Chapter 2
Nomenclature

Abstract Acridines have been known since 1870. Thus, their nomenclature has developed for long time. There are many numbering systems from which we have selected two most important ones. Moreover, plenty of trivial names exist and one has to be very careful when searching in the information databases.

This chapter provides a brief introduction for diving into the deep sea of acridine compounds without drowning, but will not show all possible names of acridines, which is far beyond the scope of the book.

Acridine was discovered and named by Graebe and Caro in 1870, when they investigated aromatic fractions of coal tar and found some basic impurity accompanying anthracene [1]: They named the new substance as "Acridin because of the sharp and biting effect that it exerts on the skin" [1] (from Latin acer = sharp, pungent, or acrid). This strong physiological effect is observable almost immediately after a drop of chloroform solutions of acridine touches a skin and persists for several minutes. The name "Acridin" (German) was imported to many languages with variations of c-k (Czech) and in some with suffixes -e (English, French) or -a (Spanish, Portuguese, Italian).

In past, the acridine ring was numbered differently than it is nowadays (Fig. 2.1) (cf. one of formers [2–5] and current [5–8] numbering). The current numbering reflects the locant order the same as was coined by Graebe [9], who applied it during understanding of 9-acridone structure. However, the numbers for carbon shared by more cycles were introduced later [5]. Thus, careful inspection of formerly published chemical structures is necessary in order to avoid confusion. For example, the most important 9-aminoacridines were called 5-aminoacridines in former works.

Concerning the numbering of acridine substituents, sometimes wrong labels are also used in literature. *m*-Amsacrine (**6**) can be named 4'-(9-acridinylamino) methanesulfon-*m*-anisidide [10], but when 1'-methanesulfonamide group is removed the priority of substituents is altered and 1' locant becomes 4' [11]. Sometimes priority of substituents is not followed and e.g. 5-hydroxymethyl is wrongly named 4-hydroxymethyl despite higher priority of carboxamide group [12].

Since the acridines are in use for more than a century, many of them have more than one trivial name [4, 6, 7, 13]: e.g. quinacrine (**11**) can be also named mepacrine,

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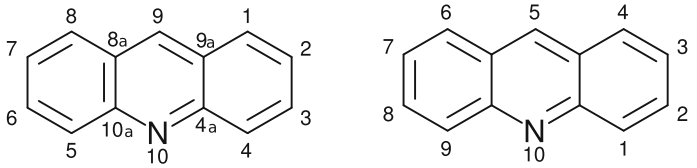

Fig. 2.1 Current (**15**) and former (**16**) numbering of acridine ring

and atabrine or atebrine. Other names for tacrine (**12**) are THA, cognex, tenakrin, or romotal [14–16]. Velnacrine (**13**) can be named 1-acridinol, 1-hydroxytacrine, and HP029 [17, 18]. Ledakrin can serve as a name for nitracrine (**8**) [19]. Thus, one has to be very careful conducing database-based search of acridines.

Some biologically active acridines are usually available not only under their trivial names but also under code numbers. Many examples can be given: GF120918 or GG918 can be named elacridar (**14**) [20] (PubChem CID: 119373); CI-921 stands for asulacrine (**7**) [12, 21, 22] (PubChem CID: 107924) ; NSC 601316 or XR 5000 is DACA (**5**) [23, 24] (PubChem CID: 107805); aminacrine (**4**) (PubChem CID: 7019); amsacrine (**6**) (PubMed CID: 2179); velnacrine (**13**) has number HP029 (PubChem CID: 3655); etc. Moreover different pharmaceutical forms have different numbers such as free proflavine (**2**) (PubChem CID: 7099); its salts: proflavine sulfate – isoflav (PubChem CID: 11111); proflavine hydrochloride (PubChem CID: 197873); proflavine hemisulfate (PubChem CID: 15741); etc.

Sometimes trivial name contained "acridine" despite the structure lacks the acridine ring i.e. acridine red is derivative of xanthene.

