

REVIEW

ACRIDINE: A VERSATILE HETEROCYCLIC NUCLEUS

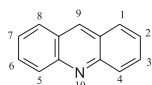
RAMESH KUMAR^{*}, MANDEEP KAUR AND MEENA KUMARI

Lord Shiva College of Pharmacy, Sirsa-125055, Haryana, India

Abstract: Acridine is a heterocyclic nucleus. It plays an important role in various medicines. A number of therapeutic agents are based on acridine nucleus such as quinacrine (antimalarial), acriflavine and proflavine (antiseptics), ethacridine (abortifacient), amsacrine and nitracine (anticancer), and tacrine. Acridine is obtained from high boiling fraction of coal tar. It is also obtained in nature from plant and marine sources. Acridine undergoes a number of reactions such as nucleophilic addition, electrophilic substitution, oxidation, reduction, reductive alkylation and photoalkylation. The present review article summarizes the synthesis, reaction, literature review and pharmaceutical importance of acridine.

Keywords: acridines, cytotoxic, antiseptic, antimicrobial

The synthesis of acridine and analogues has attracted considerable attention from organic and medicinal chemists for many years, as a number of natural sources have been reported to have this heterocyclic nucleus. Chemically, acridine is an alkaloid from anthracene. It is also known by the names of dibenzopyridine, 2,3,5,6-dibenzopyridine and 10-azaanthracene. Acridine has an irritating odor. It crystallizes in colorless to light yellow needles with melting point of 110°C and boiling point of 346°C. It is characterized by its irritating action on skin and by the blue fluorescence showed by solutions of its salts (1).



acridine

First time isolation of acridine was done in 1870, from high boiling fraction of coal tar by Carl Grabe and Heinrich Caro in Germany. In 1917, Ehrlich and Benda discovered the antimicrobial property of acridine (2). The structure activity relationship of acridine antibacterial was established by an Australian chemist Adrien Albert. The finding of his study indicated that cationic ionization and planar molecular surface area = 38 Å is necessary for antibacterial activity. During the World War II the scarcity of quinine lead to discovery of acridine based, antimalarial drug mepacrine. However, the contemporary antibacterial therapy (sulfonamide,

1935 and penicillin, 1944) superseded the acridine based therapy. But in present arena, massive increase in drug resistance bacterial infections has attracted the attention toward acridine once again. In the literature, it has been found that acridine derivatives possess widely differing activities such as anti-inflammatory and anticancer (3), antihelmintics (4), insecticidal, rodenticidal (5), fungicidal (6) and antitumor activities (7).

Chemistry

Acridine is separated from coal tar by shaking out with dilute sulfuric acid, and then precipitating from sulfuric acid solution with potassium dichromate. The resulting acridine dichromate is decomposed in the final step by ammonia. Acridine and its homologues are stable compounds of weakly basic character. Acridine has a pKa value of 5.6, similar to that of pyridine.

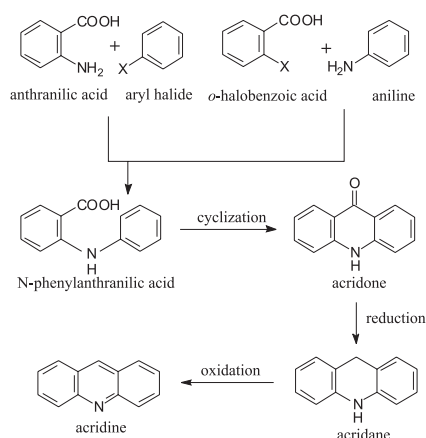
Synthesis

Although several methods are reported for the syntheses of acridines and its derivative acridinone, among them only those important are discussed below.

Ullmann synthesis

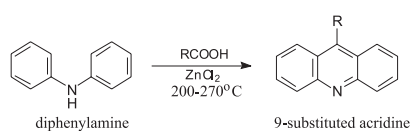
The condensation of primary amine with aromatic aldehyde/aromatic carboxylic acid in the presence of strong mineral acids (H₂SO₄/HCl), followed by dehydrogenation, yield acridines (1, 8, 9).

