WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 7, Issue 3, 1739-1749. Research Article ISSN 2277–7105

SYNTHESIS, CHARACTERIZATION AND ANTIOXIDANT ACTIVITY OF NOVEL 9-(PIPERAZIN-1-YL) ACRIDINE DERIVATIVES

P. S. Raghu*

University College of Pharmaceutical Sciences, Sri Krishnadevaraya University, A. P-515003.

Article Received on
18 Dec. 2017,
Revised on 09 Jan. 2018,
Accepted on 01 Feb. 2018
DOI: 10.20959/wjpr20183-11105

***Corresponding Author**
P. S. Raghu
University College of Pharmaceutical Sciences, Sri Krishnadevaraya University, A. P-515003.

ABSTRACT

A series of nitrogen-containing heterocyclic compounds such as substituted 9-(piperazin-1-yl) acridine derivatives were synthesized by [(4-Methyl-2-nitrophenyl) amino] benzoic acid, phosphorus oxychloride, piperazine, dichloro methane evaluated for their antioxidant activity by DPPH method. Among the screened compounds, electron rich acridine exhibited significant antioxidant activities**.** The *in vitro*. Molecular docking results shows that the compound CP-05(*2-methyl -4-nitro-9-[(4-benzyl) piperazin-1-yl] acridine***)** shows siginificant anti oxidant activity than compare with the standard compound α-Tocopherol. In all the synthesized compounds, CP-05 shows best binding energy and IC 50 value -9.27 Kcal/mol and 155.03 nano molar concentration respectively. The compound CP-05 shows molecular interactions like H-Bonds ASN10; ASN59; GLY60 and Pi-Bonds at ASP27; ASN59; PRO89; ALA92; PRO187. The ADME results of the compounds obeys Lipinski rule of five and the compounds shows the low Mutagenic and no toxicity shows on Tumerogenic, Effect on Reproductive system, Eye Irritant.

KEYWORDS: acridine derivatives, phosphorus oxychloride, anti oxidant activity, DPPH method, Molecular docking.

INTRODUCTION

The cytochrome P450 (CYP) enzymes are heme-thiolate enzymes involved in the metabolism of a large number of exogenous molecules (natural products, drugs, and environmental carcinogens) and endogenous compounds such as hormones. The human CYPs are encoded by 57 genes[1] and are classified into four classes. The Class I and Class II CYPs (majority of

the CYPs) are versatile monooxygenases catalyzing a large number of reactions such as conversion of alkenes to epoxides, alkanes to alcohols, arenes to phenols, and oxidation of sulfides. CYP enzymes belonging to the 1, 2 and 3 CYP families have been found in healthy and cancerous hepatic tissues.[2,3] The metabolism of carcinogens, pro-carcinogens, and chemotherapeutics by CYPs gives them an indisputable role in the cancer prevention and treatment strategies. CYPs 1B1 and 2W1 are indeed expressed specifically in tumors.[4-9] Numerous studies have implicated a role for CYPs in tumor formation and development.[4,5,10-14] Inhibition of CYPs is a widely pursued area of research for the treatment and prevention of cancer.[15,16] The CYP enzymes can be targeted by small molecules as delineated in three strategies: (1) inhibit the enzyme through competitive inhibitors; (2) inhibit the enzyme through mechanism-based inhibitors that result in the modification of the enzyme; and (3) design prodrugs that are activated by the CYPs. Intense effort is ongoing by many research groups to find specific and potent CYP inhibitors for the individual members of the CYP superfamily. Understanding the key structural features of the inhibitors responsible for their inhibition potency has been essential for CYP inhibitor design and development. Computational methods such as docking studies, and quantitative structure activity studies (QSAR) have been extensively employed toward this end as outlined in various review articles.[17-24]

