

REFERENCES

Adjuik, M., Agnamey, P., Babiker, A., Borrmann, S., Brasseur, P., Cisse, M., Cobelens, F., Diallo, S., Faucher, J.F., Garner, P., Gikunda, S., Kremsner, P.G., Krishna, S., Lell, B., Loolpapit, M., Matsiegui, P.B., Missinou, M.A., Mwanza, J., Ntoumi, F., Olliaro, P., Osimbo, P., Rezbach, P., Some, E. & Taylor, W.R.J. 2002. Amodiaquine-artesunate versus amodiaquine for uncomplicated *Plasmodium falciparum* malaria in African children: a randomised, multicentre trial. *Lancet*, 359:1365-1372.

Amuasi, J.H., Diap, G., Nguah, S.B., Karikari, P., Boakye, I., Jambai, A., Lahai, W.K., Louie, K.S. & Kiechel, J.R. 2012. Access to artemisinin-combination therapy (ACT) and other anti-malarials: National Policy and Markets in Sierra Leone. *Plos one*, 7:1-9.

Araújo, N.C., Barton, V., Jones, M., Stocks, P.A., Ward, S.A., Davies, J., Bray, P.G., Shone, A.E., Cristiano, M.L. & O'Neill, P.M. 2009. Semi-synthetic and synthetic 1, 2, 4-trioxaquines and 1, 2, 4-trioxolaquines: synthesis, preliminary SAR and comparison with acridine endoperoxide conjugates. *Bioorganic & medicinal chemistry letters*, 7:2038-2043.

Auparakkitanon, S., Noonpakdee, W., Ralph, R., Denny, W. & Wilairat, P. 2003. Antimalarial 9-anilinoacridine compounds directed at hemozoin. *Antimicrobial agents and chemotherapy*, 47:3708-3712.

Baird, J.K. & Hoffman, S.L. 2004. Primaquine therapy for malaria. *Clinical Infectious Diseases*, 39:1336-1345.

Basco, L.K., Mitaku, S., Skaltsounis, A.L., Ravelomanantsoa, N., Tillequin, F., Koch, M. & Le Bras, J. 1994. *In vitro* activities of furoquinoline and acridone alkaloids against *Plasmodium falciparum*. *Antimicrobial agents and chemotherapy*, 38:1169-1171.

Batty, K., Salman, S., Moore, B.R., Benjamin, J., Lee, S.T., Page-Sharp, M., Pitus, N., Ilett, K.F., Mueller, I., Hombhanje, F.W., Siba, P. & Davis, T.M. 2012. Artemisinin-naphthoquine combination therapy for uncomplicated pediatric malaria: a pharmacokinetic study. *Antimicrobial agents and chemotherapy*, 56:2472-2484.

Benjamin, J., Moore, B., Lee, S.T., Senn, M., Griffin, S., Lautu, D., Salman, S., Siba, P., Mueller, I. & Davis, T.M. 2012. Artemisinin-naphthoquine combination therapy for uncomplicated pediatric malaria: a tolerability, safety, and preliminary efficacy study. *Antimicrobial agents and chemotherapy*, 56:2465-2471.

Berman, J., Brown, L., Miller, R., Andersen, S.L., McGreevy, P., Schuster, B.G., Ellis, W., Ager, A. & Rossan, R. 1994. Antimalarial activity of WR 243251: a dihydroacridinedione. *Antimicrobial agents and chemotherapy*, 38:1753-1756.

Bergmann-Leitner, E.S., Duncan, E.H., Mullen, G.E., Burge, J.R., Khan, F., Long, C.A., Angov, E. & Lyon, J.A. 2006. Critical evaluation of different methods for measuring the functional activity of antibodies against malaria blood stage antigens. *American journal of tropical medicine and hygiene*, 75:437-442.

Biagini, G.A., Fisher, N., Berry, N., Stocks, P.A., Meunier, B., Williams, D.P., Bonar-Law, R., Bray, P.G., Owen, A., O'Neill, P.M. & Ward, S.A. 2008. Acridinediones: selective and potent inhibitors of the malaria parasite mitochondrial *bc1* complex. *Molecular pharmacology*, 73:1347-1355.

Borstnik, K., Paik, I.H., Shapiro, T.A. & Posner, G.H. 2002. Antimalarial chemotherapeutic peroxides: artemisinin, yingzhaosu A and related compounds. *International journal for parasitology*, 32:1661-1667.

Bouchaud, O., Imbert, P., Touze, J.E., Dodo, A.N.O., Danis, M. & Legros, F. 2009. Fatal cardiotoxicity related to halofantrine: a review based on a worldwide safety data base. *Malaria journal*, 8:289-296.

Briolant, S., Fusaï, T., Rogier, C. & Pradines, B. 2008. Tetracycline antibiotics in malaria. *Open tropical medicine journal*, 1:31-46.

Burgess, S.J., Selzer, A., Kelly, J.X., Smilkstein, M.J., Riscoe, M.K. & Peyton, D.H. 2006. A chloroquine-like molecule designed to reverse resistance in *Plasmodium falciparum*. *Journal of medicinal chemistry*, 49:5623-5625.

CDC (Centre for Disease Control). 2009. *Plasmodium falciparum* life cycle. Atlanta Georgia. <http://www.dpd.cdc.gov/dpdx> Date of access: 15 July 2013.

Charman, S.A., Arbe-Barnes, S., Bathurst, I.C., Brun, R., Campbell, M., Charman, W.N., Chiu, F.C.K., Chollet, J., Craft, J.C., Creek, D.J., Dong, Y., Matile, H., Maurer, M., Morizzi, J., Nguyen, T., Papastogiannidis, P., Scheurer, C., Shackelford, D.M., Sriraghavan, K., Stingelin, L., Tang, Y., Urwyler, H., Wang, X., White, K.L., Wittlin, S., Zhou, L. & Vennerstrom, J.L. 2011. Synthetic ozonide drug candidate OZ439 offers new hope for a single-dose cure of uncomplicated malaria. *Proceedings of the National Academy of Sciences*, 108:4400-4405.

Chavalitshewinkoon, P., Wilairat, P., Gamage, S., Denny, W., Figgitt, D. & Ralph, R. 1993. Structure-activity relationships and modes of action of 9-anilinoacridines against chloroquine-resistant *Plasmodium falciparum* *in vitro*. *Antimicrobial agents and chemotherapy*, 37:403-406.

- Chen, P.Q., Li, G.Q. & Guo, X.B. 1994. The infectivity of gametocytes of *Plasmodium falciparum* from patients treated with artemisinin. *Chinese medical journal*, 107:709-711.
- Chibale, K., Moss, J.R., Blackie, M., van Schalkwyk, D. & Smith, P.J. 2000. New amine and urea analogs of ferrochloroquine: synthesis, antimalarial activity *in vitro* and electrochemical studies. *Tetrahedron letters*, 41:6231-6235.
- Ciesielska, E., Pastwa, E. & Szmigiero, L. 1997. Inhibition of mammalian topoisomerase I by 1-nitro-9-aminoacridines: dependence on thiol activation. *Acta biochimica Polonica*, 44:775-780.
- Coggeshall, L.T. 1952. The treatment of malaria. *American journal of tropical medicine and hygiene*, 1:124-131.
- Coleman, R.E., Polsa, N., Eikarat, N., Kollars, T.M. & Sattabongkot, J. 2001. Prevention of sporogony of *Plasmodium vivax* in *Anopheles dirus* mosquitoes by transmission-blocking antimalarials. *American journal of tropical medicine and hygiene*, 65:214-218.
- Croft, A.M. 2007. A lesson learnt: the rise and fall of Lariam and Halfan. *Journal of the Royal Society of Medicine*, 100:170-174.
- Croft, S.L., Duparc, S., Arbe-Barnes, S.J., Craft, J.C., Shin, C-S., Fleckenstein, L., Borghini-Fuhrer, I. & Rim, H.J. 2012. Review of pyronaridine anti-malarial properties and product characteristics. *Malaria journal*, 11:270-298.
- Cui, L. & Su, X.Z. 2009. Discovery, mechanisms of action and combination therapy of artemisinin. *Expert review of anti-infective therapy*, 8:999-1013.
- Davis, T.M., Karunajeewa, H.A. & Ilett, O.F. 2005. Artemisinin-based combination therapies for uncomplicated malaria. *Medical journal of Australia*, 182:181-185.
- De, D., Krogstad, F.M., Byers, L.D., Krogstad, D.J. 1998. Structure-activity relationships for antiplasmodial activity among 7-substituted 4-aminoquinolines. *Journal of medicinal chemistry*, 41:4918-4926.
- Dinio, T., Goraka, A.P., McGinniss, A., Roepe, P.D. & Morgan, J.B. 2012. Investigating the activity of quinine analogues versus chloroquine resistant *Plasmodium falciparum*. *Bioorganic & medicinal chemistry*, 20:3292-3297.
- Dunne, M.W., Singh, N., Shukla, M., Valecha, N., Bhattacharyya, P.C., Dev, V., Patel, K., Mohapatra, M.K., Lakhani, J., Benner, R., Lele, C. & Patki, K. 2005. A multicenter study of azithromycin, alone and in combination with chloroquine, for the treatment of acute

uncomplicated *Plasmodium falciparum* malaria in India. *Journal of infectious diseases*, 191:1582-1588.

Eastman, R.T., Dharia, N.V., Winzeler, E.A. & Fidock, D.A. 2011. Piperaquine resistance is associated with a copy number variation on chromosome 5 in drug pressured *Plasmodium falciparum* parasites. *Antimicrobial agents and chemotherapy*, 55:3908-3916.

Eckstein-Ludwig, U., Webb, R.J., van Goethem, L.D.A., East, J.M., Lee, A.G., Kimura, M., O'Neill, P.M., Bray, P.G., Ward, S.A. & Krishna, S. 2003. Artemisinins target the SERCA of *Plasmodium falciparum*. *Nature*, 424:957-961.

Elueze, E.I., Croft, S.I. & Warhurst, D.C. 1996. Activity of pyronaridine and mepacrine against twelve strains of *Plasmodium falciparum* *in vitro*. *Journal of antimicrobial chemotherapy*, 37:511-518.

Fernando, D., Rodrigo, C. & Rajapakse, S. 2011. Primaquine in *vivax* malaria: an update and review on management issues. *Malaria journal*, 10:351-363.

Fink, G., Dickens, W.T., Jordan, M. & Cohen, J.L. 2013. Access to subsidized ACT and malaria treatment: evidence from the first year of the AMFm program in six districts in Uganda. *Health policy and planning*, 1-11.

Frédérich, M., Dogné, J.M., Angenot, L. & de Mol, P. 2002. New trends in anti-malarial agents. *Current medicinal chemistry*, 9:1435-1456.

Fügi, M.A., Wittlin, S., Dong, Y. & Vennerstrom, J.L. 2010. Probing the antimalarial mechanism of artemisinin and OZ277 (arterolane) with nonperoxidic isosteres and nitroxyl radicals. *Antimicrobial agents and chemotherapy*, 54:1042-1046.

Fujioka, H., Kato, N., Fujita, M., Fujimura, K. & Nishiyama, Y. 1990. Activities of new acridone alkaloid derivatives against *Plasmodium yoelii* *in vitro*. *Arzneimittelforschung*, 40:1026-1029.

Fujioka, H., Nishiyama, Y., Furukawa, H. & Kumada, N. 1989. *In vitro* and *in vivo* activities of atalaphillinine and related acridone alkaloids against rodent malaria. *Antimicrobial agents and chemotherapy*, 33:6-9.

Gogtay, N.J., Kadam, V.S., Karnad, D.R., Kanbur, A., Kamtekar, K.D. & Kshirsagar, N.A. 2000. Probable resistance to parenteral artemether in *Plasmodium falciparum*: case reports from Mumbai (Bombay), India. *Annals of tropical medicine and parasitology*, 94:519-520.

- Gomes, M., Ribeiro, I., Warsame, M., Karunajeewa, H. & Petzold, M. 2008. Rectal artemisinins for malaria: a review of efficacy and safety from individual patient data in clinical studies. *BMC infectious diseases*, 8:39.
- Harchut, K., Standley, C., Dobson, A., Klaassen, B., Rambaud-Althaus, C., Althaus, F. & Nowak, K. 2013. Over-diagnosis of malaria by microscopy in the Kilombero valley, Southern Tanzania: an evaluation of the utility and cost-effectiveness of rapid diagnostic tests. *Malaria journal*, 12:159-167.
- Hawkins, V.N., Joshi, H., Rungsihirunrat, K., Na-Bangchang, K. & Sibley, C.H. 2007. Antifolates can have a role in the treatment of *Plasmodium vivax*. *Trends in parasitology*, 23:213-222.
- Hay, S.I., Guerra, C.A., Tatem, A.T., Noor, A.M. & Snow, R.W. 2004. The global distribution and population at risk of malaria: past, present, and future. *Lancet infectious diseases*, 4:327-336.
- Haynes, R.K. & Krishna, S. 2004. Artemisinins: activities and actions. *Microbes and infection*, 6:1339-1346.
- Haynes, R.K., Monti, D., Taramelli, D., Basilio, N., Parapini, S. & Olliaro, P. 2003. Artemisinin antimalarials do not inhibit hemozoin formation. *Antimicrobial agents and chemotherapy*, 47:1175.
- Haynes, R.K., Fugmann, B., Stetter, J., Rieckmann, K., Heilmann, H.D., Chan, H.W., Cheung, M.K., Lam, W.L., Wong, H.N., Croft, S.L., Vivas, L., Rattray, L., Stewart, L., Peters, W., Robinson, B.L., Edstein, M.D., Kotecka, B., Kyle, D.E., Beckermann, B., Gerisch, M., Radtke, M., Schmuck, G., Steinke, W., Wollborn, U., Schmeer, K. & Römer, A. 2006. Artemisone: a highly active antimalarial drug of the artemisinin class. *Angewandte Chemie International Edition*, 45:2082-2088.
- Hombhanje, F.W. & Huang, Q. 2010. Review: artemisinin-naphthoquine combination (ARCO®): an overview of the progress. *Pharmaceuticals*, 3:3581-3593.
- Hombhanje, F.W., Linge, D., Saweri, A., Kuanch, C., Jones, R., Toraso, S., Jacobed, G., Geita, J., Masta, A., Kevau, I., Hiawalyer, G. & Sapuri, M. 2009. Artemisinin naphthoquine combination (ARCOTM) therapy for uncomplicated *falciparum* malaria in adults of Papua New Guinea: a preliminary report on safety and efficacy. *Malaria journal*, 8:196-204.
- Hong, Y.L., Yang, Y.Z. & Meshnick, S.R. 1994. The interaction of artemisinin with malarial hemozoin. *Molecular and biochemical parasitology*, 63:121-128.

Hulsman, N., Medema, J.P., Bos, C., Jongejan, A., Leurs, R., Smit, M.J., de Esch, I.J., Richel, D. & Wijtmans, M. 2007. Chemical Insights in the concept of hybrid drugs: the antitumor effect of nitric oxide-donating aspirin involves a quinone methide but not nitric oxide nor aspirin. *Journal of medicinal chemistry*, 50:2424-2431.

Ittarat, W., Sreepian, A., Srisarin, A. & Pathepchotivong, K. 2003. Effect of dihydroartemisinin on the antioxidant capacity of *P. falciparum*-infected erythrocytes. *South-East Asian journal of tropical medicine and public health*, 34:744-750.

Jaycox, G.D., Gribble, G.W. & Hacker, M.P. 1987. Potential DNA bis-intercalating agents: synthesis and antitumor activity of novel, conformationally restricted bis (9-aminoacridines). *Journal of heterocyclic chemistry*, 24:1405-1408.

Johansson, T., Jurva, U., Gönberg, G., Weidolf, L. & Masimirembwa, C. 2009. Novel metabolites of amodiaquine formed by CYP1A1 and CYP1B1: structure elucidation using electrochemistry, mass spectrometry, and NMR. *Drug metabolism and disposition*, 37:571-579.

Jones, M., Mercer, A.E., Stocks, P.A., La Pensée, L.J.I., Cosstick, R., Kevin Park, B., Kennedy, M.E., Piantanida, I., Ward, S.A., Davies, J., Bray, P.G., Rawe, S.L., Baird, J., Charidza, T., Janneh, O. & O'Neill, P.M. 2009. Antitumour and antimalarial activity of artemisinin-acridine hybrids. *Bioorganic & medicinal chemistry letters*, 19:2033-2037.

Kannan, R., Kumar, K., Sahal, D., Kukreti, S. & Chauhan, V.S. 2005. Reaction of artemisinin with haemoglobin: implications for antimalarial activity. *Biochemical journal*, 385:409-418.

Kannan, R., Sahal, D. & Chauhan, V.S. 2002. Heme-artemisinin adducts are crucial mediators of the ability of artemisinin to inhibit heme polymerization. *Chemistry & biology*, 9:321-332.

Karunajeewa, H.A., Manning, L., Mueller, I., Ilett, K.F. & Davis, T.M. 2007. Rectal administration of artemisinin derivatives for the treatment of malaria. *Journal of the American Medical Association*, 297:2381-2390.

Katzung, B.G., Masters, S.B. & Trevor, A.J. 2001. Basic & clinical pharmacology. New York: McGraw-Hill Medical.

Kesten, S.J., Degnan, M.J., Hung, J., McNamara, D.J., Ortwine, D.F., Uhlendorf, S.E. & Werbel, L.M. 1992. Synthesis and antimalarial properties of 1-Imino derivatives of 7-Chloro-3-substituted-3, 4-dihydro-1, 9 (2H, 10H)-acridinediones and related structures. *Journal of medicinal chemistry*, 35:3429-3447.

Kitchener, S. 2003. The military experience of mefloquine malaria chemoprophylaxis. *ADF health*, 4:34-38.

- Kokwaro, G., Mwai, L. & Nzila, A. 2007. Artemether/lumefantrine in the treatment of uncomplicated *falciparum* malaria. *Expert opinion on pharmacotherapy*, 8:75-94.
- Krishna, S., Uhlemann, A.C. & Haynes, R.K. 2004. Artemisinin: mechanisms of action and potential for resistance. *Drug resistance updates*, 7:233-244.
- Krungkrai, S.R. & Yuthavong, Y. 1987. The antimalarial action on *Plasmodium falciparum* of qinghaosu and artesunate in combination with agents which modulate oxidant stress. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 81:710-714.
- Kumar, A., Srivastava, K., Raja Kumar, S., Puri, S.K. & Chauhan, P.M.S. 2009. Synthesis of 9-anilinoacridine triazines as new class of hybrid antimalarial agents. *Bioorganic & medicinal chemistry letters*, 19:6996-6999.
- Kumar, A., Srivastava, K., Raja Kumar, S., Puri, S.K. & Chauhan, P.M.S. 2010. Synthesis of new 4-aminoquinolines and quinoline-acridine hybrids as antimalarial agents. *Bioorganic & medicinal chemistry letters*, 20:7059-7063.
- Kumar, N. & Zheng, H. 1990. Stage-specific gametocytocidal effect *in vitro* of the antimalaria drug qinghaosu on *Plasmodium falciparum*. *Parasitology research*, 76:214-218.
- Kurth, F., B elard, S., Basra, A. & Ramharter, M. 2011. Pyronaridine-artesunate combination therapy for the treatment of malaria. *Current opinion in infectious diseases*, 24:564-569.
- Kurth, F., Pongratz, P., B elard, S., Mordm uller, B., Kremsner, P.G. & Ramharter, M. 2009. *In vitro* activity of pyronaridine against *Plasmodium falciparum* and comparative evaluation of anti-malarial drug susceptibility assays. *Malaria journal*, 8:79-84.
- Lake, B.G. 1999. Coumarin metabolism, toxicity and carcinogenicity: relevance for human risk assessment. *Food and chemical toxicology*, 37:423-453.
- Li, W., Mo, W., Shen, D., Sun, L., Wang, J., Lu, S., Gitschier, J.M. & Zhou B. 2005. Yeast model uncovers dual roles of mitochondria in action of artemisinin. *PLoS genetics*, 1:e36.
- Loup, C., Lelievre, J., Benoit-Vical, F. & Meunier, B. 2007. Trioxaquinones and heme-artemisinin adducts inhibit the *in vitro* formation of hemozoin better than chloroquine. *Antimicrobial agents and chemotherapy*, 51:3768-3770.
- Luxemburger, C., Brockman, A., Silamut, K., Nosten, F.V., Gimenez, F., Chongsuphajaisiddhi, T. & White, N.J. 1998. Two patients with *falciparum* malaria and poor *in vivo* responses to artesunate. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 92:668-669.