References

1. Graebe, C., Caro, H.: Ueber Acridin. Ber. Dtsch. Chem. Ges. **3**(2), 746–747 (1870)
2. Duegan, B.S., Narang, K.S., Ray, J.N.: Acridine derivatives. Part II. J. Chem. Soc. pp. 476–478 (1939)
3. Dupre, D.J., Robinson, F.A.: *N*-Substitued 5-aminoacridines. J. Chem. Soc. 549–551 (1945)
4. Albert, A.: The Acridines: Their Preparation, Physical, Chemical, and Biological Properties and Uses. Richard Clay and Company Ltd, Bungay, Suffolk, GB (1951)
5. Acheson, R.M.: Nomenclature and Numbering System, 2 edn., chap. 1, pp. 1–8. John Wiley & Sons, Inc., New York, London, Sydney, Toronto (1973)
6. Demeunynck, M., Charmantray, F., Martelli, A.: Interest of acridine derivatives in the anticancer chemotherapy. Curr. Pharm. Des. **7**, 1703–1724 (2001)
7. Šebestík, J., Hlaváček, J., Stibor, I.: A role of the 9-aminoacridines and their conjugates in a life science. Curr. Protein Pept. Sci. **8**(5), 471–483 (2007)
8. Salem, O., Vilkova, M., Plsikova, J., Grolmusova, A., Burikova, M., Prokaiova, M., Paulikova, H., Imrich, J., Kozurkova, M.: DNA binding, anti-tumour activity and reactivity toward cell thiols of acridin-9-ylalkenoic derivatives. J. Chem. Sci. **127**(5), 931–940 (2015)
9. Graebe, C., Lagodzinski, K.: Ueber Acridon. Justus Liebigs Ann. Chem. **276**(1), 35–53 (1893)