Nitrogen containing heterocyclic compounds especially acridine compounds are indispensable structural subunit in many polycyclic natural products[25] and various medicinal leads.[26] Differently substituted acridine moieties are known to show antiedema, anti-inflammatory[27], antibacterial[28], analgesic[29], anticancer[30-31], activities and COX-2/LOX inhibitor. In the view of the facts mentioned above, free radical scavenged antioxidant activity of substituted imidazole is considered relevant. Highly reactive free radicals and oxygen species are present in biological systems from a wide variety of sources such the regular metabolism or external sources.[32,33] The action of free radicals is counteracted by free radicals endogenous or exogenous or synthetic route. Reactive oxygen species (ROS) such as superoxide anions, hydrogen peroxide, hydroxyl, and nitric oxide radicals, play an important role in oxidative stress related to the pathogenesis of various important diseases. Antioxidants act as a major defense against radical mediated toxicity by trapping the free radicals. Free radical scavenging is one of the best known mechanisms and offer rapid techniques for screening the radical scavenging activity (RSA) of specific compounds. Antioxidant activity is governed by the following method such as DPPH, ORAC, ABTS,

DMPD, FRAP, TRAP, TBA, superoxide radical scavenging, hydroxyl radical scavenging, nitric oxide radical scavenging, xanthine oxidase, cytochrome C, reducing power method, etc. The DPPH method is very common and proved as the best.[34] It is revealed from the literature that a very little attention has been given to the antioxidant activity of hetero-aromatic imidazole compound. In view of this observation synthesis and evaluation of antioxidant activity of variously substituted imidazoles are considered relevant. The free radicals and reactive oxygen species cause an phenomena called oxidative stress and that plays a decisive role in the development of various diseases, chronicle and degenerative cancer[35], atherosclerosis[36], arthritis, viral infection stroke, myocardial infarction, pulmonary condition, inflammatory bowel disease, neurogenerative disease[37] and others may be produced by reactive oxygen species, for example, hydrogen peroxide scavenging (H2O2); hypochlorous acid scavenging (HOCl); hydroxyl radical scavenging (HO radical); peroxyl radical scavenging (ROO radical).

Experimental Work

MATERIALS AND METHODS

2-[(4-Methyl-2-nitrophenyl)amino]benzoic acid, phosphorus oxychloride, piperazine, dichloro methane, hexane, ethylacetate, sodium hydroxide, potassium carbonate, ethanol.

Copper sulphate, sodium sulphate. All the reagents were purchased analytical grade. Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in the indicated solvent on Bruker WM 400 MHz spectrometer with TMS as internal standard. Infrared spectra were recorded in KBr on Perkin-Elmer AC-1 spectrophotometer.

Chemistry

9-Choloro-2methyl-4-nitroacridine**1** derivatives synthesized by cyclization of 2-[(4-Methyl-2-nitrophenyl)amino]benzoic acid with freshly distilled phosphorus oxychloride under nitrogen atmosphere (Scheme 1). Further, it was treated with piperazine to obtain 2-methyl-4-nitro-9-(piperazin-1-yl)acridine **2**. The compounds are reacted with substituted benzyl/benzoyl chloride to yield derivatives **3-7**. All chemicals used were of reagent grade and purified as per need of the reaction. Progress of the reaction was monitored by TLC using hexane:ethylacetate (7:3) as mobile phase. Column chromatography was performed on silica gel (Merck, 60-120 mesh).

Method of preparation[4]