- Maltha, J., Gillet, P., Cnops, L., van den Ende, J., van Esbroeck, M. & Jacobs, J. 2010. Malaria rapid diagnostic tests: *Plasmodium falciparum* infections with high parasite densities may generate false positive *Plasmodium vivax* pLDH lines. *Malaria journal*, 9:198-204.
- Manyando, C., Mkandawire, R., Puma, L., Sinkala, M., Mpabalwani, E., Njunju, E., Gomes, M., Ribeiro, I., Walter, V., Virtanen, M., Schlienger, R., Cousin, M., Chipimo, M. & Sullivan, F.M. 2010. Safety of artemether-lumefantrine in pregnant women with malaria: results of a prospective cohort study in Zambia. *Malaria journal*, 9:249-260.
- Mberu, E.K., Nzila, A.M., Nduati, E., Ross, A., Monks, S.M., Kokwaro, G.O., Watkins, M. & Sibley, C.H. 2002. *Plasmodium falciparum*: *in vitro* activity of sulfadoxine and dapson in field isolates from Kenya: point mutations in dihydropteroate synthase may not be the only determinants in sulfa resistance. *Experimental parasitology*, 101:90-96.
- Meshnick, S.R. 1996. Is haemozoin a target for antimalarial drugs? *Annals of tropical medicine and parasitology*, 90:367-372.
- Meshnick, S.R. 2002. Artemisinin: mechanisms of action, resistance and toxicity. *International journal for parasitology*, 32:1655-1660.
- Meunier, B. 2008. Hybrid molecules with a dual mode of action: dream or reality? *Accounts of chemical research*, 41:69-77.
- Mharakurwa, S., Thuma, P.E., Norris, D.E., Mulenga, M., Chalwe, V., Chipeta, J., Munyati, S., Mutambu, S., Mason, P.R. & for the Southern Africa ICEMR Team. 2012. Malaria epidemiology and control in Southern Africa. *Acta tropica*, 121:202-206.
- Moody, A. 2002. Rapid diagnostic tests for malaria parasites. *Clinical microbiology reviews*, 15:66-78.
- Moonasar, D., Asomugha, C., Baker, L., Blumberg, L., Barnes, K.I., Maharaj, R. & Benson, F. 2011. Preventing disease and saving lives: the malaria season is upon us. *South African medical journal*, 101:865-867.
- Moonasar, D., Nuthulaganti, T., Kruger, P.S., Mabuza, A., Rasiswi, E.S., Benson, F.G. & Maharaj, R. 2012. Malaria control in South Africa 2000-2010: beyond MDG6. *Malaria journal*, 11:294-300.
- Morphy, R. & Rankovic, Z. 2005. Designed multiple ligands: an emerging drug discovery paradigm. *Journal of medicinal chemistry*, 21:6523-6543.

- Müller, I.B. & Hyde, J.E. 2013. Folate metabolism in human malaria parasites: 75 years on. *Molecular & biochemical parasitology*, 88:63-77.
- Murray, C.K. & Bennett, J.W. 2009. Rapid diagnosis of malaria. *Interdisciplinary perspectives on infectious diseases*, 2009:1-7.
- Nagelschmitz, J., Voith, B., Wensing, G., Roemer, A., Fugmann, B., Haynes, R.K., Kotecka, B.M., Rieckmann, K.H. & Edstein, M.D. 2008. First assessment in humans of the safety, tolerability, pharmacokinetics, and ex vivo pharmacodynamic antimalarial activity of the new artemisinin derivative artemisone. *Antimicrobial agents and chemotherapy*, 52:3085-3091.
- Nasveld, P.E., Edstein, M.D., Reid, M., Brennan, L., Harris, I.E., Kitchener, S.J., Leggat, P.A., Pickford, P., Kerr, C., Ohrt, C., Prescott, W. & Tafenoquine Study Team. 2010. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. *Antimicrobial agents and chemotherapy*, 54:792-798.
- Nosten, F. & White, N.J. 2007. Artemisinin-based combination treatment of *falciparum* malaria. *American journal of tropical medicine and hygiene*, 77:181-192.
- Nussenzweig, R.S. & Long, C.A. 1994. Malaria vaccines: Multiple Targets. *Science*, 265:1381-1383.
- Nzila, A. 2006. The past, present and future of antifolates in the treatment of *Plasmodium falciparum* infection. *Journal of antimicrobial chemotherapy*, 57:1043-1054.
- O'Neill, P.M., Barton, V.E. & Ward, S.A. 2010. The molecular mechanism of action of artemisinin: the debate continues. *Molecules*, 15:1705-1721.
- Oduola, A.M., Sowunmi, A., Milhous, W.K., Kyle, D.E., Martin, R.K., Walker, O. & Salako, L.A. 1992. Innate resistance to new antimalarial drugs in *Plasmodium falciparum* from Nigeria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 86:123-126.
- Olliaro, P.L. 2001. Mode of action and mechanisms of resistance for antiplasmodial drugs. *Pharmacology & therapeutics*, 89:207-219.
- Olliaro, P.L., Haynes, R.K., Meunier, B. & Yuthavong, Y. 2001. Possible modes of action of the artemisinin-type compounds. *Trends in parasitology*, 17:122-126.
- Opsenica, D.M. & Šolaja, B.A. 2012. Artemisinins and synthetic peroxides as highly efficient antimalarials. *Macedonian journal of chemistry and chemical engineering*, 31:137-182.

- Pandey, A.V., Tekwani, B.L., Singh, R.L. & Chauhan, V.S. 1999. Artemisinin, an endoperoxide antimalarial disrupts the hemoglobin catabolism and heme detoxification systems in malaria parasite. *Journal of biological chemistry*, 274:19383-19388.
- Pérez, B., Teixeira, C., Gomes, A.S., Albuquerque, I.S., Gut, J., Rosenthal, P.J., Prudêncio, M. & Gomes, P. 2013. *In vitro* efficiency of 9-(*N*-cinnamoylbutyl)aminoacridines against blood- and liver-stage malaria parasites. *Bioorganic & medicinal chemistry letters*, 23:610-3.
- Pinto, C.M.A. & Tenreiro Machado, J.A. 2013. Fractional model for malaria transmission under control strategies. *Computers and mathematics with applications*, 66:908-916.
- Ploypradith, P. 2004. Development of artemisinin and its structurally simplified trioxane derivatives as antimalarial drugs. *Acta tropica*, 89:329-342.
- Ponts, N. & Le Roch, K.G. 2013. Malaria. (In Ginsburg, G.S. & Willard, H.F., eds. *Genomic and Personalized Medicine*. 2nd ed. Elsevier Books. p. 1191-1210.)
- Pooley, S., Fatih, F.A., Krishna, S., Gerisch, M., Haynes, R.K., Wong, H.N. & Staines, H.M. 2011. Artemisone uptake in *Plasmodium falciparum*-infected erythrocytes. *Antimicrobial agents and chemotherapy*, 55:550-556.
- Pradel, G. & Schlitzer, M. 2010. Antibiotics in malaria therapy and their effect on the parasite apicoplast. *Current molecular medicine*, 10:335-349.
- Pradines, B., Briolant, S., Henry, M., Oeuvray, C., Baret, E., Amalvict, R., Didillon, E. & Rogier, C. 2010. Absence of association between pyronaridine *in vitro* responses and polymorphisms in genes involved in quinoline resistance in *Plasmodium falciparum*. *Malaria journal*, 9:1-7.
- Pretorius, S.I., Breytenbach, J.W., de Kock, C., Smith, P.J. & N'Da, D.D. 2013. Synthesis, characterization and antimalarial activity of quinoline-pyrimidine hybrids. *Bioorganic & medicinal chemistry*, 21:269-277.
- Price, R.N. 2013. Potential of artemisinin-based combination therapies to block malaria transmission. *Journal of infectious diseases*, 207:1627-1629.
- Price, R.N., Nosten, F., Luxemburger, C., ter Kuile, F.O., Paiphun, L., Chongsuphajaisiddhi, T. & White, N.J. 1996. Effects of artemisinin derivatives on malaria transmissibility. *The Lancet*, 347:1654-1658.
- Price, R., van Vugt, M., Phaipun, L., Luxemburger, C., Simpson, J., McGready, R., Kuile, F.T., Khan, A., Chongsuphajaisiddhi, T., White, N.J. & Nosten, F. 1999. Adverse effects in patients

with acute *falciparum* malaria treated with artemisinin derivatives. *American journal of tropical medicine and hygiene*, 60:547-555.

Randrianarivelojosa, M., Raharimalala, L.A., Randrianasolo, L., Ratsimbasoa, A., Rason, M.A., Arie, F. & Jambou, R. 2001. Madagascan isolates of *Plasmodium falciparum* showing low sensitivity to artemether *in vitro*. *Annals of tropical medicine and parasitology*, 95:237-243.

Reyburn, H., Mbatia, R., Drakeley, C., Bruce, J., Carneiro, I., Olomi, R., Cox, J., Nkya, W.M., Lemnge, M., Greenwood, B.M. & Riley, E.M. 2005. Association of transmission intensity and age with clinical manifestations and case fatality of severe *Plasmodium falciparum* malaria. *Journal of the American Medical Association*, 293:1461-1470.

Ridley, R.G., Hofheinz, W., Matile, H., Jaquet, C., Dorn, A., Masciadri, R., Jolidon, S., Richter, W.F., Guenzi, A., Girometta, M.A., Urwyler, H., Huber, W., Thaithong, S. & Peters, W. 1996. 4-aminoquinoline analogs of chloroquine with shortened side chains retain activity against chloroquine-resistant *Plasmodium falciparum*. *Antimicrobial agents and chemotherapy*, 40:1846-1854.

Rogers, W.O., Sem, R., Tero, T., Chim, P., Lim, P., Muth, S., Socheat, D., Arie, F. & Wongsrichanalai, C. 2009. Failure of artesunate-mefloquine combination therapy for uncomplicated *Plasmodium falciparum* malaria in southern Cambodia. *Malaria journal*, 8:10-18.

Rudrapal, M. 2011. A brief review on malaria and current antimalarial drugs. *Current pharma research*, 1:286-292.

Sahr, F., Willoughby, V.R., Gbakima, A.A. & Bockarie, M.J. 2001. Apparent drug failure following artesunate treatment of *Plasmodium falciparum* malaria in Freetown, Sierra Leone: four case reports. *Annals of tropical medicine and parasitology*, 95:445-449.

Salcedo-Sora, J.E. & Ward, S.A. 2013. The folate metabolic network of *falciparum* malaria. *Molecular & biochemical parasitology*, 188:51-62.

Sashidhara, K.V., Kumar, A., Dodda, R.P., Krishna, N.N., Agarwal, P., Srivastava, K. & Puri, S.K. 2012. Coumarin-trioxane hybrids: synthesis and evaluation as a new class of antimalarial scaffolds. *Bioorganic & medicinal chemistry letters*, 22:3926-3930.

Schlagenhauf, P & Petersen, E. 2013. Current challenges in travelers' malaria. *Current infectious disease reports*, 15:307-315.

Schlagenhauf, P., Adamcova, M., Regep, L., Schaerer, M.T. & Rhein, H. 2010. The position of mefloquine as a 21st century malaria chemoprophylaxis. *Malaria journal*, 9:357-371.

- Schlitzer, M. 2008. Antimalarial drugs: what is in use and what is in the pipeline. *Archiv der Pharmazie: Chemistry in life sciences*, 341:149-163.
- Schneider, J., Evans, E.L., Grunberg, E. & Ian Fryer, R. 1972. Synthesis and biological activity of acronycine analogs. *Journal of medicinal chemistry*, 15:266-270.
- Shapiro, T.A. & Goldberg, D.E. 2006. Chemotherapy of parasitic infections. (In Brunton, L.L., Lazo, J.S. & Parker, K.L., eds. Goodman & Gilman's: the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill. p. 1021-1094.)
- Skinner, T.S., Manning, L.S., Johnston, W.A. & Davis, T.M. 1996. *In vitro* stage-specific sensitivity of *Plasmodium falciparum* to quinine and artemisinin drugs. *International journal for parasitology*, 26:519-525.
- Smith, T., Killeen, G.F., Maire, N., Ross, A., Molineaux, L., Tediosi, F., Hutton, G., Utzinger, J., Dietz, K. & Tanner, M. 2006. Mathematical modeling of the impact of malaria vaccines on the clinical epidemiology and natural history of *Plasmodium falciparum* malaria: overview. *American journal of tropical medicine and hygiene*, 72:1-10.
- Svensson, U.S., Maki-Jouppila, M., Hoffmann, K.J. & Ashton, M. 2003. Characterisation of the human liver *in vitro* metabolic pattern of artemisinin and auto-induction in the rat by use of nonlinear mixed effects modelling. *Biopharmaceutics & drug disposition publishers*, 24:71-85.
- Svoboda, G.H., Poore, G.A., Simpson, P.J. & Boder, G.B. 1966. Alkaloids of *Acronychia Baueri* Schott I: isolation of the alkaloids and a study of the antitumor and other biological properties of acronycine. *Journal of pharmaceutical sciences*, 55:758-768.
- Tambo, E., Adedeji, A.A., Huang, F., Chen, J-H., Zhou, S-S. & Tang, L-H. 2012. Scaling up impact of malaria control programmes: a tale of events in sub-Saharan Africa and People's Republic of China Tambo. *Infectious diseases of poverty*, 1:7-21.
- Tun, T., Tint, H.S., Lin, K., Kyaw, T.T., Myunt, M.K., Khaing, W. & Tun, Z.U. 2009. Efficacy of oral single dose therapy with artemisinin-naphthoquine phosphate in uncomplicated *falciparum* malaria. *Acta tropica*, 111:275-278.
- Valdés, A.F.C. 2011. Acridine and acridinones: old and new structures with antimalarial activity. *Open medicinal chemistry journal*, 5:11-20.
- Vale, N., Moreira, R. & Gomes, P. 2009. Primaquine revisited six decades after its discovery. *European journal of medicinal chemistry*, 44:937-953.

Valecha, N., Krudsood, S., Tangpukdee, N., Mohanty, S., Sharma, S.K., Tyagi, P.K., Anvikar, A., Mohanty, R., Rao, B.S., Jha, A.C., Shahi, B., Singh, J.P., Roy, A., Kaur, P., Kothari, M., Mehta, S., Gautam, A., Paliwal, J.K., Arora, S. & Saha, N. 2012. Arterolane maleate plus piperazine phosphate for treatment of uncomplicated *Plasmodium falciparum* malaria: a comparative, multicenter, randomized clinical trial. *Clinical infectious diseases*, 55:663-671.

Valecha, N., Looareesuwan, S., Martensson, A., Abdulla, S.M., Krudsood, S., Tangpukdee, N., Mohanty, S., Mishra, S.K., Tyagi, P.K., Sharma, S.K., Moehrle, J., Gautam, A., Roy, A., Paliwal, J.K., Kothari, M., Saha, N., Dash, A.P. & Björkman, A. 2010. Arterolane, a new synthetic trioxolane for treatment of uncomplicated *Plasmodium falciparum* malaria: a phase II, multicenter, randomized, dose-finding clinical trial. *Clinical infectious diseases*, 51:684-961.

Van Eijk, A.M. & Terlouw, D.J. 2011. Azithromycin for treating uncomplicated malaria. New York: Wiley.

Van Heerden, L., Cloete, T.T., Breytenbach, J.W., De Kock, C., Smith, P.J., Breytenbach, J.C. & N'Da, D.D. 2012. Synthesis and *in vitro* antimalarial activity of a series of bisquinoline and bispyrrolo [1,2a] quinoxaline compounds. *European journal of medicinal chemistry*, 55:335-345.

Vennerstrom, J.L., Arbe-Barnes, S., Brun, R., Charman, S.A., Chiu, F.C., Chollet, J., Dong, Y., Dorn, A., Hunziker, D., Matile, H., McIntosh, K., Padmanilayam, M., Santo Tomas, J., Scheurer, C., Scoreneaux, B., Tang, Y., Urwyler, H., Wittlin, S. & Charman, W.N. 2004. Identification of an antimalarial synthetic trioxolane drug development candidate. *Nature*, 430:900-904.

Waknine-Grinberg, J.H., Hunt, N., Bentura-Marciano, A., James, A., McQuillan, J., Chan, H-W., Chan, W.C., Barenholz, Y., Haynes, R.K. & Golenser, J. 2010. Artemisone effective against murine cerebral malaria. *Malaria journal*, 9:227-241.

Walsh, J.J. & Bell, A. 2009. Hybrid drugs for malaria. *Current pharmaceutical design*, 15:2970-2985.

Walsh, J.J., Coughlan, D., Heneghan, N., Gaynor, C. & Bell, A. 2007. A novel artemisinin-quinine hybrid with potent antimalarial activity. *Bioorganic & medicinal chemistry letters*, 17:3599-3602.

Wang, J.Y., Cao, W.C., Shan, C.Q., Zhang, M., Li, G.F., Ding, D.D., Shi, Y.I. & Wu, B.A. 2004. Naphthoquine phosphate and its combination with artemisinin. *Acta tropica*, 89:375-381.

Warhurst, D.C. & Williams, J.E. 1996. Laboratory diagnosis of malaria. *Journal of clinical pathology*, 49:533-538.

Wells, T.N. & Poll, E.M. 2010. When is enough enough?: the need for a robust pipeline of high-quality antimalarials. *Discovery medicine*, 9:389-398.

Werbel, L.M., Hung, J., McNamara, D. & Ortwine, D.F. 1985. 3-Aryl-7-chloro-3, 4-dihydro-1, 9(2H, 10H) acridinedione: 1-hydrazones as potent antimalarial agents (1, 2). *European journal of medicinal chemistry*, 20:363-370.

White, N.J. 2002. Malaria. (In Cook, G.C. & Zumla, A.I., eds. *Manson's tropical diseases*. Philadelphia, Pa.: Saunders. p. 1201-1300.)

White, N.J. & Breman, J.G. 2008. Malaria. (In Fauci, A.S., Braunwald, E., Kasper, D.L., eds. *Harrison's principles of internal medicine*. 17th ed. New York: McGraw-Hill. p. 1280-93.)

WHO **see** World Health Organization.

World Health Organization. 2010. World malaria report 2010. Geneva: World Health Organization. <http://www.who.int/malaria/publications/atoz/9789241564106/en/index.html> Date of access: 20 April 2013.

World Health Organization. 2011. World malaria report 2011. Geneva: World Health Organization. <http://www.who.int/malaria/publications/atoz/9789241564403/en/index.html> Date of access: 20 April 2013.

World Health Organization. 2012. World malaria report 2012. Geneva: World Health Organization. http://www.who.int/malaria/publications/world_malaria_report_2012/report/en/index.html Date of access: 20 April 2013.

Winter, R.W., Kelly, J.X., Smilkstein, M.J., Dodean, R., Bagby, G.C., Keaney Rathbun, R., Levin, J.I., Hinrichs, D. & Riscoe, M.K. 2006. Evaluation and lead optimization of anti-malarial acridones. *Experimental parasitology*, 114:47-56.