* Corresponding author: e-mail: rjangra_pchem@yahoo.com



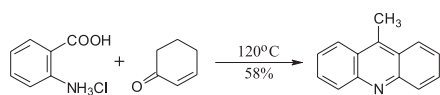
Berthsen synthesis

Berthsen synthesis involves the reaction of diphenylamine with carboxylic acid in the presence of zinc chloride, resulting in the formation of acridine (10, 11).



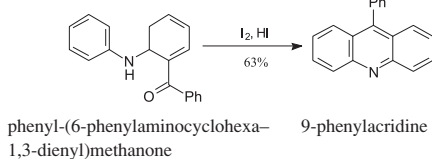
Friedlander synthesis

In this synthesis the salt of anthranilic acid is treated with cyclohex-2-enone at 120°C to obtain 9-methylacridine (12):



From C-acylated diphenylamines

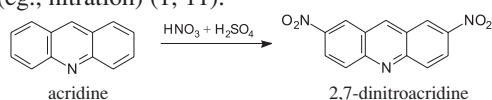
In this reaction diphenylamine is heated in the presence of I_2/HI to give 9-phenylacridine (12).



Reactions of acridine

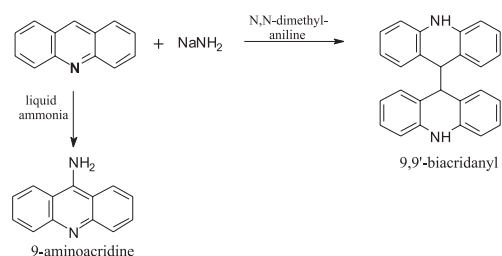
Electrophilic substitutions of acridine

Electrophilic substitutions of acridine often results in disubstitution at the 2- and 7-positions (eg., nitration) (1, 11):



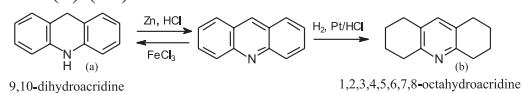
Reactions towards nucleophiles

Acridine shows variable regiochemistry towards nucleophiles. Reaction with NaNH_2 in liquid ammonia leads to 9-aminoacridine, whereas in *N,N*-dimethylaniline the main product is 9,9'-biacridanyl (1).



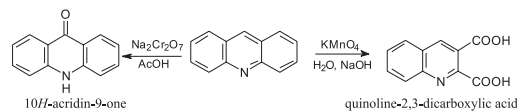
Reduction of acridine

Reduction of acridine with Zn/HCl results in the formation of pyridine ring in acridine (a) giving 9,10-dihydroacridine, whereas reduction with Pt/HCl results in reduction of benzene rings of acridine (b) (11).



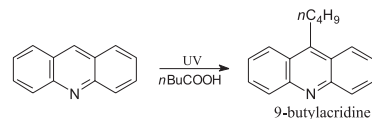
Oxidation of acridine

Acridine is oxidized by dichromate in acetic acid giving acridone whereas it get degraded by permanganate in alkaline medium forming quinoline-2,3-dicarboxylic acid (1, 11).



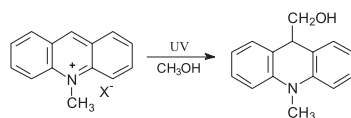
Reductive alkylation

Acridine on reaction with *n*-pentanoic acid, in the presence of ultraviolet light, gives 9-*n*-butylacridine. This is an example of reductive alkylation (13):



Photoalkylation

In the presence of ultraviolet light, *N*-methylacridine hydrochloride reacts with methanol to give 10-methyl-9,10-dihydroacridin-9-yl-methanol (14).