Synthesis of 9-Chloro-2-methyl-4-nitroacridine 1

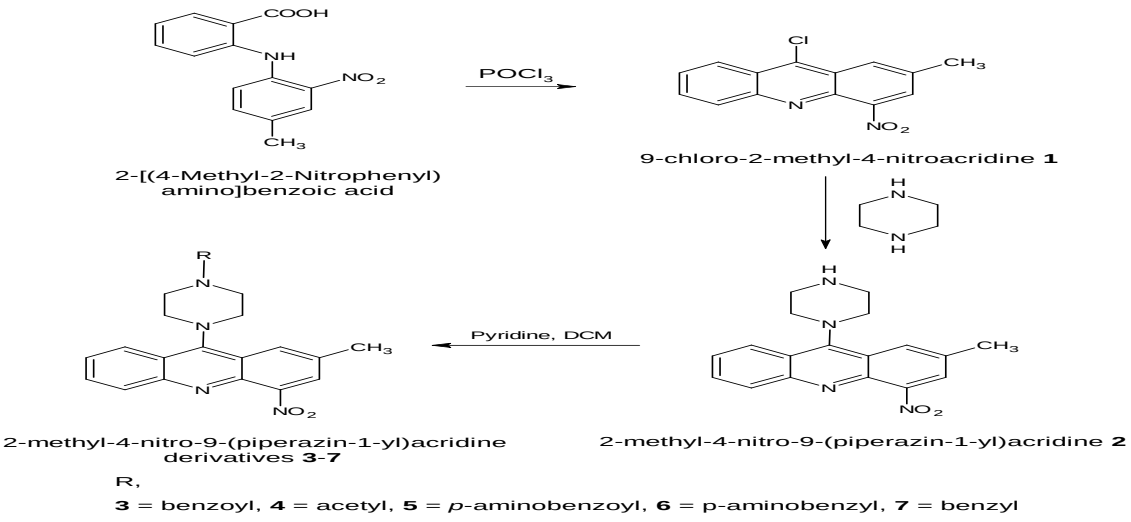
2-[(4-Methyl-2-nitrophenyl)amino]benzoic acid (1mmol) was suspended in phosphorous oxychloride (5 mmol) and heated at 100°C for 10 mins. The mixture was poured onto ice and neutralised dropwise to pH 7 at 0°C with cold 2M NaOH (6.5 ml). The white precipitate obtained was filtered, dried by suction and sublimed at 60°C[38] *Caution:* The Procedure should be carried out in an efficient hood and exposure to $POCl_3$ should be avoided.

Synthesis of 2-methyl-4-nitro-9-(piperazin-1-yl)acridine 2

In DMF - 1 mmol of 9-Chloro-2-methyl-4-nitroacridine **1**was suspended and was mixed by shaking, and then 1.5 mmol K_2CO_3 and 1.2 mmol piperazine were added to the solution and kept for magnetic stirring for 10 hours at room temperature followed by refrigeration. The mixture was poured onto ice water and stirred well. The solution was filtered for the solid settles and then it was dried in an oven to get a fine powder.[39] The product was recrystallized with ethanol.

Method of synthesis of compounds 3-7

To a solution of 2-methyl-4-nitro-9-(piperazin-1-yl)acridine**2**(1mmol) in 10ml of DCM taken in a round bottomed flask, pyridine-0.1ml and various benzyl/benzoyl chloride (1 mmol) were added and the reaction mixture was stirred for 1 hr at room temperature. Then the mixture was extracted with 10 ml of 1% $CuSO_4$ solution subsequently with ice cold water. The organic layer was separated and filtered through Na_2SO_4 and evaporated to get the product.



Scheme. 1: Synthesis of 9-piperzinyl acridine derivatives 3-7.

Antioxidant activity by DPPH method

Antioxidant behaviour of these imidazole derivatives (1-16) is measured *in vitro* by the inhibition of generated stable 2,2-diphenyl- 1-picrylhydrazyl (DPPH) free radical. Methods vary greatly as to the generated radical, the reproducibility of the generation process, and the end point that is used for the determination. The DPPH solution was prepared by dissolving accurately weighed 22 mg of DPPH in 100 ml of ethanol. From this stock solution, 18 ml was diluted to 100 ml with ethanol to obtain 100 µM DPPH solutions. The sample solution was prepared by accurately weighed 2.1 mg of each of the compounds and dissolved in 1 ml of freshly distilled DMSO separately to obtain solutions of 2.1 mg/ml concentration and the standard solution of was prepared by accurately weighed 10.5 mg of α-Tocopherol and dissolved in 1 ml of freshly distilled DMSO to get 10.5 mg/ml concentration.

A solution of test compound in ethanol (500 µl) was added to the ethanolic solution of DPPH radical. The reaction mixture was vortexed thoroughly and left in the dark at room temperature for 30 min. The absorbance of the mixture was measured spectrophotometrically at 517 nm against the corresponding blank solution. The final concentration of the samples and standard α-Tocopherol solutions used is 100 µg/ml. The percentage scavenging DPPH radical inhibitions were calculated by using the following formula.

$$\text{DPPH radical scavenging activity (\%)} = \frac{(\text{Abs control} - \text{Abs sample})}{\text{Abs control}} \times 100$$

Where, Abs control was the absorbance of DPPH radical and ethanol, Abs sample was the absorbance of DPPH radical and sample/standard.