Witkowski, B., Berry, A. & Benoit-Vical, F. 2009. Resistance to antimalarial compounds: methods and applications. *Drug resistance updates*, 12:42-50.

Wongsrichanalai, C. 2013. Artemisinin resistance or artemisinin-based combination therapy resistance? *Lancet*, 13:114-115.

Wongsrichanalai, C., Barcus, M.J., Muth, S., Sutamihardja, A. & Wernsdorfer, W.H. 2007. A review of malaria diagnostic tools: microscopy and rapid diagnostic test (RDT). *American journal of tropical medicine and hygiene*, 77:119-127.

Woodrow, C.J., Haynes, R.K. & Krishna, S. 2005. Artemisinins. *Postgraduate medical journal*, 81:71-78.

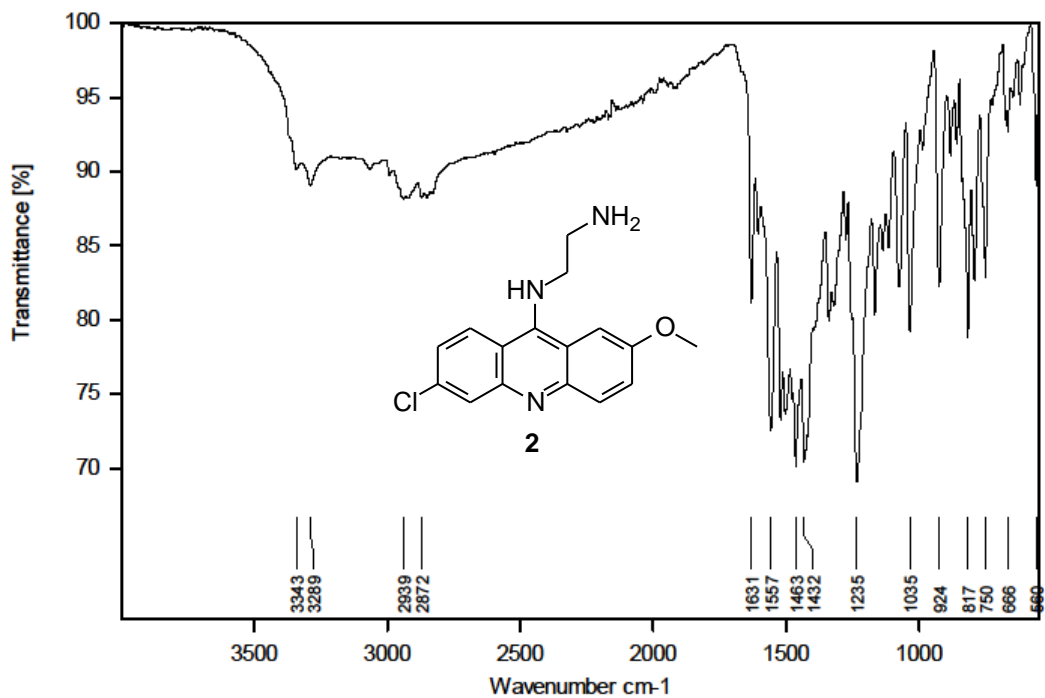
Yang, H., Liu, D., Yang, Y., Fan, B., Yang, P., Li, X., Li, C., Dong, Y. & Yang, C. 2003. Changes in susceptibility of *Plasmodium falciparum* to artesunate *in vitro* in Yunnan Province, China. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 97:226-228.

Yuthavong, Y. 2002. Basis for antifolate action and resistance in malaria. *Microbes and infection*, 4:175-182

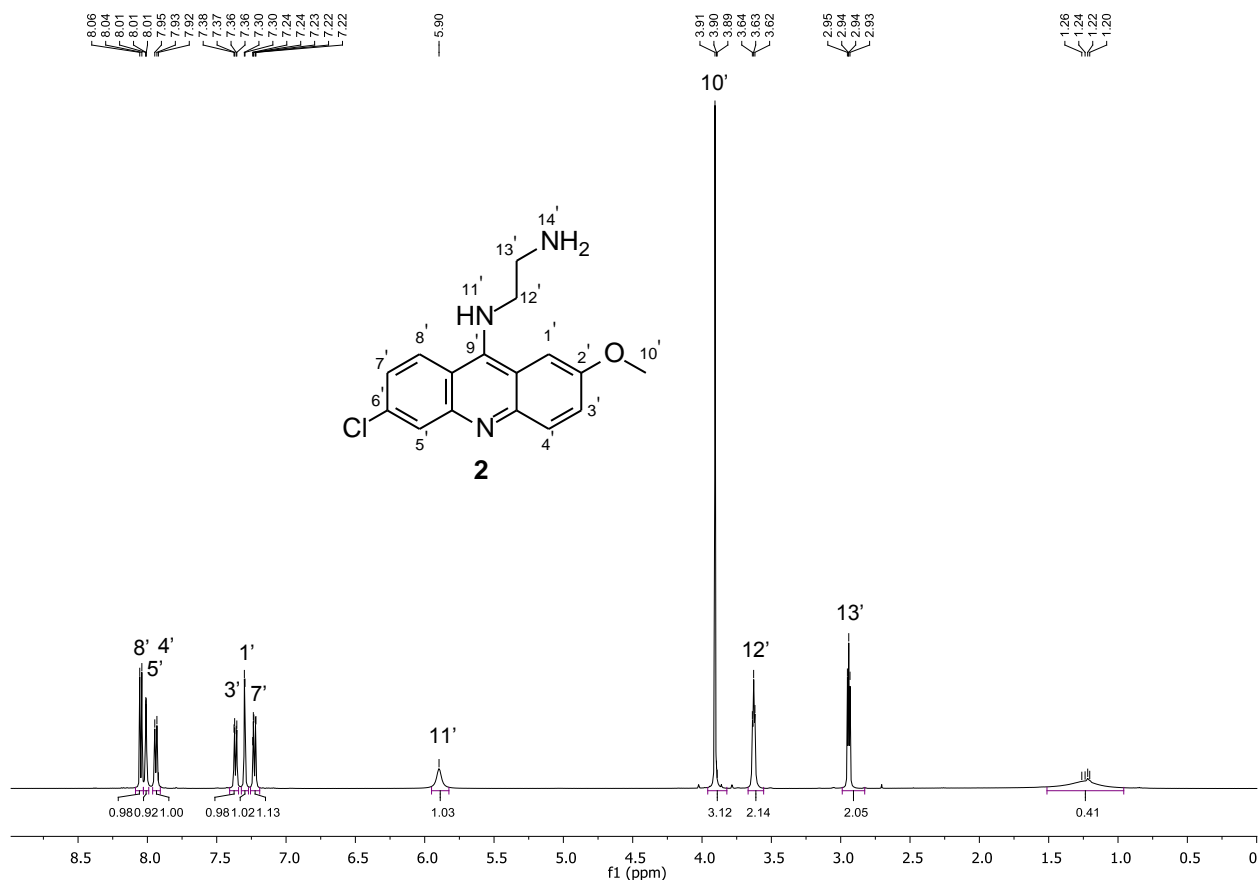
APPENDIX A: SPECTRA

Compound 2:

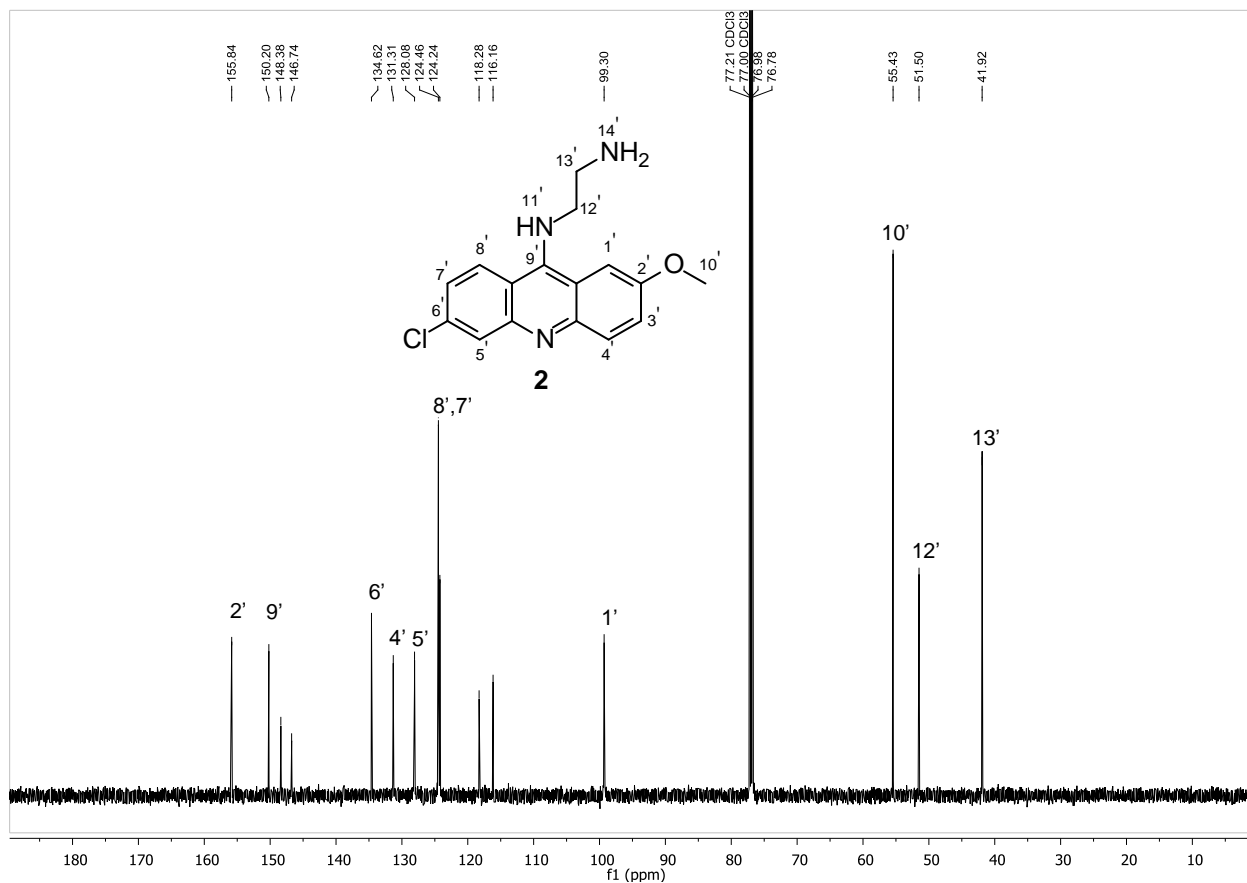
IR



¹H NMR



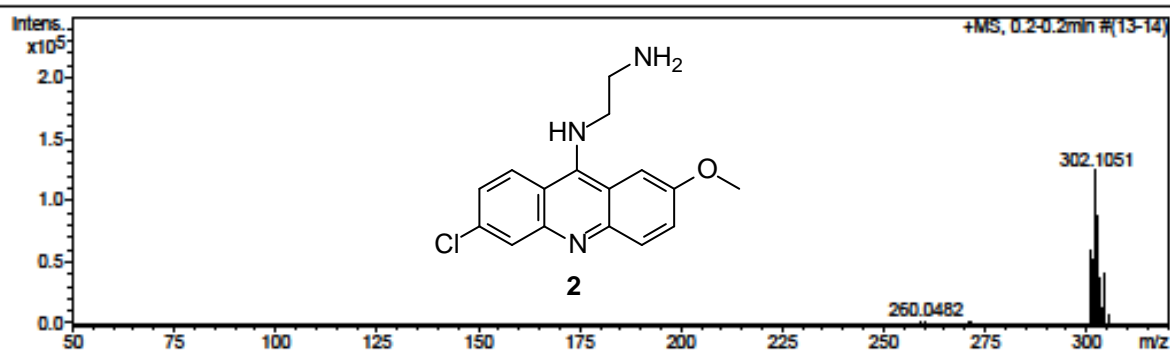
¹³C NMR



HRMS

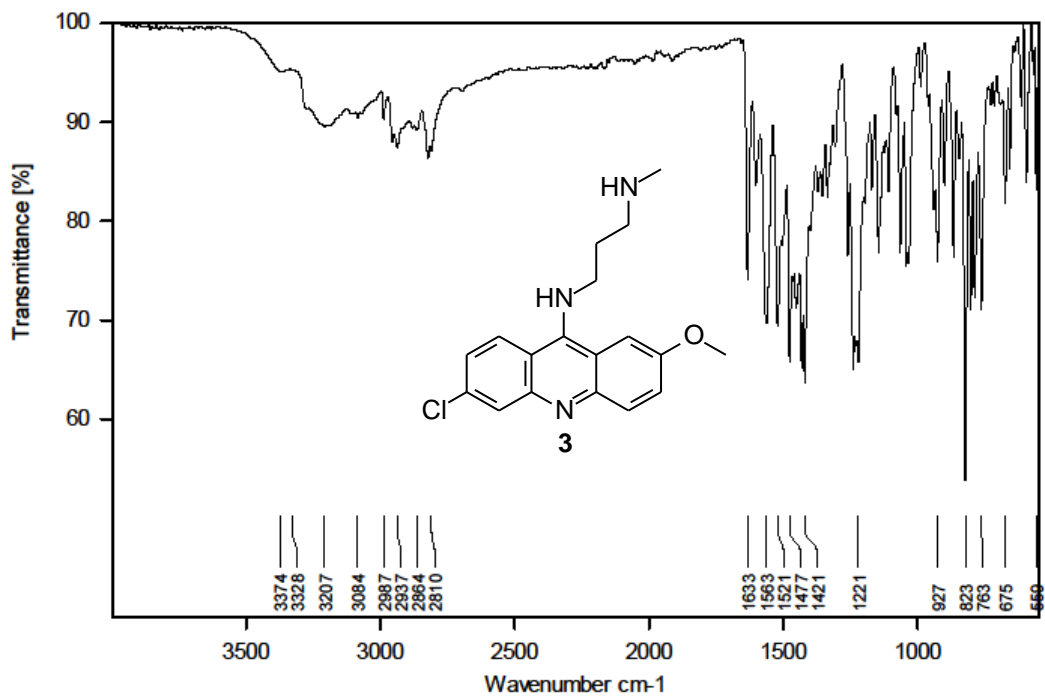
Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	1.6 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	8.0 l/min
Scan End	1500 m/z	Set Collision Cell RF	100.0 Vpp	Set Divert Valve	Waste

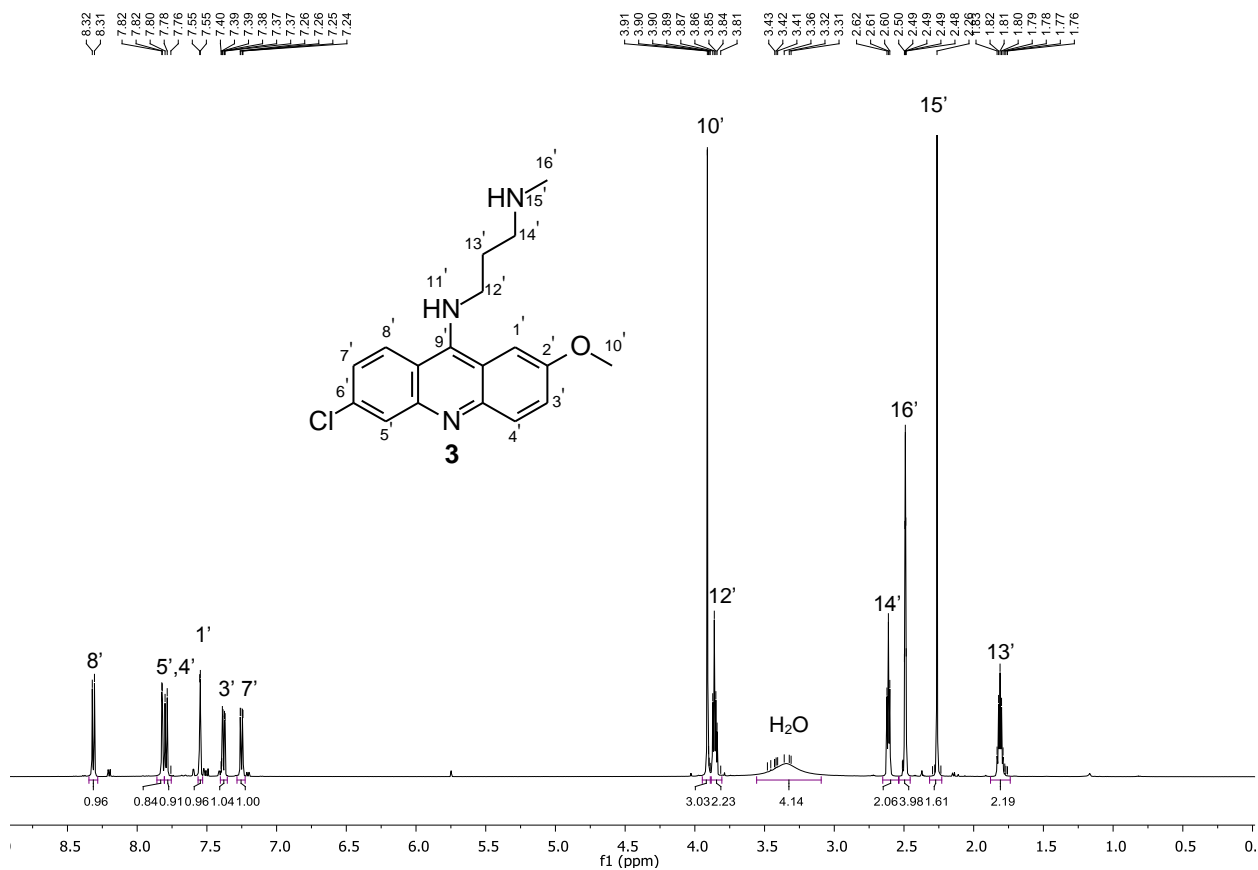


Compound 3:

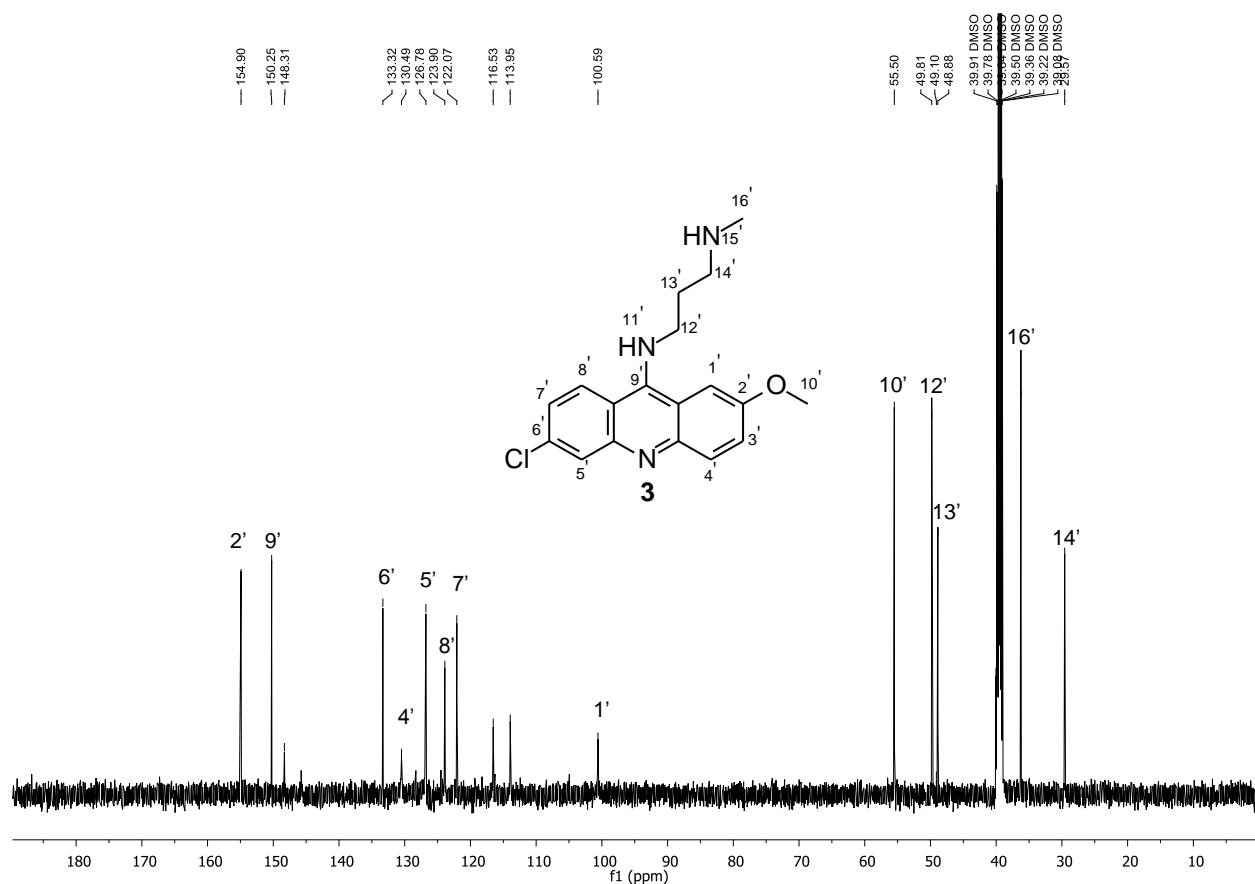
IR



¹H NMR



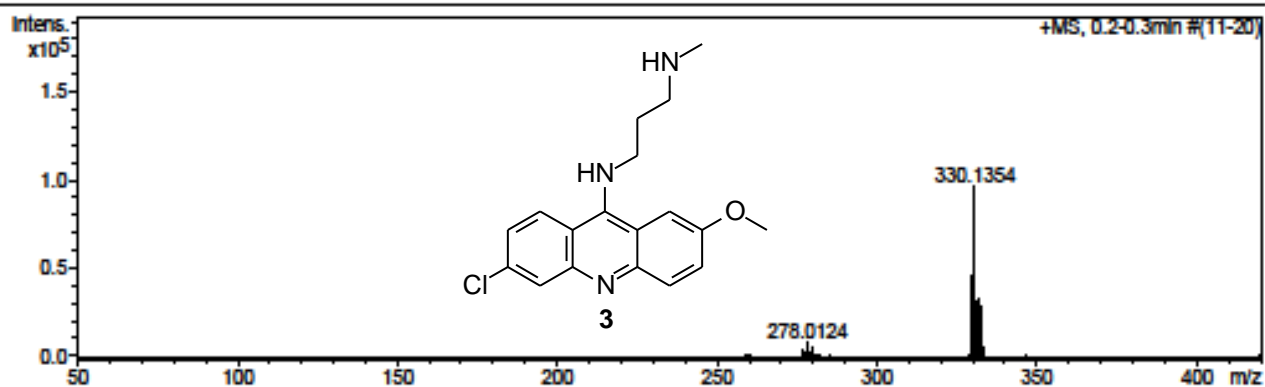
¹³C NMR



HRMS

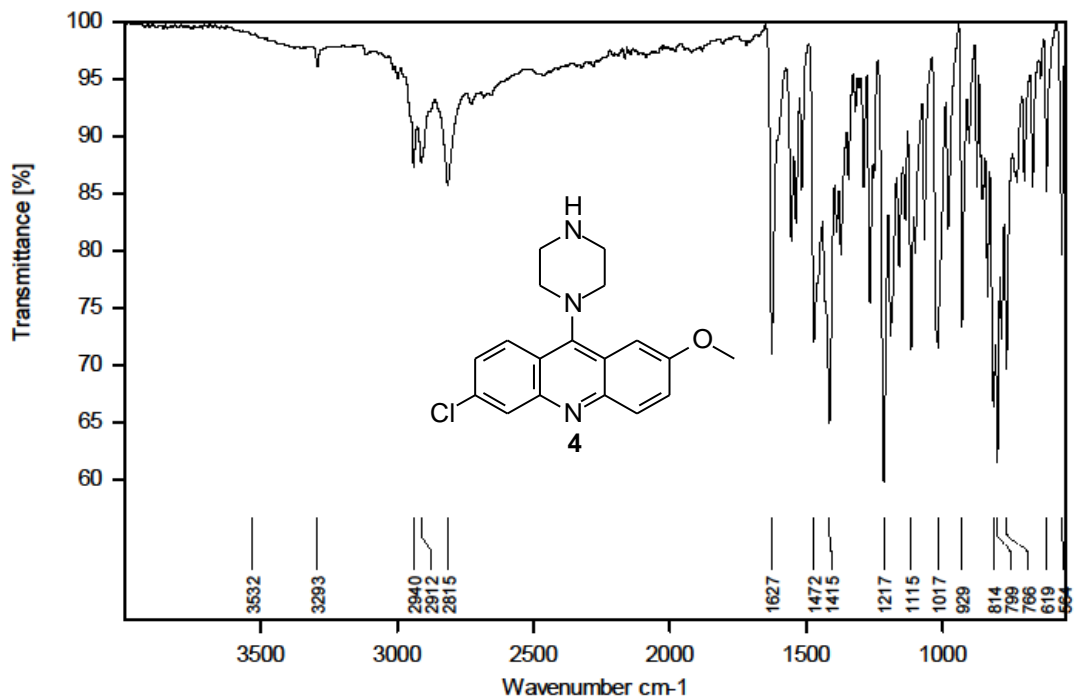
Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	1.6 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	8.0 l/min
Scan End	1500 m/z	Set Collision Cell RF	100.0 Vpp	Set Divert Valve	Waste

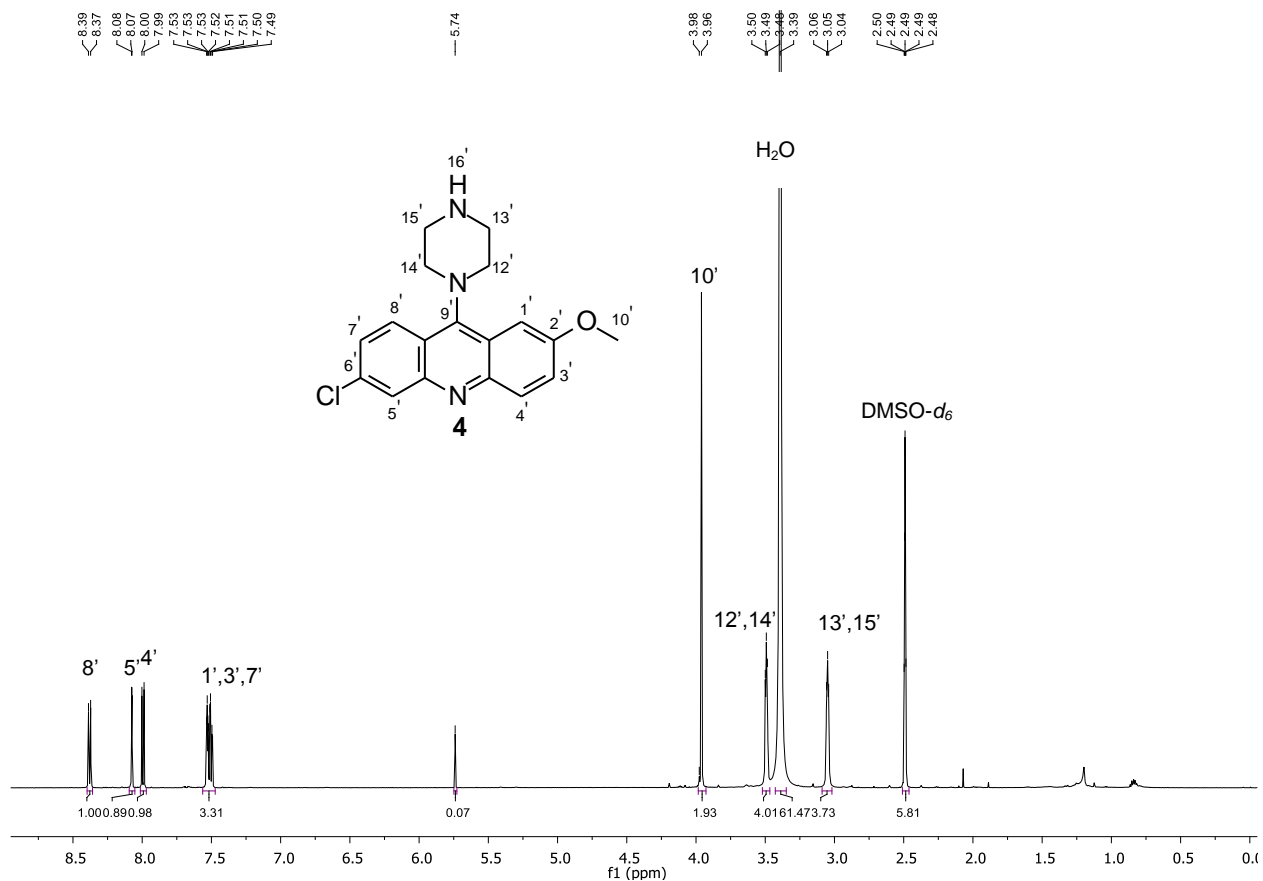


Compound 4:

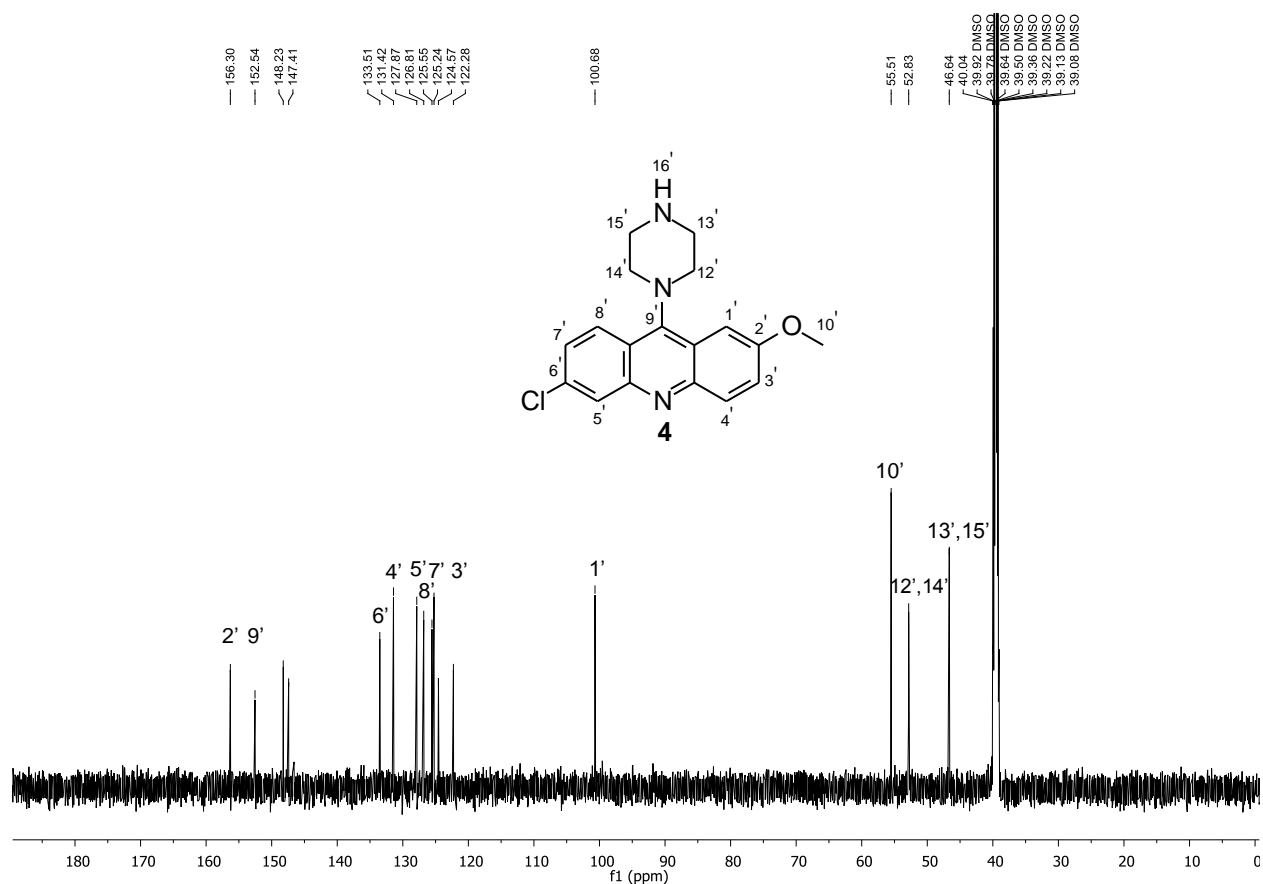
IR



¹H NMR



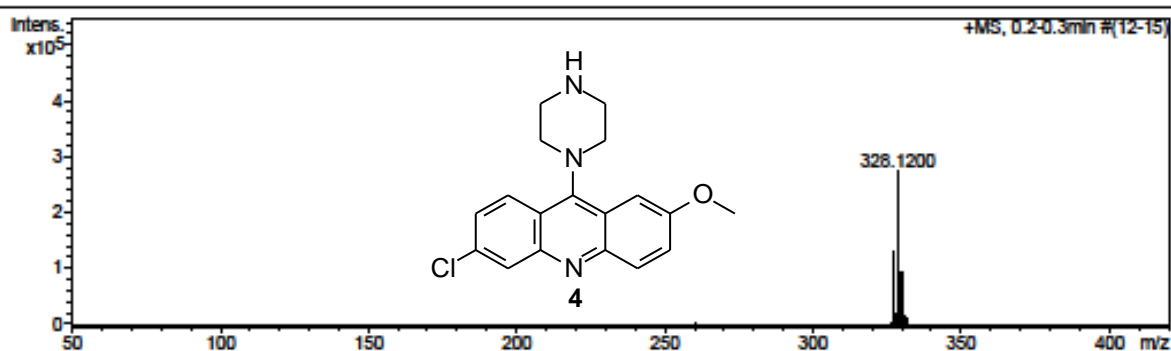
¹³C NMR



HRMS

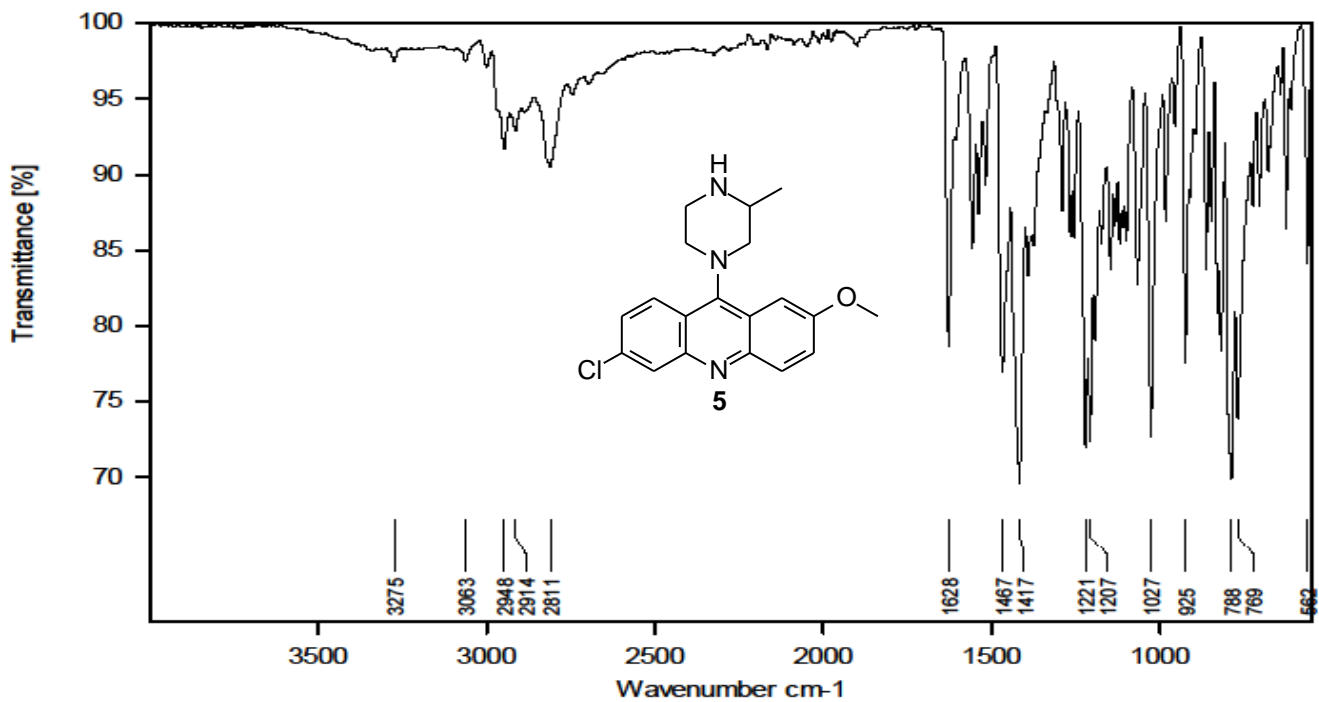
Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulzer	1.6 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	8.0 l/min
Scan End	1500 m/z	Set Collision Cell RF	100.0 Vpp	Set Divert Valve	Waste

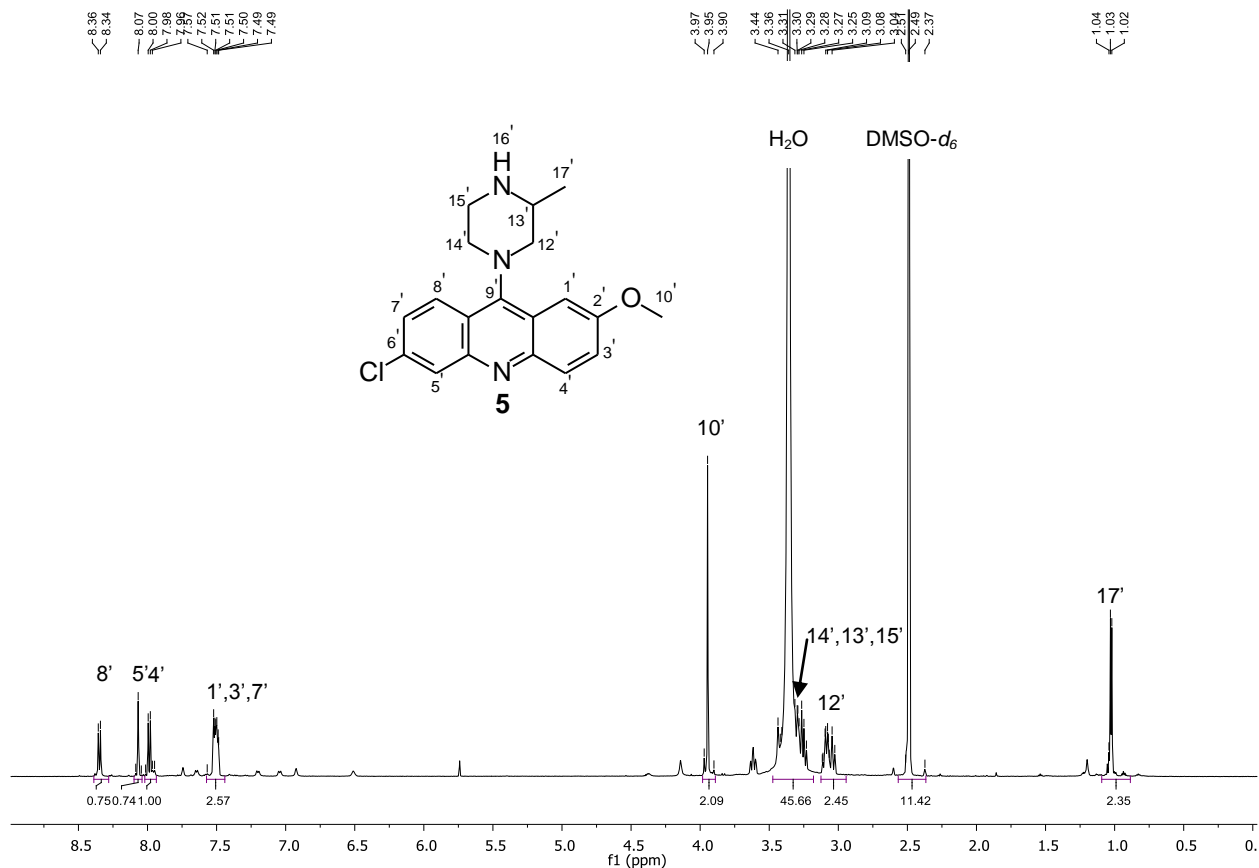


Compound 5:

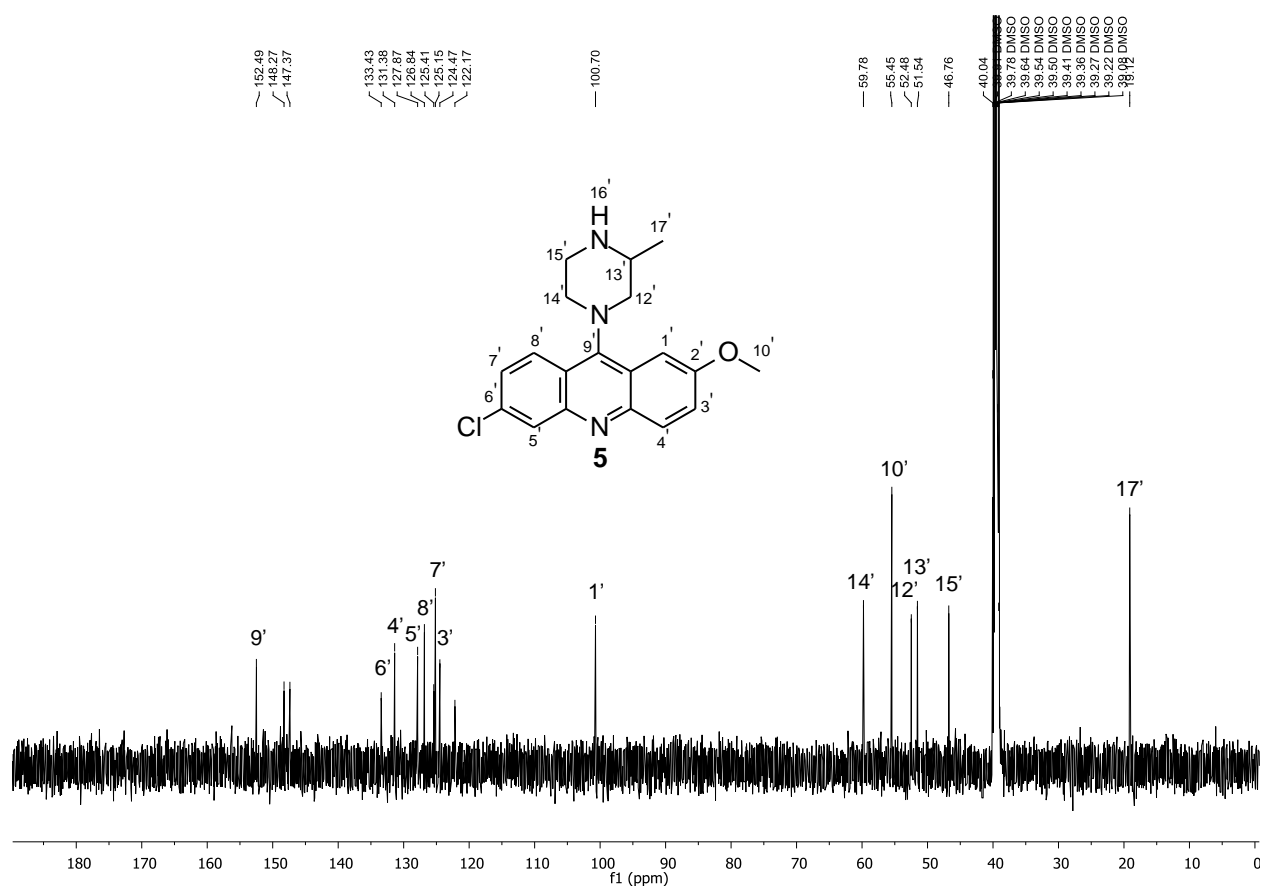
IR



¹H NMR



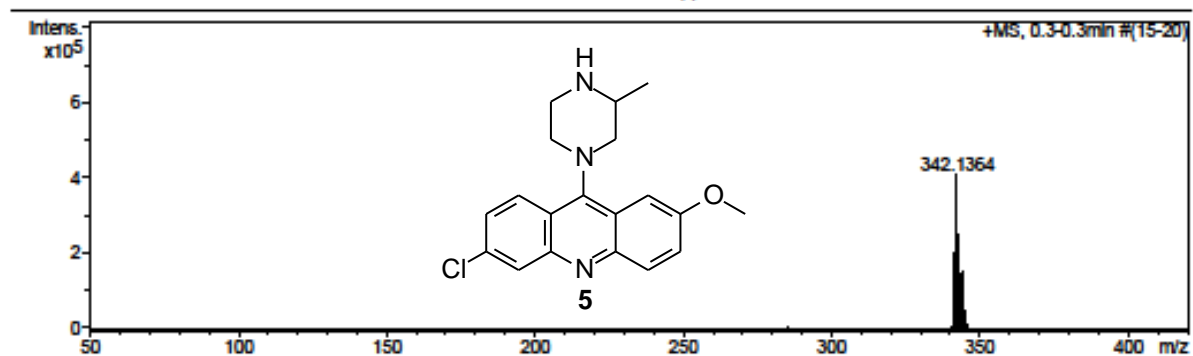
¹³C NMR



HRMS

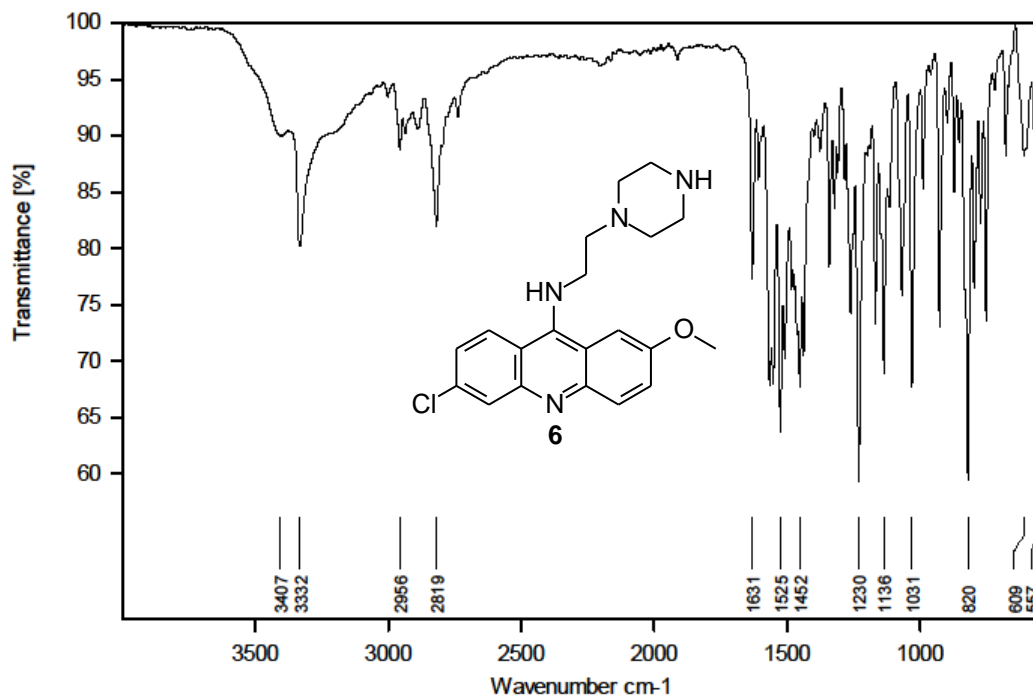
Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	1.6 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	8.0 l/min
Scan End	1500 m/z	Set Collision Cell RF	100.0 Vpp	Set Divert Valve	Waste

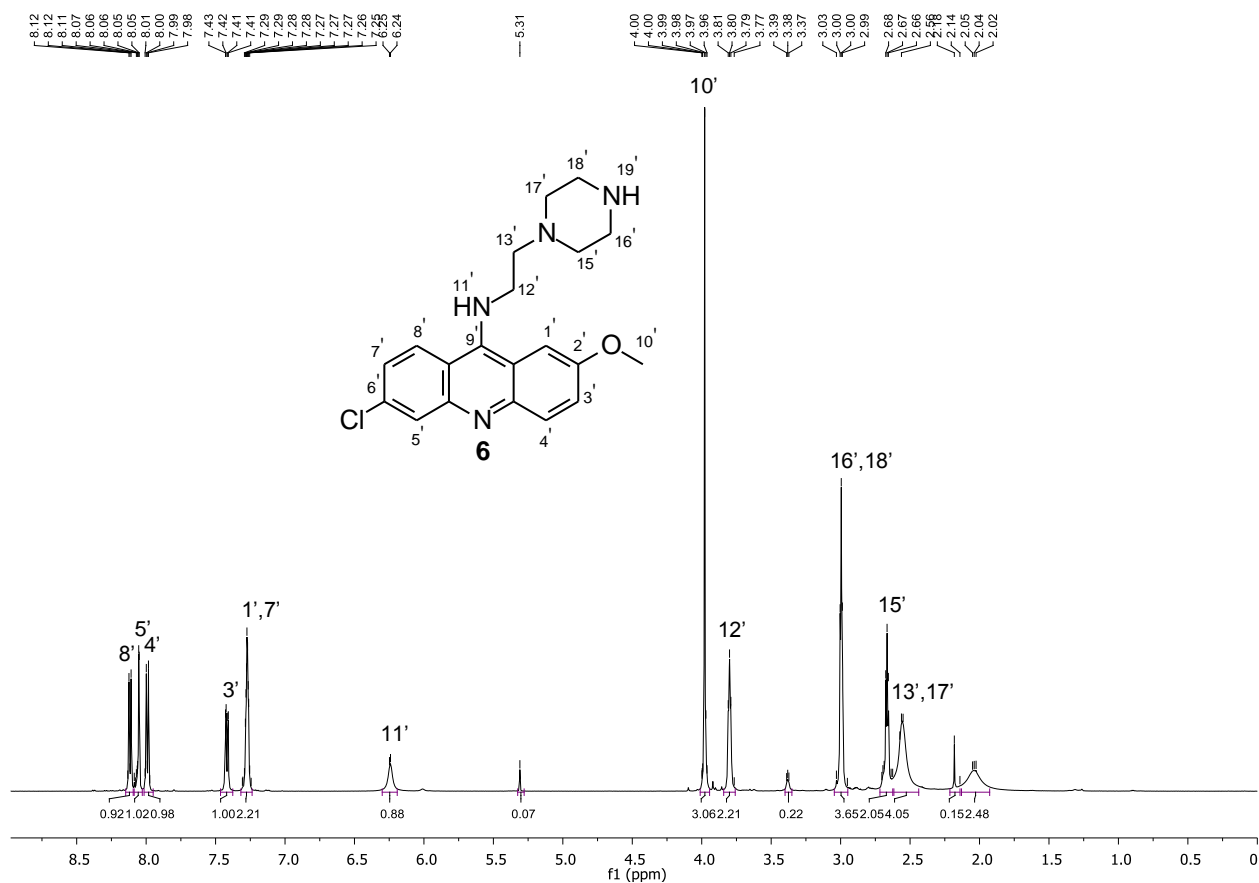


Compound 6:

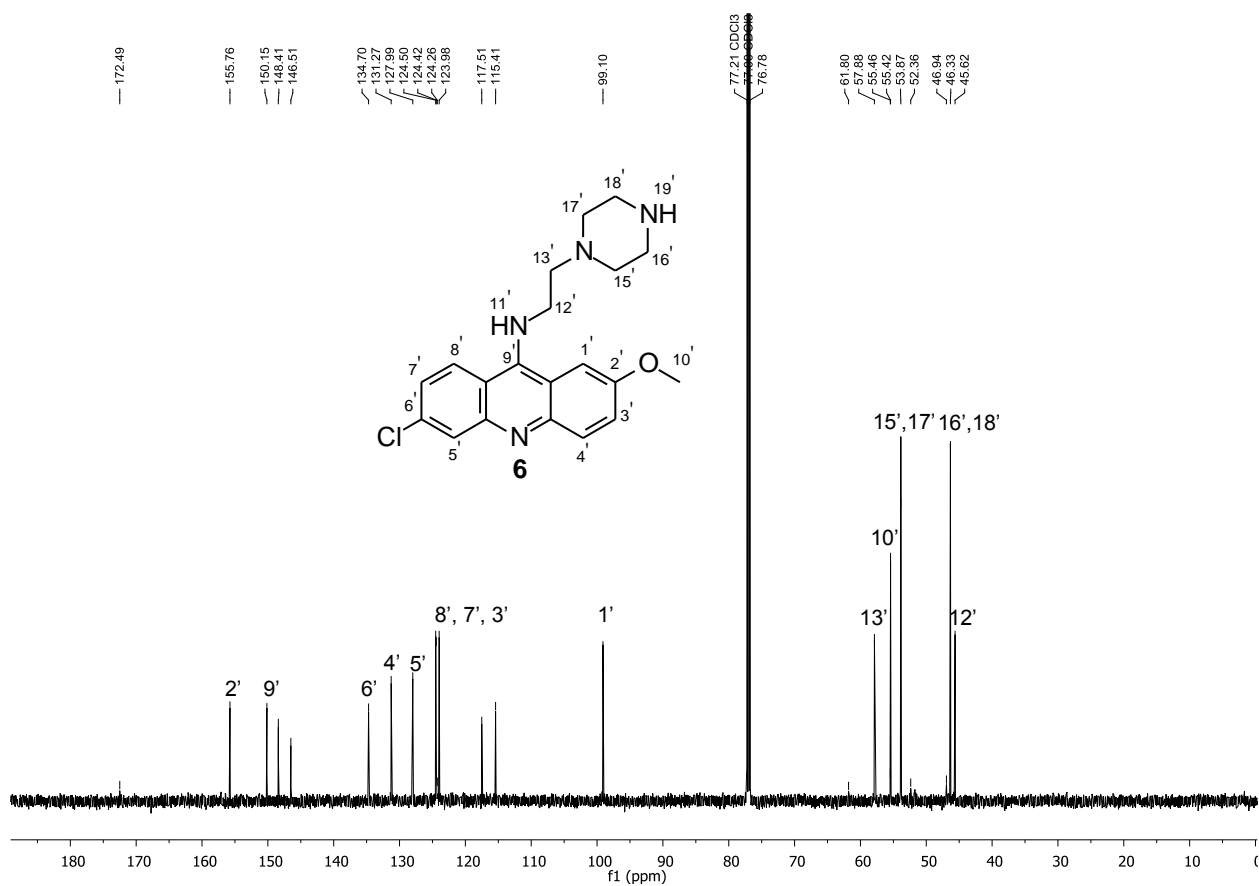
IR



¹H NMR



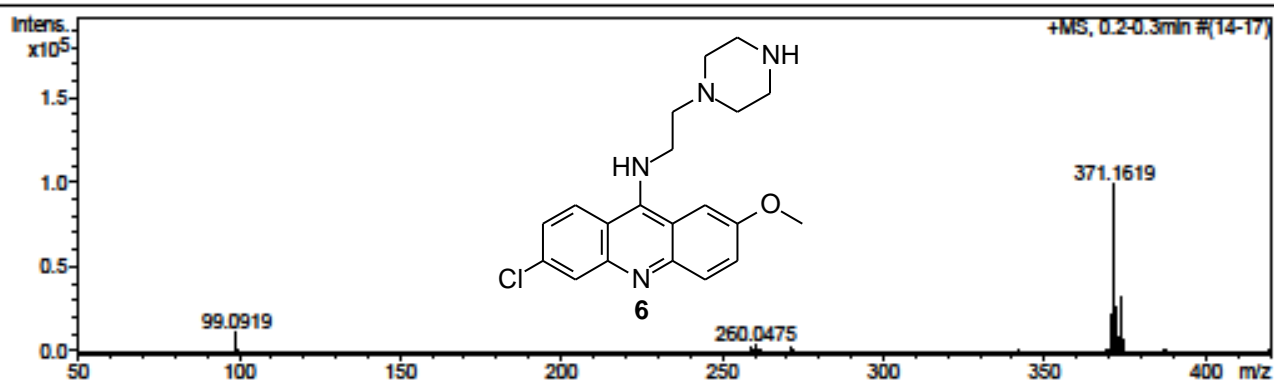
¹³C NMR



HRMS

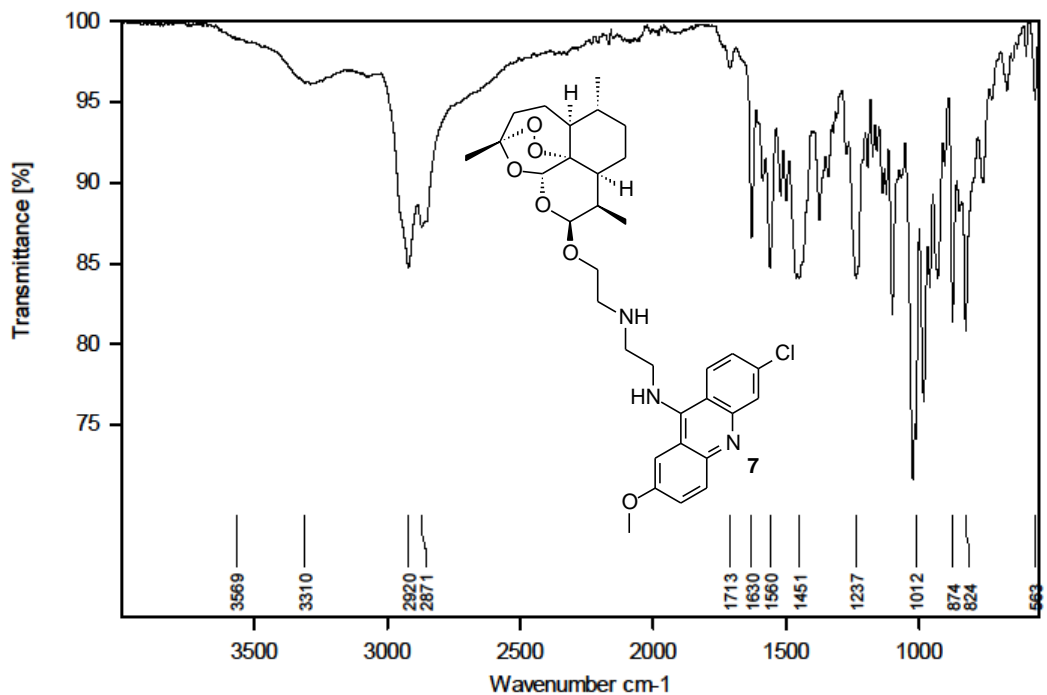
Acquisition Parameter

Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	1.6 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	8.0 l/min
Scan End	1500 m/z	Set Collision Cell RF	100.0 Vpp	Set Divert Valve	Waste