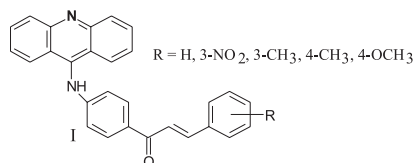
Pharmacological uses

A number of marketed preparations based on the acridine nucleus are available. These preparations represent various pharmacological activities. Bucricaine [butyl-(1,2,3,4-tetrahydroacridin-9-yl)-amine] is used topically for surface anesthesia of eye and given by injection for infiltration anesthesia, peripheral nerve block and spinal anesthesia. Quinacrine [2-methoxy-6-chloro-9-(1-diethylamino-3-methylpropanamine)-acridine] is also known as mepacrine. It acts as gametocytocide. It destroys the sexual erythrocytic forms of plasmodia and act as antimalarial agent. 9-Aminoacridine acts as disinfectant. Proflavin (3,6-diaminoacridine) is found to be active as bacteriostatic against many Gram positive bacteria (15). Nitracrine [1-nitro-9-(dimethylaminopropylamino)acridine] causes the DNA damage and acts as an anticancer agent (16). Acriflavin (3,6-diamino-10-methylacridinium chloride) is used as antiseptic for skin and mucous membranes (17). 9-Arylacridine derivatives interact strongly with topoisomerase-I (Topo-1) and act as anticancer agents (18).

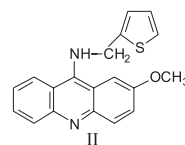
Review of the literature

Owing to the versatile chemotherapeutic activities of acridine, a significant amount of research activity has been directed toward this class in recent years. Herein we discuss the recent and important literature of acridine and its derivatives:

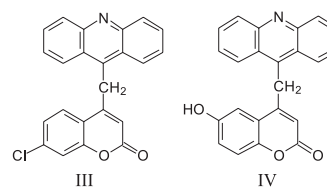
Tomar et al. carried out the reaction between various 3'-aminochalcone or 4'-aminochalcones and 9-chloroacridine through noncatalyzed nucleophilic aromatic substitution. The synthesized chalcone derivatives (**I**) have been screened for antimalarial activity against *Plasmodium falciparum*. All the chalcones showed complete inhibition at concentration of 10 µg/mL (19).



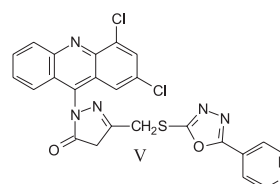
Sondhi et al. performed the condensation of 9-chloro-2,4-(un)substituted acridines with various amines and 9-isothiocyanato-2,4-(un)substituted acridines with different amines, which gave condensed products. Compound **II** showed 41.17% anti-inflammatory activity, which was better than the most commonly used drug ibuprofen having 39% anti-inflammatory activity (20).



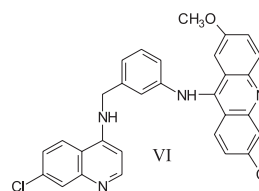
Patel et al. reported the condensation reaction of diphenylamine with 2-oxo-2H-(substituted chromen)-4-yl acetic acid in the presence of anhydrous zinc chloride to afford 4-(acridin-9-ylmethyl)-2H-(substituted chromen)-2-one. The synthesized compounds were screened for their *in vitro* antimicrobial and anticancer activity. Compound **III** showed excellent activity against *E. coli*. On the other hand, cytotoxicity was shown by compound **IV** (21).



Chandra et al. synthesized the substituted acridinyl pyrazoline derivatives and evaluated for anti-inflammatory and analgesic activity. Compound **V** showed better anti-inflammatory and analgesic activities at the three graded dose of 25, 50 and 100 mg/kg (22).

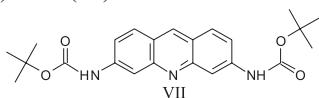


Kumar et al.; synthesized the quinoline-acridine hybrids and evaluated them against N54 strain of the *Plasmodium falciparum*. Among the evaluated compounds, compound **VI** showed the promising antimalarial activity (23).

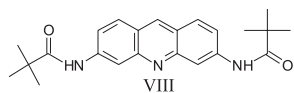


Benchabane et al. prepared a series of eighteen 3,6-disubstituted acridines and evaluated them for cytotoxicity and photo-enhanced cytotoxicity. Two compounds: *tert*-butyl N-[(6-*tert*-butoxycarbonyl-amino)acridin-3-yl] carbamate (**VII**) and N-[6-(pivalamino) acridin-3yl]pivalamide (**VIII**) dis-

played specific cytotoxicity on CHO (Chinese hamster ovary) cells (24).