The scavenging activity was expressed in terms of IC50, the concentration of the samples required to give a 50% reduction in the intensity of the signal of the DPPH radical. The results were done at least in triplicate.

RESULTS AND DISCUSSION

Synthesis of 9-Chloro-2-methyl-4-nitroacridine1

Yield – 79 %, m.p. 186 °C.IR (KBr, cm^{-1}) 3028, 1630, 1578, 1457, 1265, 1085, 1022, 809, 751.^{1}H-NMR d (d_6-DMSO, ppm) 8.42 (d, 1H, J¼8.7 Hz), 8.23 (d, 1H, J¼8.7 Hz), 7.82 (dd, 1H, J¼7.3 Hz), 7.64 (dd, 1H, J¼7.3 Hz), Anal. Found (Calc.%) for $C_{14}H_9ClN_2O_2$:C 60.38 (61.66), H3.12 (3.33), Cl12.85 (13.00), N10.11 (10.27), O11.52 (11.73), M^+:272.03 Da.

Synthesis of2-methyl-4-nitro-9-(piperazin-1-yl)acridine2

Yield – 62 % , m.p. 136 °C. IR (KBr, cm^{-1}) 3018, 1648, 1562, 1465, 1402, 1262, 1092, 1013, 812, 772.^{1}H-NMR d (d_6-DMSO,ppm) 8.42 (d, 2H aromatic), 8.22 (d, 2H aromatic), 7.80 (t, 2H, aromatic), 7.67 (m, 2H, aromatic),Anal. Found (Calc.%) for$C_{18}H_{18}N_4O_2$: C66.89 (67.07), H5.56 (5.63), N17.14 (17.38), O9.72 (9.93), M^+:322.14 Da.

Synthesis of 2-methyl-4-nitro-9-[(4-benzoyl)piperazin-1-yl]acridine 3 **(CP-01)**

Yield – 52%, m.p. 140 °C. IR (KBr, cm^{-1}) 3032, 1642, 1568, 1461, 1407, 1258, 1094, 1030, 818, Anal. Found (Calc.%) for $C_{25}H_{22}N_4O_3$: C70.38 (70.41), H5.18(5.20), N13.08(13.14), O11.04 (11.25); M^+:426.16 Da

Synthesis of 2-methyl-4-nitro-9-[(4-acetyl)piperazin-1-yl]acridine4 **(CP-02)**

Yield – 47%, m.p. 128 °C. IR (KBr, cm^{-1}) 3033, 1650, 1552, 1482, 1278, 1098, 1027, 768.Anal. Found (Calc.%) for $C_{20}H_{20}N_4O_3$: C65.78(65.92), H5.42(5.53), N15.12(15.38), O13.01 (13.17), M^+:364.15 Da

Synthesis of 2-methyl-4-nitro-9-[(4-(4-aminobenzoyl))piperazin-1-yl]acridine5 **(CP-03)**

Yield – 65%, m.p. 156 °C. IR (KBr, cm^{-1}) 3017, 1669, 1568, 1482, 1402, 1258, 1076, 1018, 768.Anal. Found (Calc.%) for$C_{25}H_{23}N_5O_3$: C67.88 (68.01), H5.09 (5.25), N15.52 (15.86), O10.55 (10.87), M^+:441.17Da

Synthesis of 2-methyl-4-nitro-9-[(4-(4-aminobenzyl))piperazin-1-yl]acridine6 **(CP-04)**

Yield – 53%, m.p. 164 °C. IR (KBr, cm^{-1}) 3380, 3128, 1614, 1590, 1528, 1440, 1366, 1268, 1134, 1088, 958,Anal. Found (Calc.%) for $C_{25}H_{25}N_5O_2$: C70.01 (70.24), H5.68 (5.89), N16.11 (16.38), O7.16 (7.49), M^+:427.20 Da