10. Wadkins, R.M., Graves, D.E.: Thermodynamics of the interactions of *m*-AMSA and *o*-AMSA with nucleic acids: influence of ionic strength and DNA base composition. Nucl. Acids Res. **17**(23), 9933–9946 (1989)
11. Gamage, S., Figgitt, D., Wojcik, S., Ralph, R., Ransijn, A., Mauel, J., Yardley, V., Snowdon, D., Croft, S., Denny, W.: Structure-activity relationships for the antileishmanial and antitrypanosomal activities of 1'-substituted 9-anilinoacridines. J. Med. Chem. **40**(16), 2634–2642 (1997)
12. Robertson, I.G., Palmer, B.D., Paxton, J.W., Shaw, G.J.: Differences in the metabolism of the antitumour agents amsacrine and its derivative CI-921 in rat and mouse. Xenobiotica **22**, 657–669 (1992)
13. Ehsanian, R., Van Waes, C., Feller, S.M.: Beyond DNA binding - a review of the potential mechanisms mediating quinacrine's therapeutic activities in parasitic infections, inflammation, and cancers. Cell. Commun. Signal. **9**, art. no. 13 (2011)
14. Gracon, S.I., Knapp, M.J., Berghoff, W.G., Pierce, M., DeJong, R., Lobbestael, S.J., Symons, J., Dombey, S.L., Luscombe, F.A., Kraemer, D.: Safety of tacrine: clinical trials, treatment IND, and postmarketing experience. Alzheimer Dis. Assoc. Disord. **12**, 93–101 (1998)
15. Farlow, M., Gracon, S.I., Hershey, L.A., Lewis, K.W., Sadowsky, C.H., Dolan-Ureno, J.: A controlled trial of tacrine in Alzheimer's disease. J. Am. Med. Assoc. **268**(18), 2523–2529 (1992)
16. Knapp, M.J., Knopman, D., Solomon, P.R., Pendlebury, W.W., Davis, C.S., Gracon, S.I., Apter, J.T., Lazarus, C.N., Baker, K.E., Barnett, M., Baumel, B., Eisner, L.S., Bennett, D., Forchetti, C., Levin, A., Blass, J.P., Nolan, K.A., Gaines, E.R., Relkin, N., Borison, R.L., Diamond, B., Celesia, G.G., Ross, A.P., Dexter, J., Doody, R., Lipscomb, L., Kreiter, K., DuBoff, E.A., Block, P., Marshall, D., Westergaard, N., Earl, N.L., Wyne, S.V., Hinman-Smith, E., Farlow, M., Hendrie, H.C., Caress, J.A., Farmer, M., Harper, J.E., Ferguson, J., Foster, N.L., Barbas, N.R., Bluemlein, L.A., Gelb, D.J., Berent, S., Giordani, B., Greenwald, M., Bergman, S., Roger, L.F., Groenendyk, A., Wood, M., Jurkowski, C., Katz, I., Doyle, S., Smith, B.D., Kellner, C., Bernstein, H.J., Bachman, D.L., Deinard, S., Langley, L., Bridges, S., Margolin, R.A., Burger, M.C., Wiser, S.L., Crenshaw, C., Morris, J.C., Rubin, E.H., Coats, M.A., Reyes, P.F., Bentz, C., Doyle, L.L., Rymer, M.M., Bettinger, I.E., Laubinger, M.P., Sadowsky, M.C.H., Martinez, W., Zuniga, J., Stone, R., Winner, P., Maté, L., Lessard, C., Schneider, L., Pawluczyk, S., Smith, W.T., Losk, S.N., Marambe, L., Groccia-Ellison, M.E., Edwards, K.R., Taylor, J., Calabrese, V.P., Harkins, S.W., Thein, Stephen G., J., Dewar, J.A., Williams, G., Drennan, C., Tuttle, P., Principi, N., Ford, E.M., Tyndall, R.J., Kelley, C.K.: A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. J. Am. Med. Assoc. **271**(13), 985–991 (1994)
17. Butterfield, D., Hensley, K., Hall, N., Umhauer, S., Carney, J.: Interaction of tacrine and velnacrine with neocortical synaptosomal membranes: Relevance to Alzheimer's-disease. Neurochem. Res. **18**(9), 989–994 (1993)
18. Braga, M.F., Harvey, A.L., Rowan, E.G.: Effects of tacrine, velnacrine (HP029), suronacrine (HP128), and 3,4-diaminopyridine on skeletal neuromuscular transmission in vitro. Br. J. Pharmacol. **102**, 909–915 (1991)
19. Gniazdowski, M., Szmigiero, L.: Nitracrine and its congeners - an overview. Gen. Pharmacol. **26**(3), 473–481 (1995)
20. Chufan, E.E., Kapoor, K., Ambudkar, S.V.: Drug-protein hydrogen bonds govern the inhibition of the ATP hydrolysis of the multidrug transporter P-glycoprotein. Biochem. Pharmacol. **101**, 40–53 (2016)
21. Kettle, A.J., Robertson, I.G., Palmer, B.D., Anderson, R.F., Patel, K.B., Winterbourn, C.C.: Oxidative metabolism of amsacrine by the neutrophil enzyme myeloperoxidase. Biochem. Pharmacol. **44**, 1731–1738 (1992)
22. Afzal, A., Sarfraz, M., Wu, Z., Wang, G., Sun, J.: Integrated scientific data bases review on asulacrine and associated toxicity. Crit. Rev. Oncol. Hematol. **104**, 78–86 (2016)
23. Caponigro, F., Dittrich, C., Sorensen, J.B., Schellens, J.H.M., Duffaud, F., Paz Ares, L., Lacombe, D., de Balincourt, C., Fumoleau, P.: Phase II study of XR 5000, an inhibitor of topoisomerases I and II, in advanced colorectal cancer. Eur. J. Cancer **38**, 70–74 (2002)

24. Dittrich, C., Coudert, B., Paz-Ares, L., Caponigro, F., Salzberg, M., Gamucci, T., Paoletti, X., Hermans, C., Lacombe, D., Fumoleau, P.: European organization for research and treatment of cancer-early clinical studies group/new drug development programme (EORTC-ECSG/NDDP): phase II study of XR 5000 (DACA), an inhibitor of topoisomerase I and II, administered as a 120-h infusion in patients with non-small cell lung cancer. Eur. J. Cancer **39**, 330–334 (2003)

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Ježek, J.; Hlaváček, J.; Šebestík, J.

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