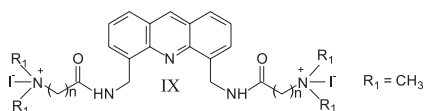


tert-butyl N-[(6-tert-butoxycarbonylamino)acridin-3-yl] carbamate

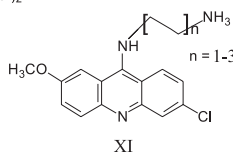
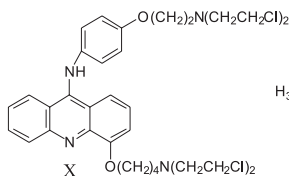


N-[6-(pivalamino)acridin-3-yl]pivalamide

Cochard et al. synthesized 4,5-bis-(dialkylaminoalkyl) substituted acridines (**IX**) and evaluated them for their telomerase G-quadruplex stabilizing properties using FRET melting and TRAP assay. The results showed that the compounds containing quaternary ammonium function were more active species in both quadruplex stabilization and TRAP assays (25).



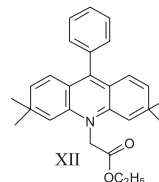
Chen et al. synthesized a series of 9-anilinoacridines having an alkylated N-mustard pharmacophore and evaluated their cytotoxicity against human lymphoblastic leukemia (CCRF-CEM) cell growth *in vitro*. The result indicates that compound **X** was found to be most cytotoxic with an IC_{50} value of 1.3 nM and is as potent as taxol (26).



Guetzoyan et al. synthesized a series of acridine derivatives and evaluated their antimalarial activity against one chloroquine-susceptible strain and 3-chloroquine-resistant strains of *Plasmodium falciparum*. Structure-activity relationships showed that 6-chloro and 2-methoxy substituents (**XI**) on the acridine ring were required to exert a good antimalarial activity. The best compounds possessing these features inhibited the growth of chloroquine susceptible strain with an IC_{50} value of 0.07 μ M, close to that of chloroquine itself and that of three chloroquine-resistant strains better than chloroquine with an IC_{50} value of 0.3 μ M (27).

Sabbagh et al. used cyclic β -ketone to prepare the different chemical entities whether cyclic such

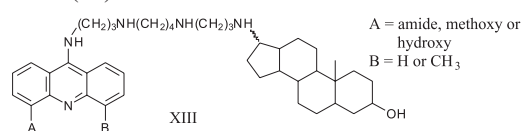
as acridines (compound **XII**), thiaziazole or acyclic system as hydrazide, hydrazones. The antiviral activity of these compounds against Hepatitis A Virus (HAV) revealed that the acridine and hydrazone were more active than the reference drug, amantadine (28).



Jones et al. prepared artemensin-acridine hybrids and evaluated them for their *in vitro* activity against tumor cell lines and a chloroquine sensitive strain of *Plasmodium falciparum*. They showed a 2–4 fold increase in activity against HL-60 and MCF-7 cells in comparison with dihydroartemisinin (29).

Guendel et al. described the molecular mechanism of 9-aminoacridine (9AA) mediated HIV-1 inhibition, that was highly dependent on the presence and location of the amino moiety. Importantly, virus replication was found to be inhibited in HIV-1 infected cell lines by 9AA in a dose-dependent manner without inhibiting cellular proliferation or including cell death (30).

Maurice et al. linked acridine with testosterone *via* a polyamine linker to obtain a compound with trifunctional characteristics. These trifunctional compounds and their derivatives (**XIII**) demonstrated the cytotoxic activity at the micromolar concentration (31).