Synthesis of 2-methyl-4-nitro-9-[(4-benzyl) piperazin-1-yl]acridine7 **(CP-05)**

Yield – 54%, m.p. 149 °C. IR (KBr, cm^{-1}) 3338, 3027, 2923, 2844, 1581, 1546, 1438, 1318, 1230, 1190, 1018, 984. Anal. Found (Calc.%) for $C_{25}H_{24}N_4O_2$: C72.59 (72.80), H5.51(5.86), N13.39 (13.58), O7.60 (7.76), M^+:412.18 Da

Anti oxidant activity by DPPH method

Table 1: Results of anti oxidant activity

S. No	CODE	Antioxidant activity (%inhibition)
1	CP01	62
2	CP02	84
3	CP03	74
4	CP04	61
5	**CP05**	**51**
6	**α-Tocopherol**	**48**

DISCUSSION

Based on the results, the evaluation of antioxidant activity by DPPH reagent method with CP-01 to CP-05 were done shows that the compound CP-05 (*2-methyl-4-nitro-9-[(4-benzyl)piperazin-1-yl]acridine***)** shows better activity than compare with other synthesised compounds but less than the standard compound α-Tocopherol.

CONCLUSION

From the results of *in vitro* antioxidant activity, it is concluded that these molecules can be designed as potential drugs with a slight modification in the structure of the molecules. The DPPH radical scavenging activity was undertaken to evaluate the effect of substituent on the antioxidant activities of the all synthesized compounds and shows promising activity. Among all synthesized compounds, CP-05 exhibited good radical scavenging activities compared to α-Tocopherol, which are also, supported by docking studies with cytochrome P450 (CYP) proteins. The reason for higher antioxidant activity of compound CP-05, due to presence of piperizine group adjacent to acridine ring that can stabilize an unpaired electron in general boosts up the antioxidant capacity of the molecule. There for, these molecules could be developed for antioxidant agent.

ACKNOWLEDGEMENT

The author Dr P.S. Raghu gratefully thankful to the Sri Krishnadevaraya University authorities, especially the Honble Vice Chancellor Dr .K Rajagopal, Rector Dr . Lajapathi Rai and the Registrar Prof.Sudhakar Babu for providing constant encouragement and support during the performance of the research work and preparation of the manuscript.

REFERENCES

1. Nelson, D.R.; Zeldin, D.C.; Hoffman, S.M.; Maltais, L.J.; Wain, H.M.; Nebert, D.W. Comparison of cytochrome p450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants. Pharmacogenetics, 2004; 14: 1–18.
2. Rodriguez-Antona, C.; Ingelman-Sundberg, M. Cytochrome p450 pharmacogenetics and cancer. Oncogene, 2006; 25: 1679–1691.
3. Nebert, D.W.; Dalton, T.P. The role of cytochrome p450 enzymes in endogenous signalling pathways and environmental carcinogenesis. Nat. Rev. Cancer, 2006; 6: 947–960.
4. Gibson, P.; Gill, J.H.; Khan, P.A.; Seargent, J.M.; Martin, S.W.; Batman, P.A.; Griffith, J.; Bradley, C.; Double, J.A.; Bibby, M.C.; et al. Cytochrome p450 1b1 (CYP1B1) is overexpressed in human colon adenocarcinomas relative to normal colon: Implications for drug development. Mol. Cancer Ther., 2003; 2: 527–534.
5. . Murray, G.I.; Taylor, M.C.; McFadyen, M.C.; McKay, J.A.; Greenlee, W.F.; Burke, M.D.; Melvin, W.T. Tumor-specific expression of cytochrome p450 CYP1B1. Cancer Res., 1997; 57: 3026–3031.
6. Tokizane, T.; Shiina, H.; Igawa, M.; Enokida, H.; Urakami, S.; Kawakami, T.; Ogishima, T.; Okino, S.T.; Li, L.C.; Tanaka, Y.; et al. Cytochrome p450 1b1 is overexpressed and regulated by hypomethylation in prostate cancer. Clin. Cancer Res., 2005; 11: 5793–5801.
7. Su, J.M.; Lin, P.; Wang, C.K.; Chang, H. Overexpression of cytochrome p450 1b1 in advanced non-small cell lung cancer: A potential therapeutic target. Anticancer Res., 2009; 29: 509–515.
8. Aung, P.P.; Oue, N.; Mitani, Y.; Nakayama, H.; Yoshida, K.; Noguchi, T.; Bosserhoff, A.K.; Yasui, W. Systematic search for gastric cancer-specific genes based on sage data: Melanoma inhibitory activity and matrix metalloproteinase-10 are novel prognostic factors in patients with gastric cancer. Oncogene, 2006; 25: 2546–2557.
9. Karlgren, M.; Gomez, A.; Stark, K.; Svard, J.; Rodriguez-Antona, C.; Oliw, E.; Bernal, M.L.; Ramon y Cajal, S.; Johansson, I.; Ingelman-Sundberg, M. Tumor-specific expression of the novel cytochrome p450 enzyme, CYP2W1. Biochem. Biophys. Res. Commun, 2006; 341: 451–458.
10. Bruno, R.D.; Njar, V.C. Targeting cytochrome p450 enzymes: A new approach in anti-cancer drug development. Bioorg. Med. Chem, 2007; 15: 5047–5060.

