance of acridine derivatives containing thiazolidine moieties. The yield of the synthesized compounds was found to be in the range from 66 to 84\%.

Table 2: Cytotoxic activity of novel acridine derivatives on MCF-7 and SKVO3 cell

| Sample description | Test parameters IC\textsubscript{50} (\(\mu\)g) |
|--------------------|---------------------------------|
| MCF7               | SKVO3                           |
| 5a                 | 17.98                           | 18.12                           |
| 5b                 | 24.07                           | 25.05                           |
| 5c                 | 50.75                           | 49.15                           |
| 5d                 | 52.6                            | 47.06                           |
| 5e                 | 25.35                           | 42.12                           |
| 5f                 | 21.88                           | 35.12                           |
| 5g                 | 72.72                           | 19.01                           |
| 5h                 | 23.21                           | 28.03                           |
| Doxorubicin        | 10.8                            | 09.7                            |

REFERENCES

1. Kumar R, Kaur M, Kumari M. Acridine: A versatile heterocyclic nucleus. Acta Pol Pharm 2012;69:3-9.
2. Berntsen A. Synthesis of acridines by the [4 + 2] annulation of arynes and 2-aminomethyl ketones. Ann 1884;224:1.
3. Chen YL, Lu CM, Chen IL, Tsaoan LT, Wang JP. Synthesis and antitumor evaluation of 2-substituted acridine and 9-phenoxycarboxamide derivatives. J Med Chem 2002;45:4689-94.
4. Yaraseva LV, Isayevand SG, Svechnikova OM. Synthesis and antiproflliferative activity of acridine-sulfonamide conjugates. Farm Zh 2003;5:66.
5. Gamage SA, Spicer JA, Atwell GJ, Finlay GI, Baguley BC, Denny WA. Structure-activity relationships for substituted bis(acridine-4-carboxamides): A new class of anticancer agents. J Med Chem 1999;42:2383-93.
6. Kaya M, Yildirir Y, Celik GY. Synthesis and antimicrobial activities of novel bisacridine-1,8-dione derivatives Med Chem Res 2011;20:293-9.
7. Aty El, Adabi AH. Synthesis and antibacterial activity of 6-chloro (unsubstituted)-2-methoxy-9-substituted acridine derivatives. Arch Pharm Res 2004;27:713-9.
8. Tripathi RP, Verma SS, Pandey J, Agarwal KC, Chaturvedi V, Manju YK, et al. Search of antibacterial activity in tetrahydroacridines: Synthesis and biological evaluation. Bioorg Med Chem Lett 2006;16:5144-7.
9. DiGiorgio C, DeMeo M, Chiron J, Delmas F, Nkoyan A, Jean S, et al. Synthesis and antileishmanial activities of 4,5-di-substituted acridines as compared to their 4-mono-substituted homologues. Bioorg Med Chem 2005;13:5560.
10. Kumar A, Srivastava K, Kumar SR, Puri SK, Chauhan MS. Synthesis of 9-anilinoacridine triazines as new class of hybrid antimalarial agents. Bioorg Med Chem Lett 2009;19:6996-9.
11. Tomar V, Bhattacherjee G, Kothari acridinyl mandelic acid derivatives as antimalarial agents. Tetrahedron Asymmetry 2009;20:1984-91.
12. Gupta HC, Jaiswal V. Recent developments in the synthesis and biological activity of acridine/ acridine analogues. J Heterocycl Chem 2009;16:409.
13. Tonelli M, Vettoretti G, Tasso B, Novelli F, Boido V, Saporato F, et al. Acridine derivatives as anti-BVDV agents. Antivir Res 2011;91:133-41.
14. Srivastava A, Nizamuddin A. Synthesis and fungicidal activity of some acridine derivatives. Indian J Heterocycl Chem 2004;13:261-4.
15. Vinayak MG, Dhamak KB, Khotade KB. Synthesis, antimicrobial and antifungal activity of novel acridine and acridine derivatives. Eur J Med Chem 2010;45:745.
16. Yu XM, Ramiandrasoa F, Guetzoyan F, Pradines B, Quintino E, Gadielle D, et al. Chem and biological evaluation of acridine derivatives as antimalarial agents. ChemMedChem 2009;12:877-805.
17. Gupta HC, Jaiswal V. Recent developments in the synthesis and biological activity of acridine/acridine analogues. J Heterocycl Chem 2010;19:409.
18. Tonelli M, Vettoretti G, Tasso B, Novelli F, Boido V, Saporato F, et al. Acridine derivatives as anti-BVDV agents. Antivir Res 2011;91:133-41.
19. Srivastava A, Nizamuddin A. Synthesis and fungicidal activity of some acridine derivatives. Indian J Heterocycl Chem 2004;13:261-4.
20. Vinayak MG, Dhamak KB, Khotade KB. Synthesis, antimicrobial and antifungal activity of novel acridine and acridine derivatives. Eur J Med Chem 2010;45:745.
21. Cavalluzzi MM, Bruno C, Lentinii G, Lovece A, Catalano A, Carocci A, et al. One-step synthesis of homochiral O-aryl and O-heteroaryl mandelic acids and their use as efficient 1H NMR chiral solvating agents. Tetrahedron Asymmetry 2009;12:20184-91.
22. Rajyalakshmi G, Narayana NA, Sarangapani M. Synthesis, characterization and antitumor activity of certain 3-(4-5-mecapto-1, 3, 4-oxadiazole2yl) phenylimino) indole-2-one derivatives Saudi Pharm J 2011;19:153-5.
23. Leena KP, Subin MZ, Deepthy CH. In silico design, synthesis and characterization of some novel benzothiazole derivatives as antitumor agents. Asian J Pharm Clin Res 2017;10:50-15.
24. Venkanna A, Siva B, Poornima B, Vadaparthi PR, Prasad KR, Reddy KA, et al. Phytochemical investigation of sesquiterpenes from the fruits of Schisandra chinensis and their cytotoxic activity. Fitoterapia 2014;95:102-8.