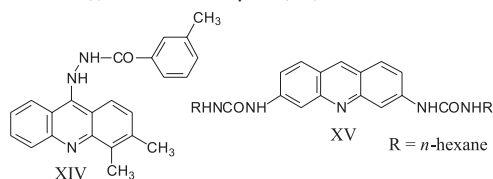


Oppegard et al. identified the small library of novel substituted 9-aminoacridine derivatives that inhibit cell proliferation of pancreatic cancer cell lines by inducing apoptosis (32).

Azim et al. identified the acridinyl derivatives (**XIV**) as potent aspartic protease inhibitors by virtual screening of in-house library of synthetic compounds. Enzyme inhibition experiments showed that the compounds inhibit human cathepsin D and *Plasmodium falciparum* plasmepsin-II in nanomolar ranges (33).

Kozurkova et al. reported the synthesis of novel 1',1''-(acridin-3,6-diyl)-3',3''-dialkyldiureas (**XV**). The synthesized compounds were evaluated

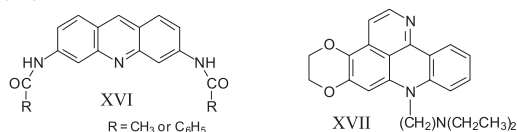
for anticancer activity using MTT assay on two cell lines, HeLa and HCT-116. Compound 1',1''-(acridin-3,6-diyl)-3',3''-dihexylyldiurea hydrochloride was found to be active on a HCT-116 cell line with an IC_{50} value of 3.1 μ M (34).



Petrikaite et al. synthesized new antimicrobial compounds containing three or more pharmacophores in one molecule. These compounds were screened for antimicrobial activity. Results indicate that new compounds act as more effective antimicrobial agents than the initial preparation – ethacridine (35).

Giorgio et al. synthesized two new series of diaminoacridinic derivatives (XVII) from proflavine. Two compounds, N-[6-(acetylamino)-3-acridinyl]acetamide and N-[6-(benzoylamino)-3-acridinyl]benzamide demonstrated highly specific antileishmanial properties against the intracellular amastigote form of parasite (36).

Sánchez et al. prepared a series of new acridines (e.g., XVII) having a dioxygenated ring fused to acridine. These compounds were evaluated for their cytotoxic activity. The results indicate that the new 11-O-substituted compounds are of considerable interest with high levels of cytotoxic activity (37).



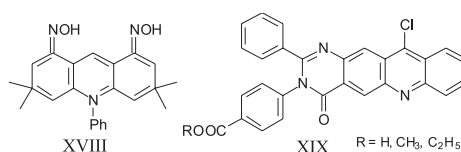
Goodell et al. tested a series of substituted triaryl heterocyclic compounds including acridines, acridones and xanthenes. The results indicate that acridine derivatives having substituted carboxamide and bulky 9-amino functionalities act as anti-herpes agents and inhibit the topoisomeraseII relaxation of supercoiled DNA (38).

Su et al. synthesized a series of 9-anilinoacridine and acridine derivatives bearing an alkylating N-mustard residue at C4 of the acridine chromophore. These agents were DNA cross-linking agents rather than topoisomerase II inhibitors (39).

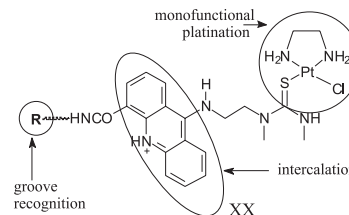
Sayed et al. performed the microwave irradiation synthesis of acridine and xanthenes derivatives from dimedone, and evaluated them for antimicro-

bial activity. Compound XVIII showed lower activity against *Staphylococcus aureus* (40).

Patel et al. synthesized 11-chloropyrimido-[4,5-*b*]acridin-4(3*H*)-one derivatives (XIX) using Ullmann synthesis and screened them for antimicrobial activity. The results showed that the synthesized compounds exhibited moderate antimicrobial activity (41).

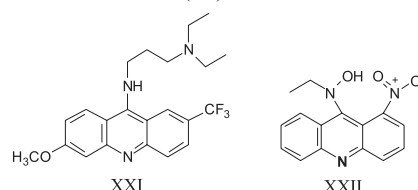


Gudneppanavar et al. synthesized and evaluated a novel platinum-acridine conjugates (XX) for DNA damage by intercalation. They appear to be the first platinum based drug capable of targeting DNA sequences critical for transcription initiation (42).