11. Mace, K.; Bowman, E.D.; Vautravers, P.; Shields, P.G.; Harris, C.C.; Pfeifer, A.M. Characterisation of xenobiotic-metabolising enzyme expression in human bronchial mucosa and peripheral lung tissues. Eur. J. Cancer, 1998; 34: 914–920.
12. Hashizume, T.; Imaoka, S.; Mise, M.; Terauchi, Y.; Fujii, T.; Miyazaki, H.; Kamataki, T.; Funae, Y. Involvement of CYP2J2 and CYP4F12 in the metabolism of ebastine in human intestinal microsomes. J. Pharmacol. Exp. Ther., 2002; 300: 298–304.
13. Murray, G.I. The role of cytochrome p450 in tumour development and progression and its potential in therapy. J. Pathol, 2000; 192: 419–426.
14. Gonzalez, F.J. The use of gene knockout mice to unravel the mechanisms of toxicity and chemical carcinogenesis. Toxicol. Lett. 2001; 120: 199–208.
15. Lohr, M.; McFadyen, M.C.; Murray, G.I.; Melvin, W.T. Cytochrome p450 enzymes and tumor therapy. Mol. Cancer Ther. 2004; 3, 1503; author reply 1503–1504.
16. McFadyen, M.C.; Melvin, W.T.; Murray, G.I. Cytochrome p450 enzymes: Novel options for cancer therapeutics. Mol. Cancer Ther. 2004; 3: 363–371.
17. Roy, K.; Roy, P.P. Qsar of cytochrome inhibitors. Expert Opin. Drug Metab. Toxicol. 2009; 5: 1245–1266.
18. Williams DE, Davies J, Patrick BO, Bottriell H, Tarling T, et al. Cladoniamides A-G, tryptophan-derived alkaloids produced in culture by Streptomyces uncialis. Org Lett, 2008; 10: 3501-3504.
19. Raheem IT, Thiara PS, Peterson EA, Jacobsen EN Enantioselective Pictet-Spengler-type cyclizations of hydroxylactams: H-bond donor catalysis by anion binding. J Am Chem Soc, 2007; 129: 13404-13405.
20. Le Quement ST, Nielsen TE, Meldal M Scaffold diversity through intramolecular cascade reactions of solid-supported cyclic N-acyliminium intermediates. J Comb Chem, 2007; 9: 1060-1072.
21. Sedgwick NV, Miller IT, Springall HD (1996) Clarendon Press, Oxford University, Oxford, England.
22. Breslin HJ, Cai C, Miskowski TA, Coutinho SV, Zhang SP, et al. Identification of potent phenyl imidazoles as opioid receptor agonists. Bioorg Med Chem Lett, 2006; 16: 2505-2508.
23. Yadav MR, Puntambekar DS, Sarathy KP, Vengurlekar S, Giridhar R Quantitative structure activity relationships studies of diarylimidazoles as selective COX-2 inhibitors. Ind J Chem, 2005; 45B: 475-482.

24. Matysiak J, Niewiadomy A, Krajewska-Kułak E, Macik-Niewiadomy G Synthesis of some 1-(2,4-dihydroxythiobenzoyl)imidazoles, -imidazolines and -tetrazoles and their potent activity against Candida species. Farmaco, 2003; 58: 455-461.
25. Ramesh kumar, mandeep kaur and meena kumari, Acridine: a versatile heterocyclic nucleus, Acta Poloniae Pharmaceutica - Drug Research, 2012; 69(1): 3-9.
26. Dahiya R Synthesis, Characterization and Antimicrobial Studies on Some Newer Imidazole Analogs. Sci Pharm, 2008; 76: 217-239.
27. Sondhi, Sham M., et al. "Synthesis, anti-inflammatory and anticancer activity evaluation of some novel acridine derivatives." European journal of medicinal chemistry, 2010; 45.2: 555-563.
28. Patel, Mehul M., Mimansha D. Mali, and Saurabh K. Patel. "Bernthsen synthesis, antimicrobial activities and cytotoxicity of acridine derivatives." Bioorganic & medicinal chemistry letters, 2010; 20.21: 6324-6326.
29. Chandra, Trilok, et al. "Synthesis of substituted acridinyl pyrazoline derivatives and their evaluation for anti-inflammatory activity." European journal of medicinal chemistry, 2010; 45.5: 1772-1776.
30. Benchabane, Yohann, et al. "Photo-inducible cytotoxic and clastogenic activities of 3, 6-di-substituted acridines obtained by acylation of proflavine." European journal of medicinal chemistry, 2009; 44.6: 2459-2467.
31. Chen, Ching-Huang, et al. "Synthesis and in vitro cytotoxicity of 9-anilinoacridines bearing N-mustard residue on both anilino and acridine rings." European journal of medicinal chemistry, 2009; 44.7: 3056-3059.
32. Navidpour L, Shadnia H, Shafaroodi H, Amini M, Dehpour AR, et al. Design, synthesis, and biological evaluation of substituted 2-alkylthio-1,5-diarylimidazoles as selective COX-2 inhibitors. Bioorg Med Chem, 2007; 15: 1976-1982.
33. Suthakaran R, Kavimani S, Venkapayya P, Suganthi K synthesis and antimicrobial activity of 3 -(2-(4z) - 4 - substituted benzylidene-4,5-dihydro-5- oxo-2-phenyl imidazol-1-yl)ethyl)-6,8- un /dibromo subtituted-2-substituted quinazoline-(3h)-one. Int J Pharmco Bio Sci., 2008; 1: 22-29.
34. Hossain SU, Bhattacharya S Synthesis of O-prenylated and O-geranylated derivatives of 5-benzylidene2,4-thiazolidinediones and evaluation of their free radical scavenging activity as well as effect on some phase II antioxidant/ detoxifying enzymes. Bioorg Med Chem Lett, 2007; 17: 1149-1154.

35. Davies KJ Oxidative stress: the paradox of aerobic life. Biochem Soc Symp, 1995; 61: 1-31.
36. Ames BN Dietary carcinogens and anticarcinogens. Oxygen radicals and degenerative diseases. Science, 1983; 221: 1256-1264.
37. Berliner JA, Heinecke JW The role of oxidized lipoproteins in atherogenesis. Free Radic Biol Med., 1996; 20: 707-727.
38. Avat Arman Teherpour David Kvaskoff, Paul V. Bernhardt and Curt Wentrup 9-Azidoacridine and 9-acridinylnitrene, J. Phys. Org. Chem, 2010; 23: 382-389.
39. Yanqing Liu, Enkun Zhou, Kunqian Yu, Jin Zh, Yu Zhang, Xin Xie, Jian Li and Hualiang Jiang, Discovery of a Novel CCR5 Antagonist Lead Compound Through Fragment Assembly. Molecules, 2008; 13: 2426-2441.