Anderson et al. synthesized 9-aminoacridine scaffold (compound XXI) for antimalarial drugs using parallel synthesis. A library of 175 compounds was designed, although only 93 of the final products had purities acceptable for screening. The library was screened against two strains of *Plasmodium falciparum*. Among them, six 9-aminoacridine derivatives with diamine component showed the inhibitory effect on the chloroquine resistant W2 strain (43).

Narayanan et al. explained the anticancer effect of 1-nitro-9-hydroxyethylaminoacridine (XXII) derivatives. The introduction of methyl group at C4 resulted in compounds which showed higher therapeutic efficacy and being developed as anticancer agent for solid tumors (44).



CONCLUSION

In this review, an attempt has been made to compile the chemistry, pharmacological uses and

recent literature on acridine. Although several methods are available for the synthesis of acridine, only important are discussed here. Besides these, acridine can also be prepared by the reduction of acridone. The study also showed that although acridines have versatile activity but the great majority of the known compounds either has antibacterial or cytotoxic activity.

REFERENCES

- Eicher T., Hauptmann S.: *The Chemistry of Heterocycles. Structure, Reactions, Syntheses and Applications*. pp. 354–358. George Thieme Verlag, Stuttgart, New York 1995.
- Mark W.: *J. Antimicrob. Chemother.* 47, 1 (2001).
- Srivastava A., Nizamuddin.: *Indian J. Heterocycl. Chem.* 13, 261 (2004).
- Elslager E.F., Worth D.F.: *J. Med. Chem.* 12, 955 (1969).
- Mayer D., Hermann G., Sasse K.: *Ger. Offen*, 1, 811, 409 (1970). *Chem. Abstr.* 73 55983k (1970).
- Pathak R.B., Bahel S.C.: *J. Antibact. Antifung. Agents (Japan)*, 8, 15 (1980). *Chem. Abstr.* 92, 198288 (1980).
- Takemura Y., Ju-ichi M., Ito C., Furukawa H., Tokuda H.: *Planta Med.* 61, 366 (1995).
- Abraham D.J.: *Burgers Medicinal Chemistry and Drug Discovery*. 6th edn., vol. 1, p. 890, John Wiley and Sons, New York 2007.
- Mann F.G., Saunders B.C.: *Practical Organic Chemistry*. 4th edn., p. 393, Orient Longman Private Ltd., New Delhi 2003.
- Bruce F.C., Ralph N.S., Graham J.A.: *J. Med. Chem.* 17, 923 (1974).
- Bernthsen A.: *Ann.* 1, 224 (1884).
- Acheson R.M.: *Introduction to the Chemistry of Heterocyclic Compounds*. 3rd edn., pp. 332–335, Wiley Interscience, New York 2008.
- Noyori R., Kato M., Kawanisi M., Nozaki H.: *Tetrahedron* 25, 1125 (1969).
- Tan. P., Auersperg N.: *Cancer Res.* 33, 2320 (1973).
- Harkishan S., Kapoor V. K.: *Medicinal and Pharmaceutical Chemistry*, 2nd edn., pp. 364–365, 473–475, Vallabh Prakashan, Delhi (2005).
- Gniazdowski M., Szmigiero L.: *Gen. Pharmacol.* 26, 473 (1995).
- <http://en.wikipedia.org/wiki/Acriflavine> (assessed on 2005-08-16).
- Takemura Y., Ju-ichi M., Ito C., Furukawa H., Tokuda H.: *Planta Med.* 61, 366 (1995).
- Tomar V., Bhattacharjee G., Kamaluddin., Rajakumar S., Srivastava K., Puri S.K.: *Eur. J. Med. Chem.* 45, 745 (2010).
- Sondhi S.M., Singh J., Rani R., Gupta P.P., Aggrawal S.K., Saxena A.K.: *Eur. J. Med. Chem.* 45, 555 (2010).
- Patel M.M., Mali M.D., Patel S.K.: *Bioorg. Med. Chem. Lett.* 20, 6324 (2010).
- Chandra T., Garg N., Lata S., Saxena K.K., Kumar A.: *Eur. J. Med. Chem.* 45, 1772 (2010).
- Kumar A., Srivastava K., Kumar S.R., Puri S.K., Chauhan P.M.S.: *Bioorg. Med. Chem. Lett.* 20, 7059 (2010).
- Benhabane Y., Di Giorgio C., Boyer G., Sabatier AS., Allergo D., Peyrot V., De Méo M.: *Eur. J. Med. Chem.* 44, 2459 (2009).
- Cochard M.L., Kim Y.M., Brassart B., Riou J.F., Laronze J.Y., Sapi J.: *Eur. J. Med. Chem.* 44, 3880 (2009).
- Chen C.H., Lin Y.W., Zhang X., Chou T.C., Tsai T.J., Kapuria N., Kakadiya R., Su T.L.: *Eur. J. Med. Chem.* 44, 3056 (2009).
- Guetzoyan L., Yu X.M., Raminandrasoa F., Pethe S., Rogier C., Pradines B., Cresteil T., Fauvet M.P., Mahy J.P.: *Bioorg. Med. Chem.* 17, 8032 (2009).
- Sabbagh O.I.E.I., Rady H.M.: *Eur. J. Med. Chem.* 44, 3680 (2009).
- Jones M., Mercer A. E., Stocks P.A., Pensee L.J.I.L., Cosstick R., Park K., Kennedy M.E. et al.: *Bioorg. Med. Chem. Lett.* 19, 2033 (2009).
- Guendel I., Carpio L., Easley R., Duyne R.V., Coley W., Agbottah E., Dowd C.Kashanchi F., Kehn-Hall K.: *Viol. J.* 6, 1743 (2009).
- Maurice H.B., Phillips R., Karodia N.: *Afr. J. Pharm. Pharmacol.* 3, 602 (2009).
- Oppgard M., Ougolkov A., Luchini D.N., Schoon R.A.: *Eur. J. Pharmacol.* 602, 223 (2009).
- Azim M.K., Ahmed W., Khan I.A., Rao N.A., Khan K.M.: *Bioorg. Med. Chem. Lett.* 18, 3011 (2008).
- Kozurkova M., Sabolova D., Janovec L., Mikes J., Koval., Ungvarsky J., Stefanisnova M. et al.: *Bioorg. Med. Chem.* 16, 3976 (2008).
- Petrikaite V., Tarasevicius E., Pavilonis A.: *Medicina (Kaunas)*. 43, 657 (2007).
- Giorgio C.D., Shimi K., Boyer G., Delmas F., Galy J.P.: *Eur. J. Med. Chem.* 42, 1277 (2007).
- Sánchez I., Reches R., Caignard D.H., Renard P., Pujol M.D.: *Eur. J. Med. Chem.* 41, 340 (2006).

38. John R. Goodell., Avni A. Madhok., Hiroshi H., David M.F.: *Bioorg. Med. Chem.* 14, 5467 (2006).
39. Su T.L., Lin Y.W., Chou T.C., Zhang X., Bacherikov V.A., Chen C.H., Liu L.F., Tsai T.J.: *J. Med. Chem.* 49, 3710 (2006).
40. Sayed E.H., Ashry E.: *ARKIVOC* 2, 178 (2006).
41. Patel B.B., Patel R.G., Patel M.P.: *J. Serb. Chem. Soc.* 71, 1015 (2006).
42. Guddneppanavar R., Bierbach U.: *J. Med. Chem.* 49, 3204 (2006).
43. Anderson M.O., Sherrill J., Madrid P.B., Liou A.P., Weisman J.L., Derisib J.L., Guya R.K.: *Bioorg. Med. Chem.* 14, 334 (2006).
44. Narayanan R., Tiwari P., Inoa D., Ashok B.T.: *Life Sci.* 77, 2312 (2005).

Received: 25. 10. 2010