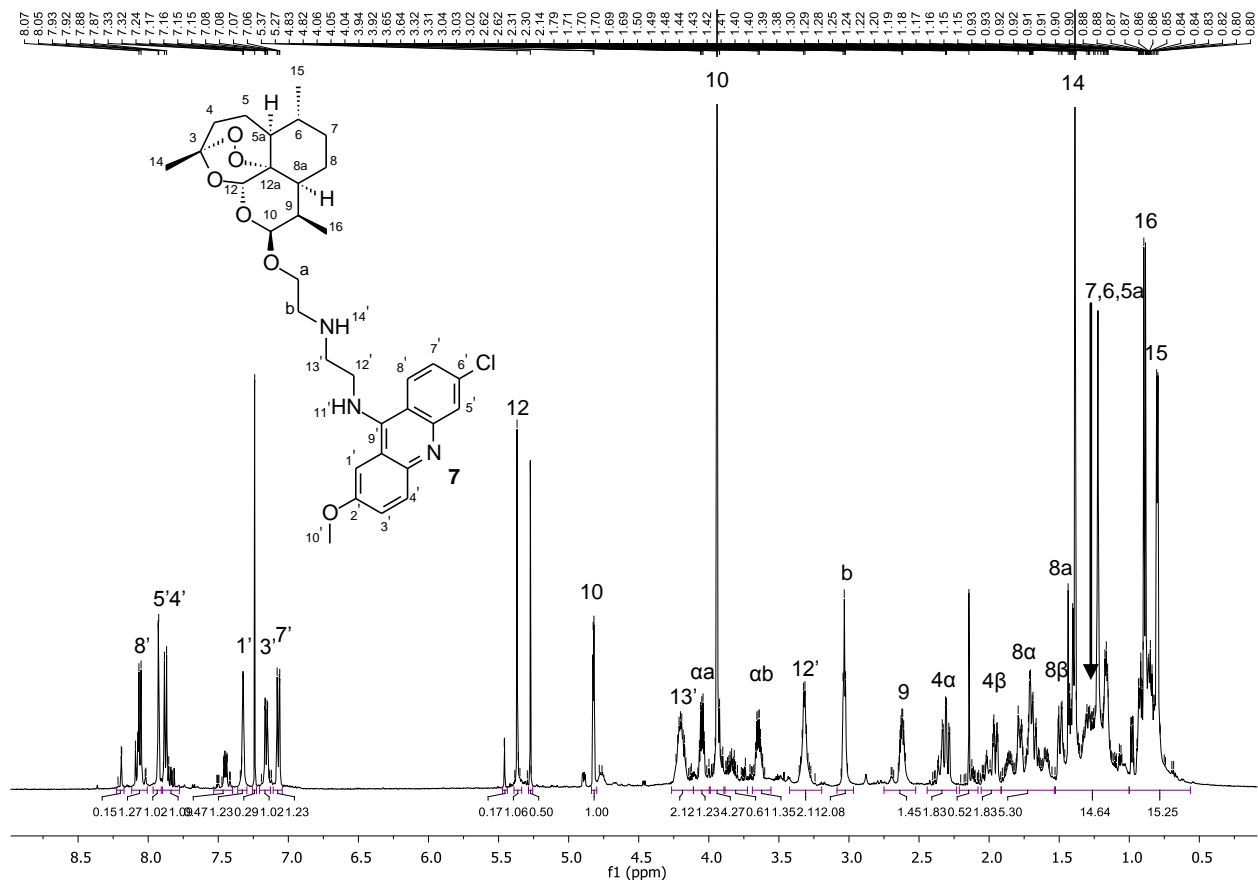


Compound 7:

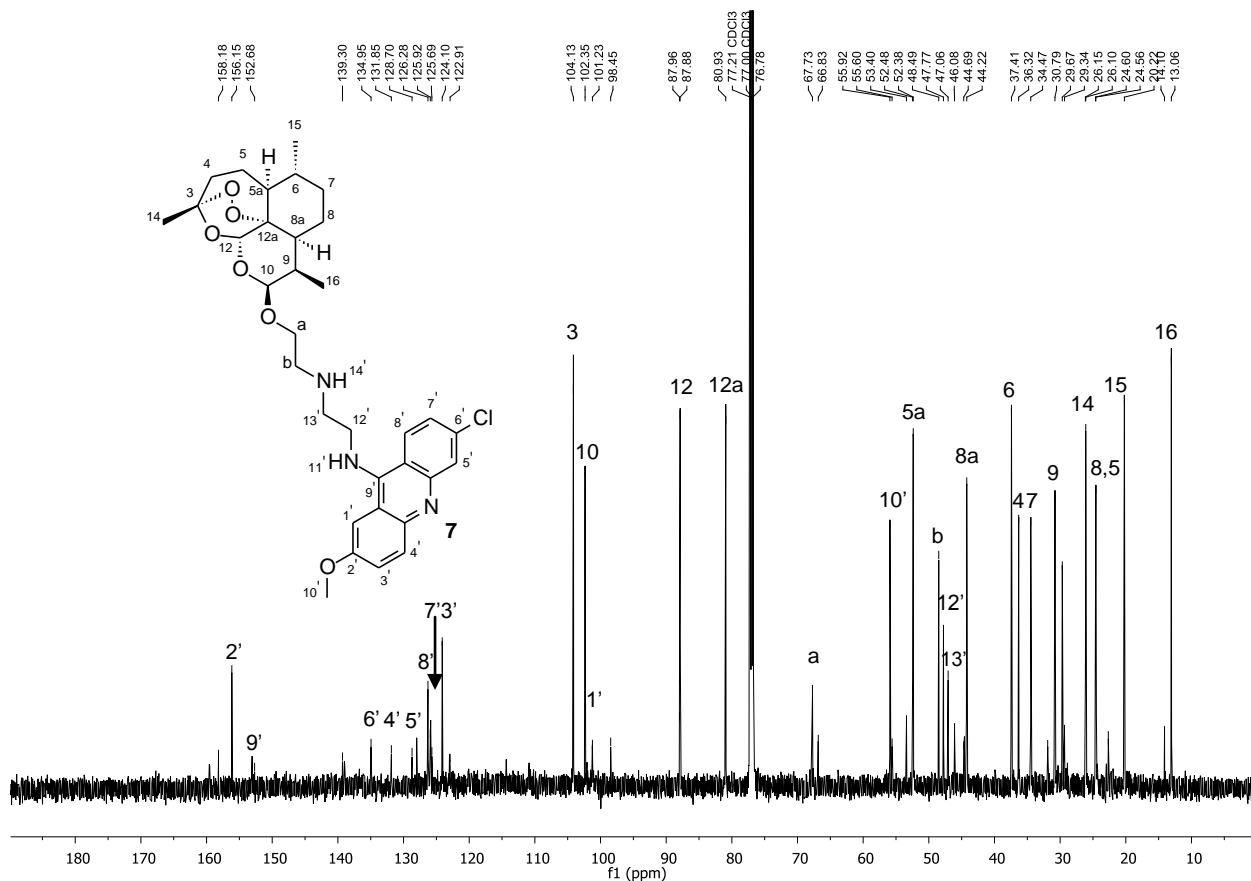
IR



¹H NMR



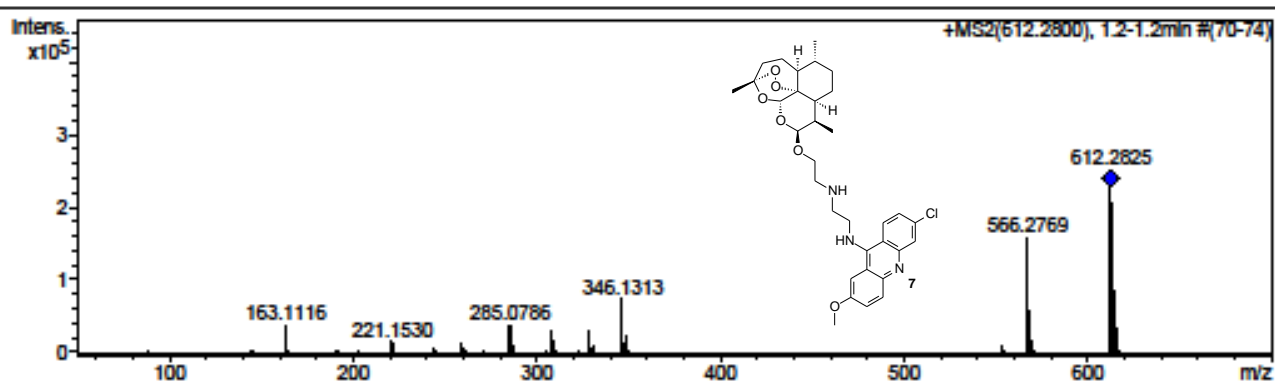
¹³C NMR



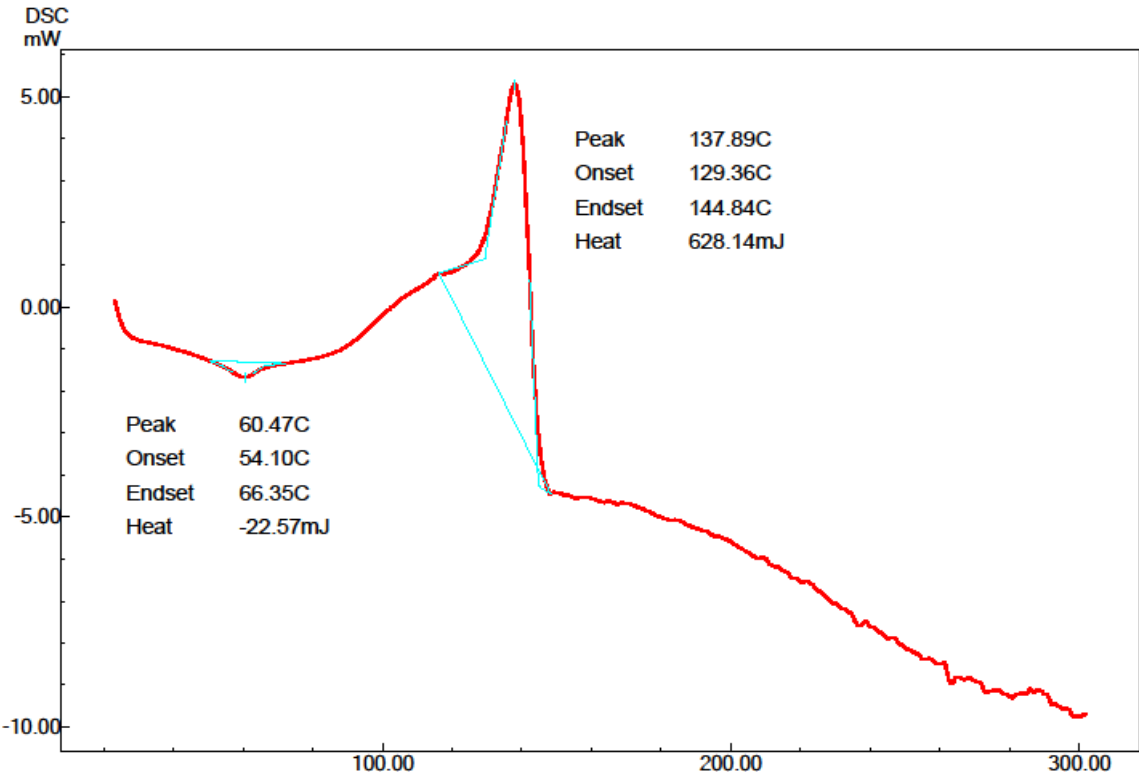
HRMS

Acquisition Parameter

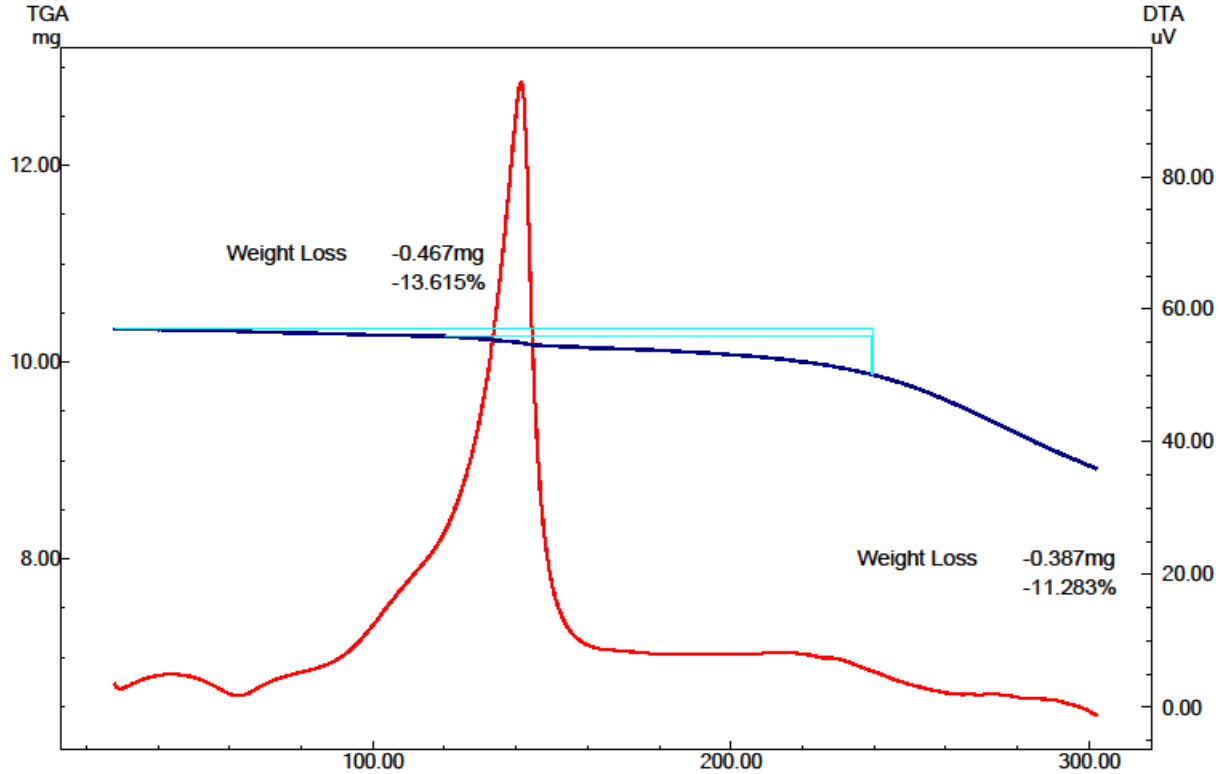
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1500 m/z	Set Collision Cell RF	100.0 Vpp	Set Divert Valve	Waste



DSC

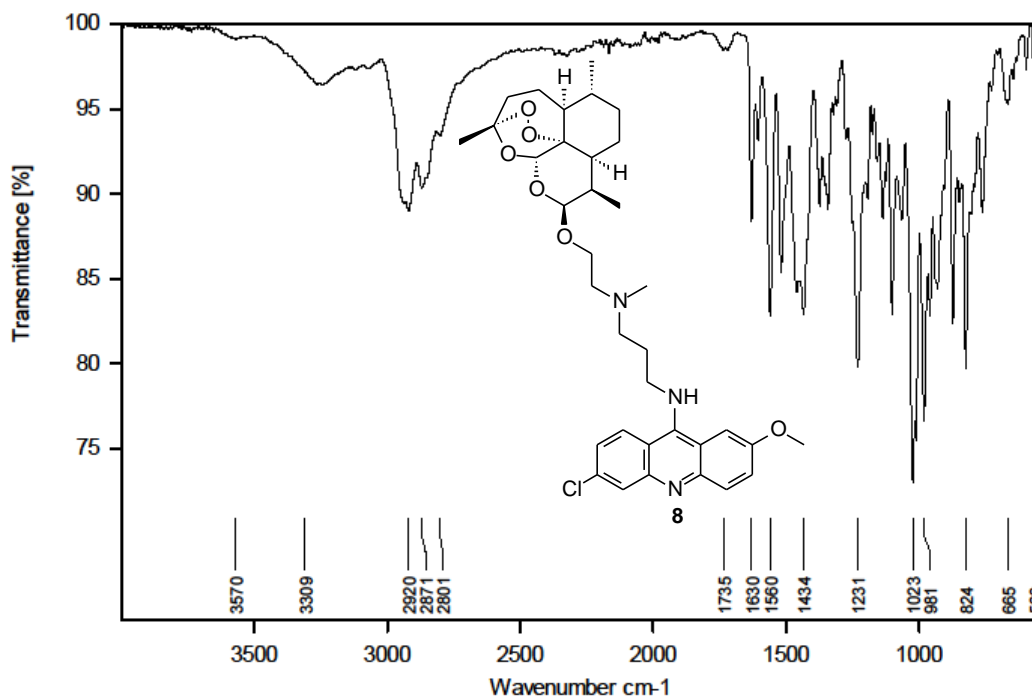


TGA

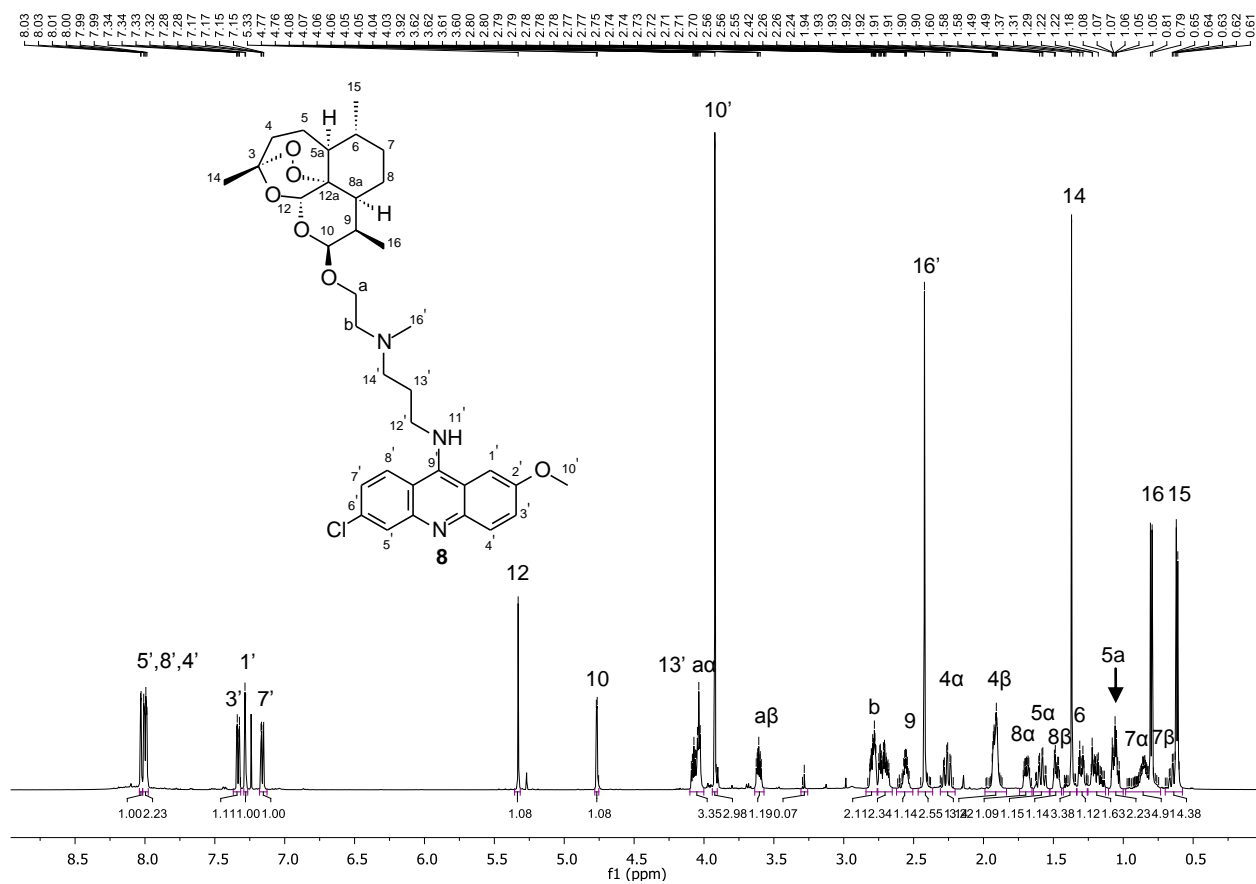


Compound 8:

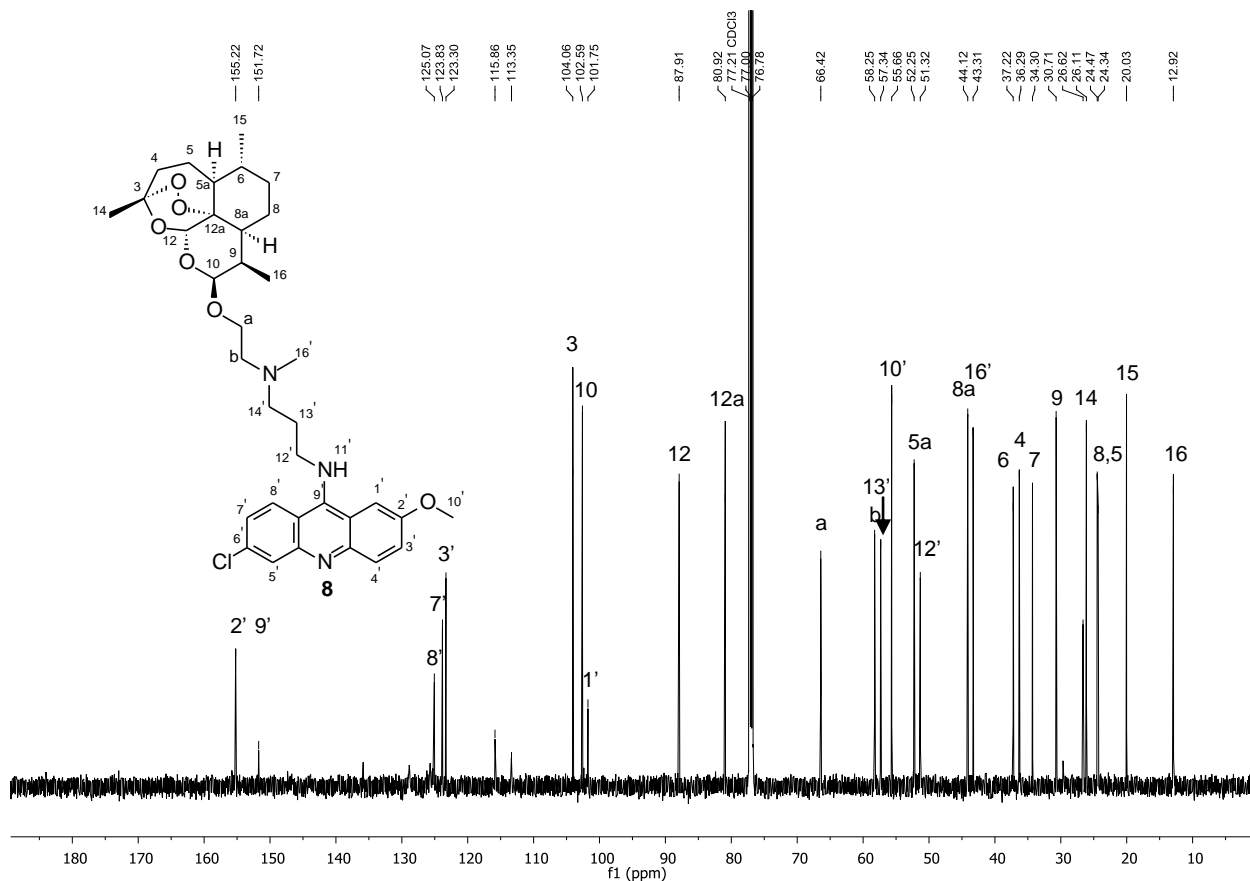
IR



¹H NMR



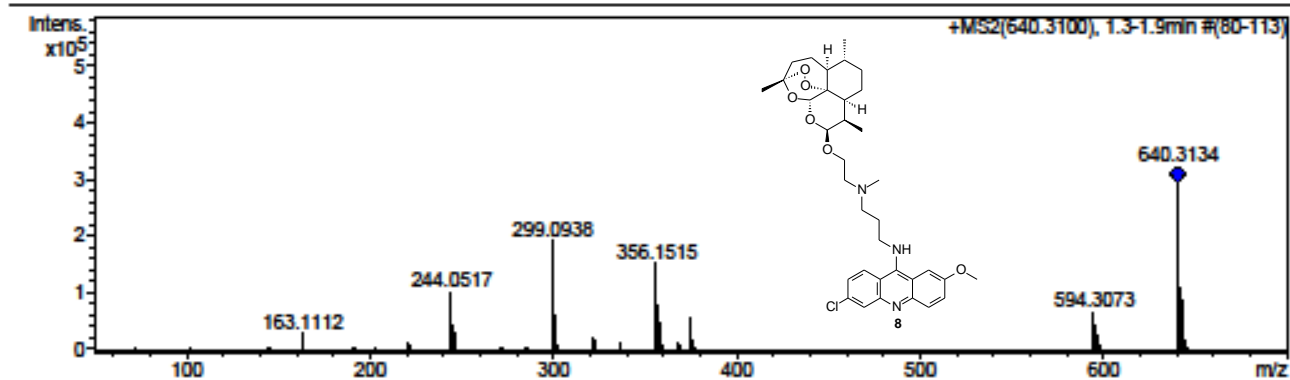
¹³C NMR



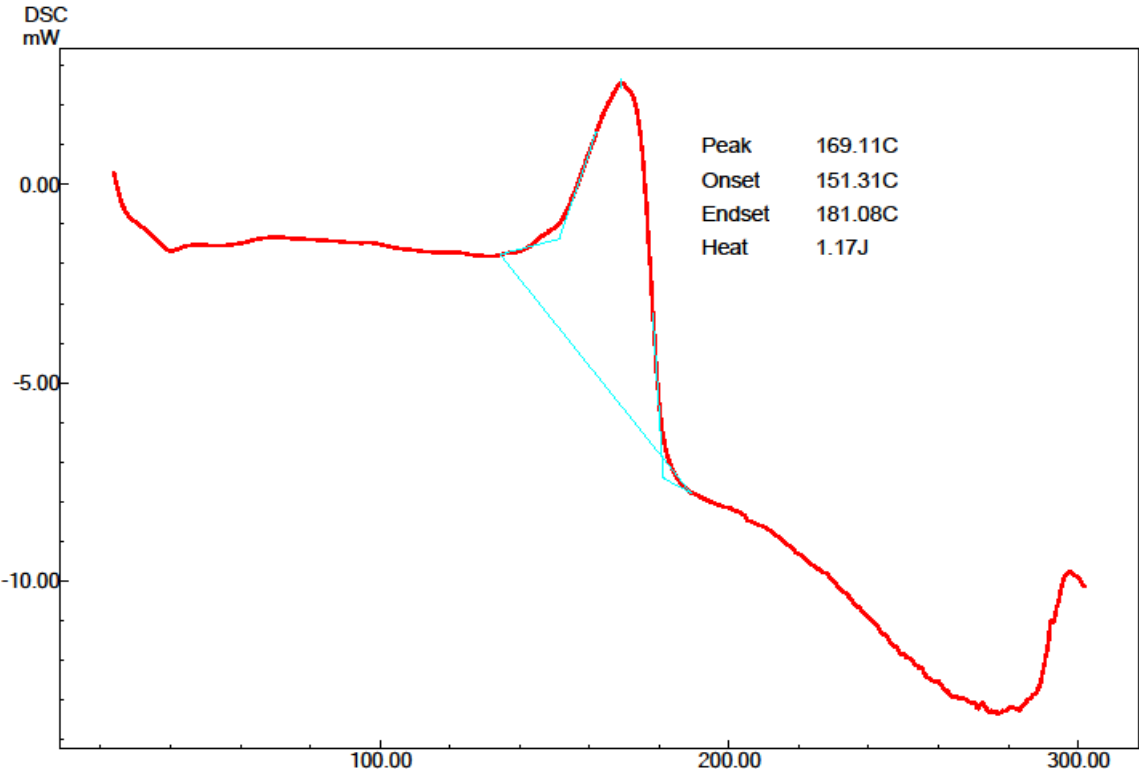
HRMS

Acquisition Parameter

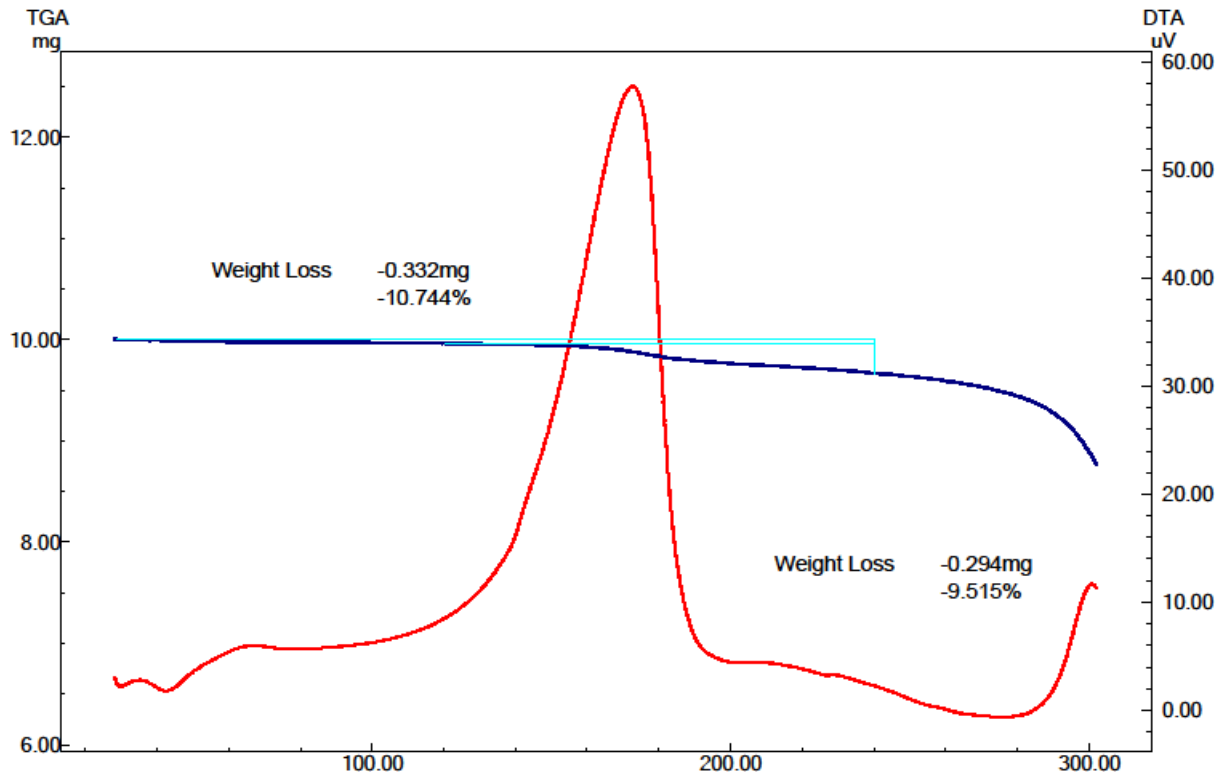
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1500 m/z	Set Collision Cell RF	100.0 Vpp	Set Divert Valve	Waste



DSC

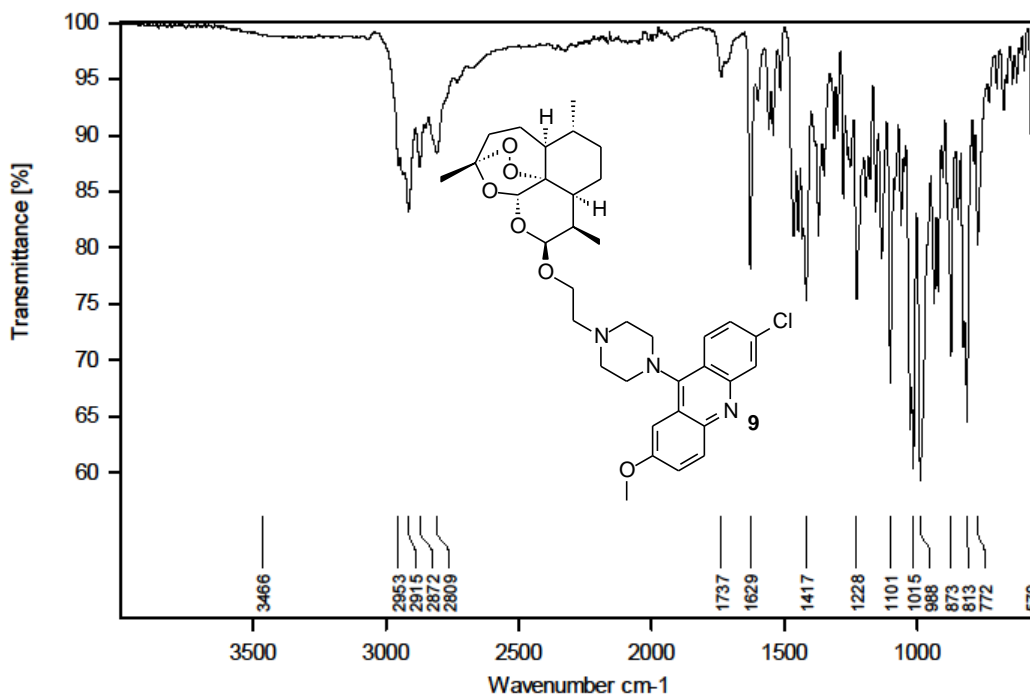


TGA

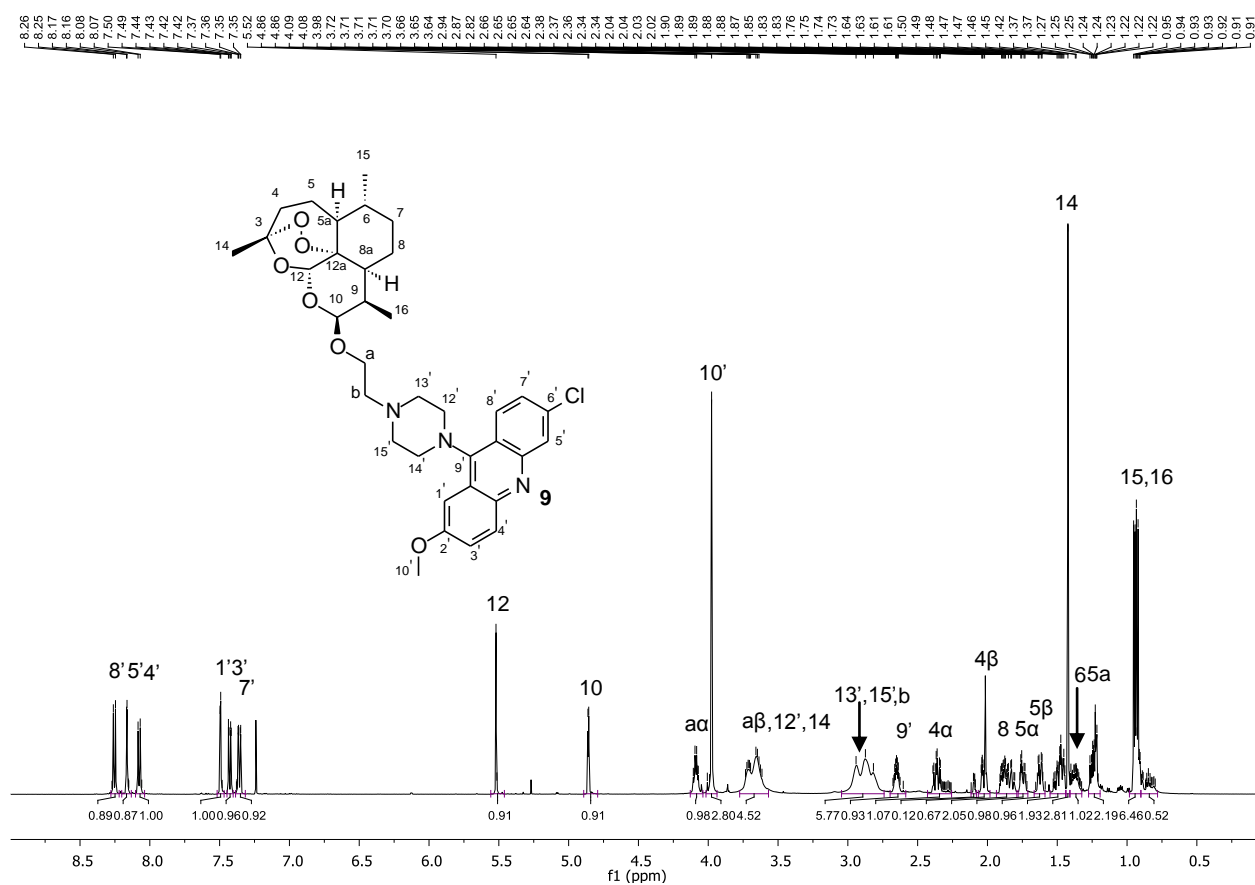


Compound 9:

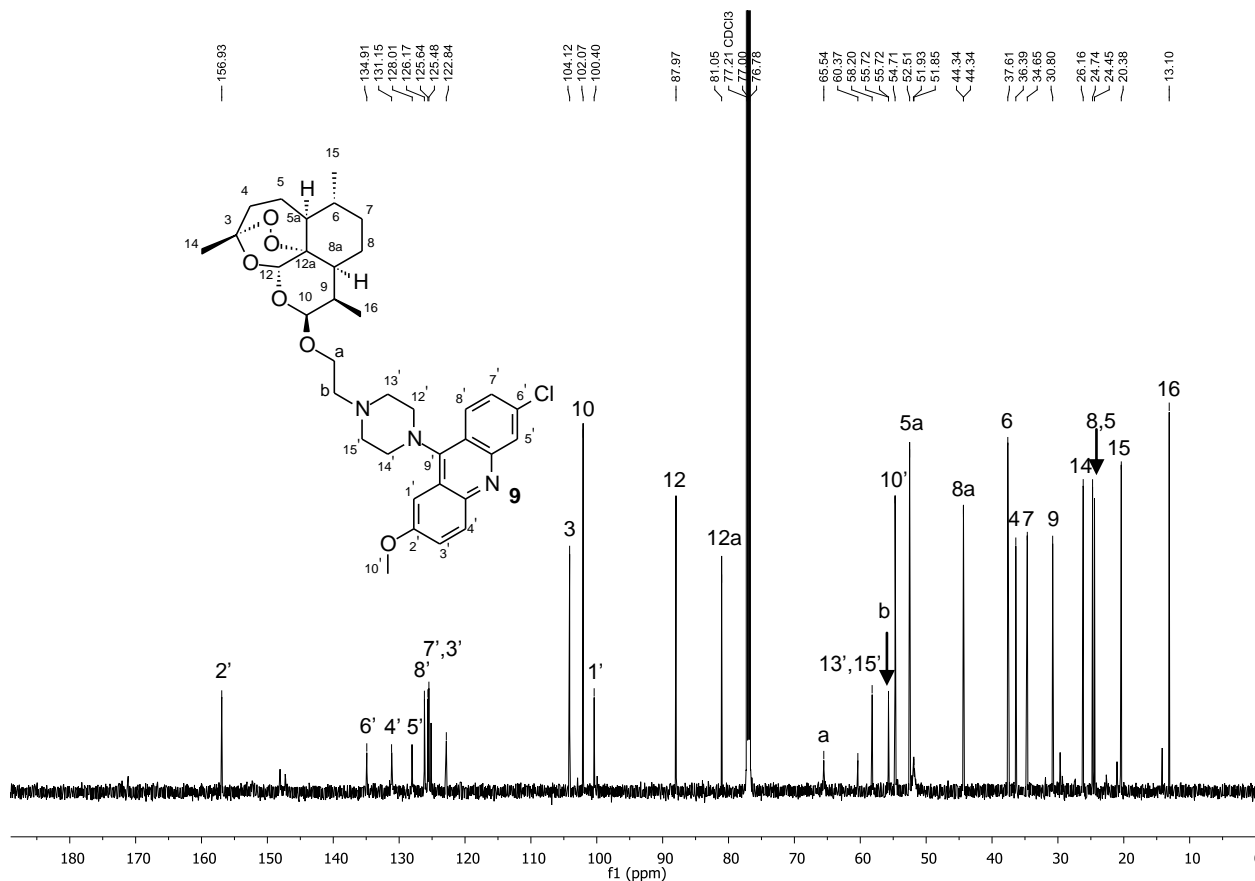
IR



¹H NMR



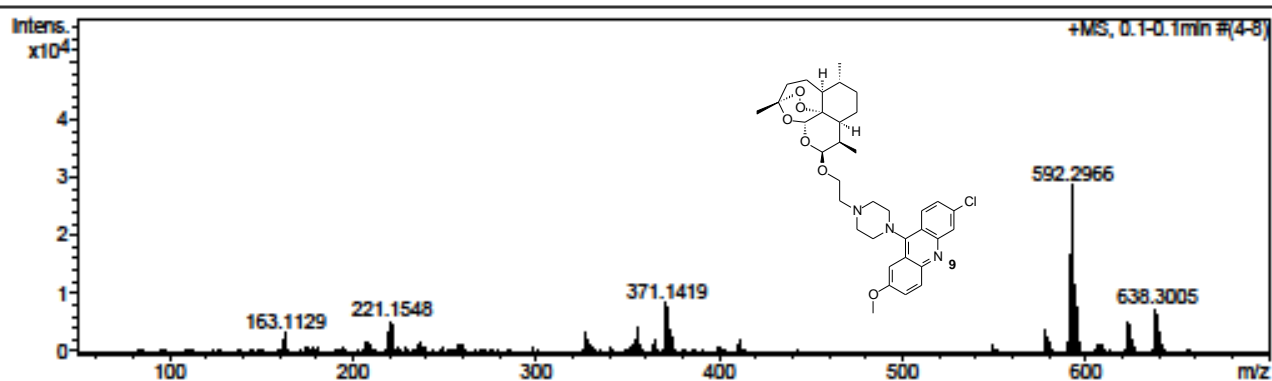
¹³C NMR



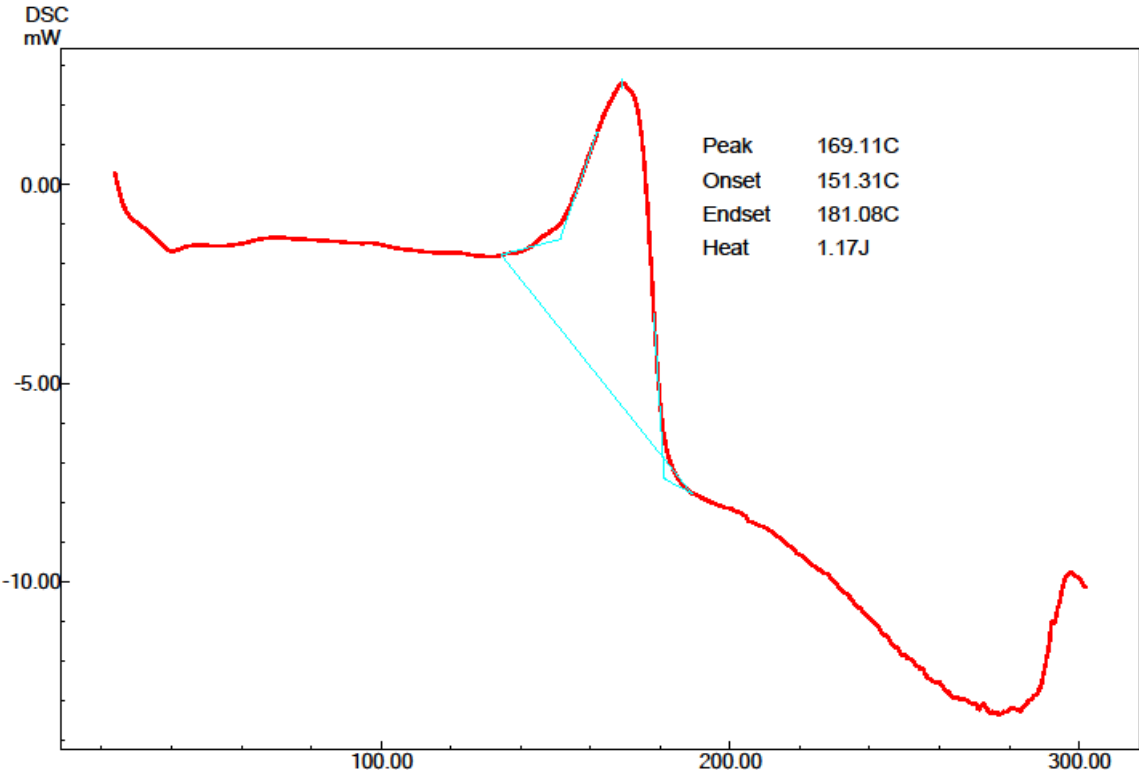
HRMS

Acquisition Parameter

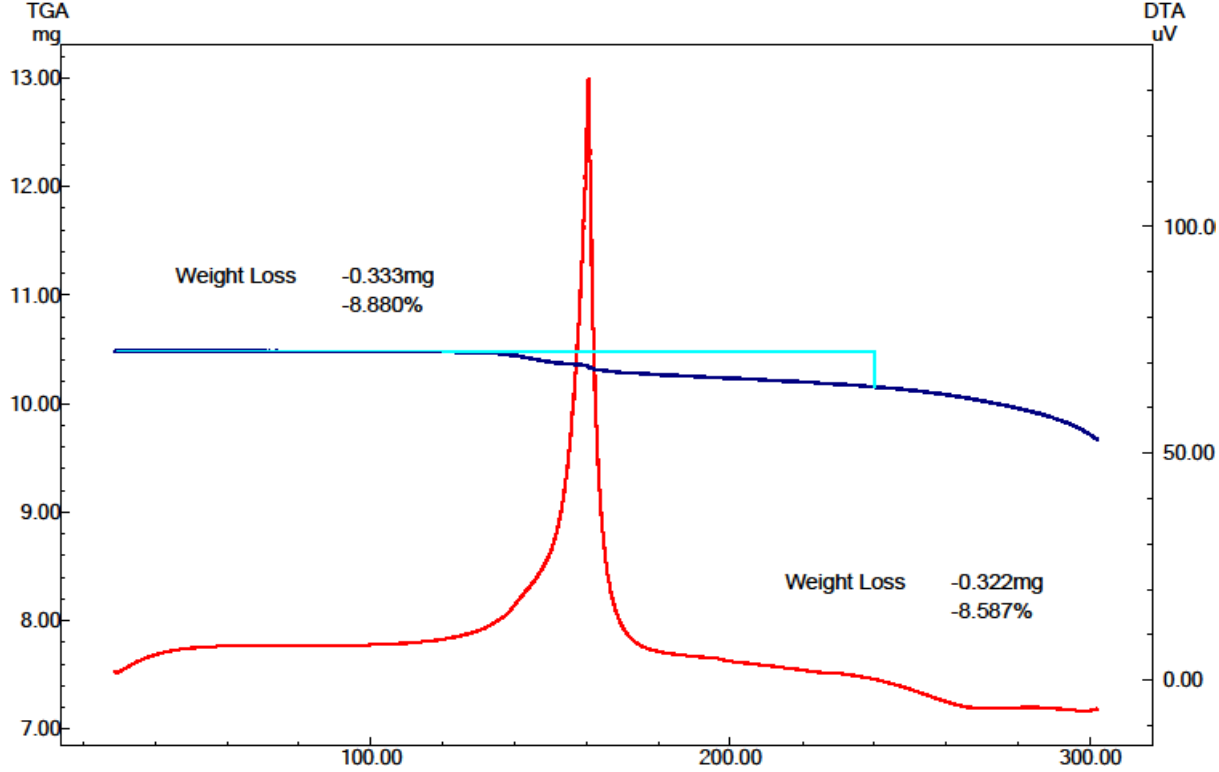
Source Type	APCI	Ion Polarity	Positive	Set Nebulizer	1.6 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	8.0 l/min
Scan End	1500 m/z	Set Collision Cell RF	100.0 Vpp	Set Divert Valve	Waste



DSC

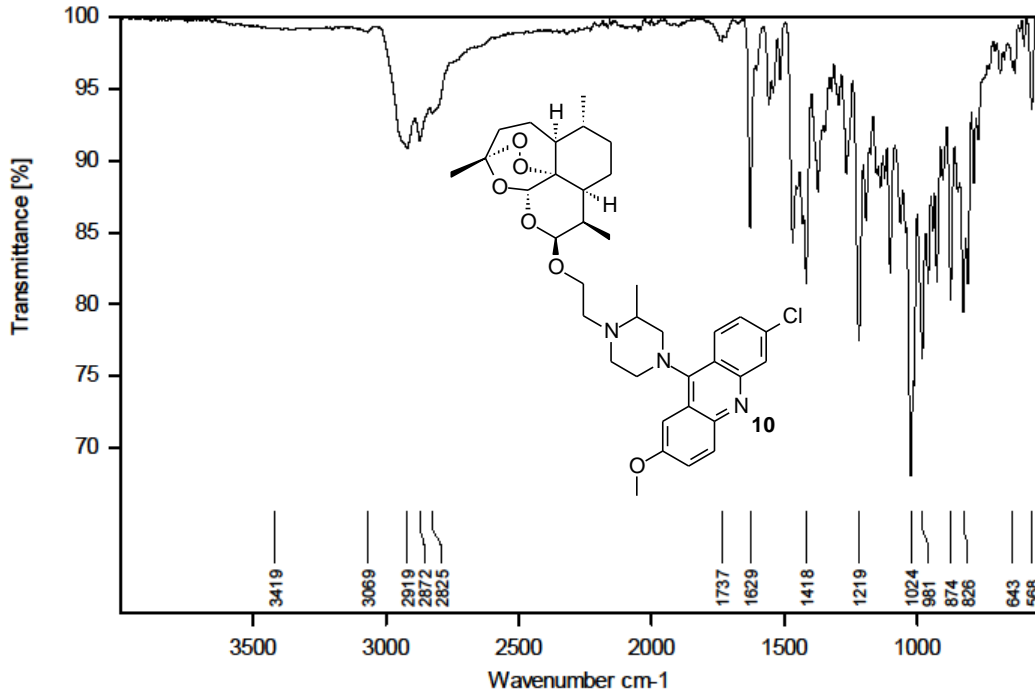


TGA

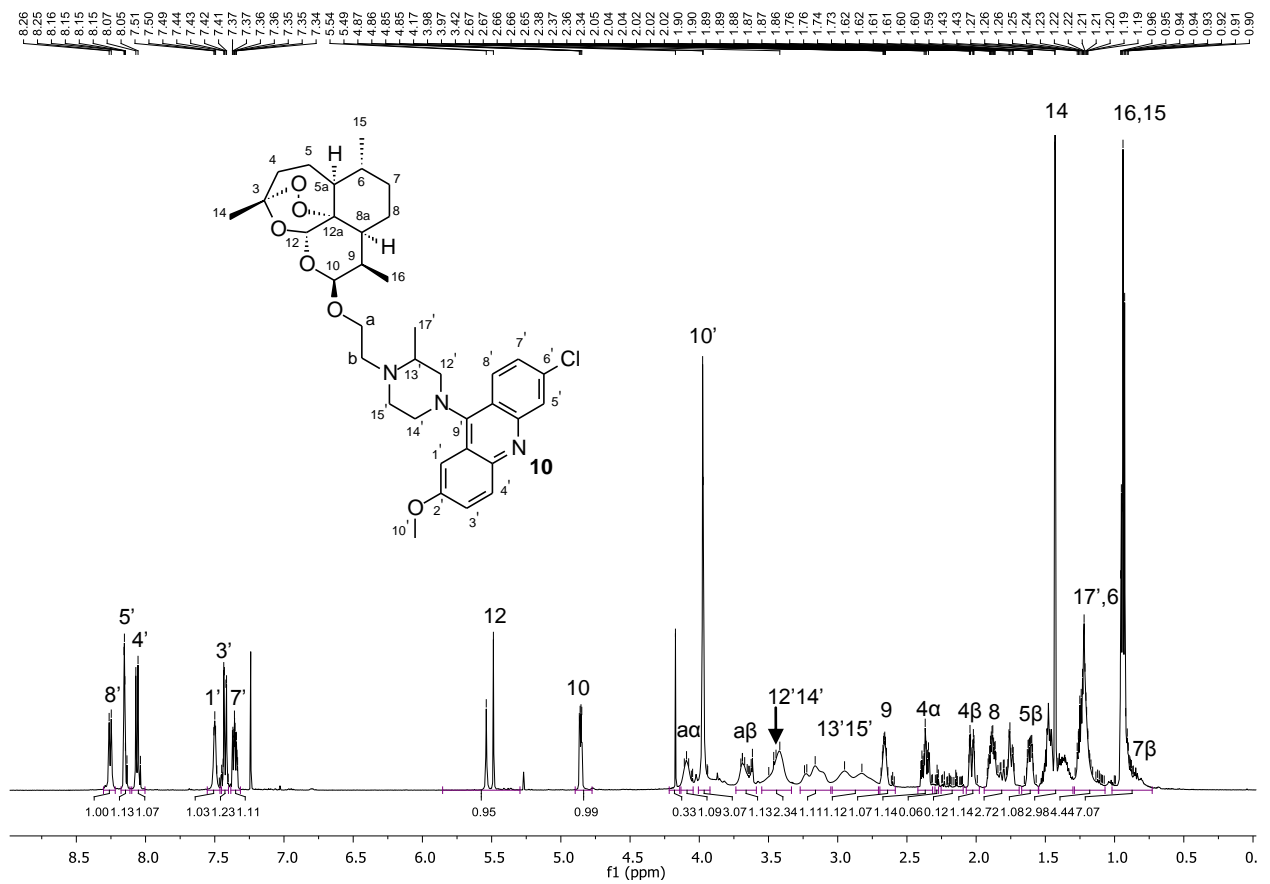


Compound 10:

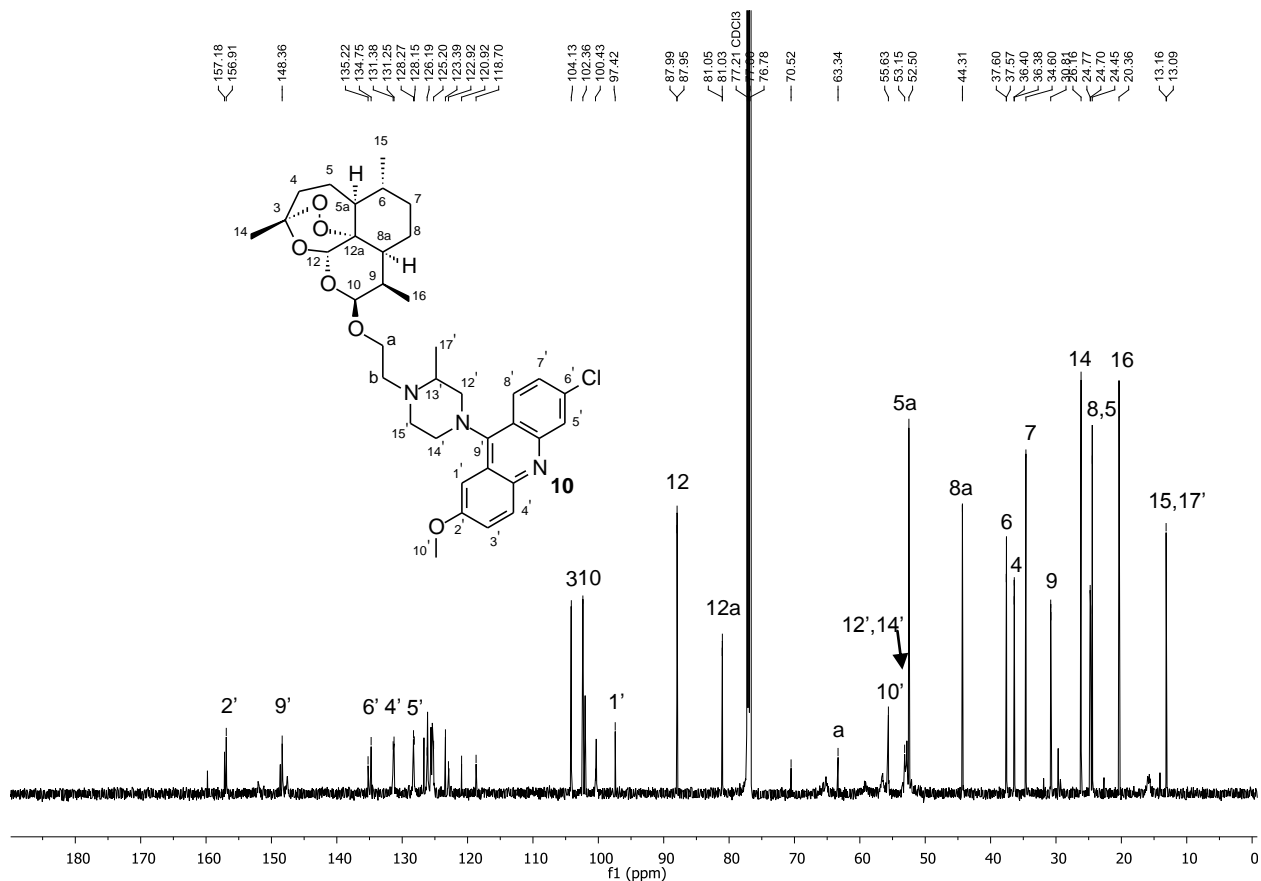
IR



¹H NMR



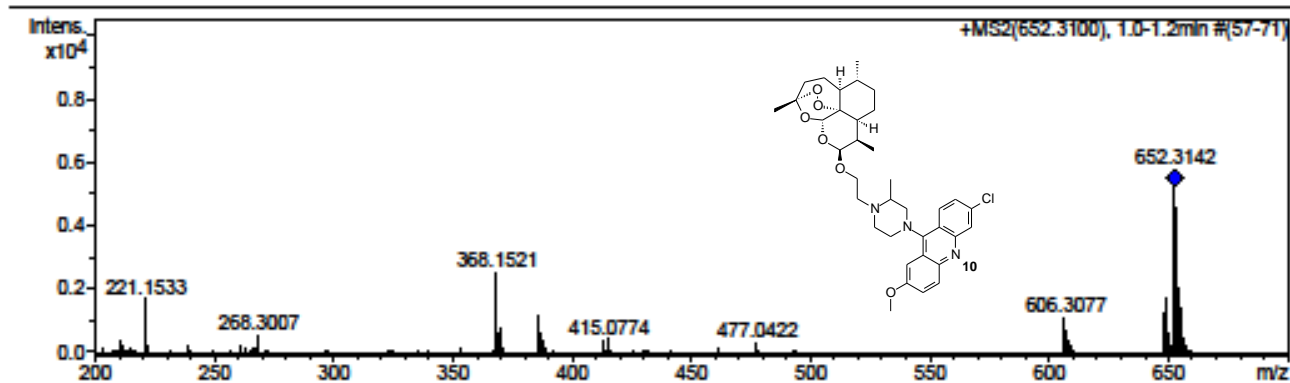
¹³C NMR



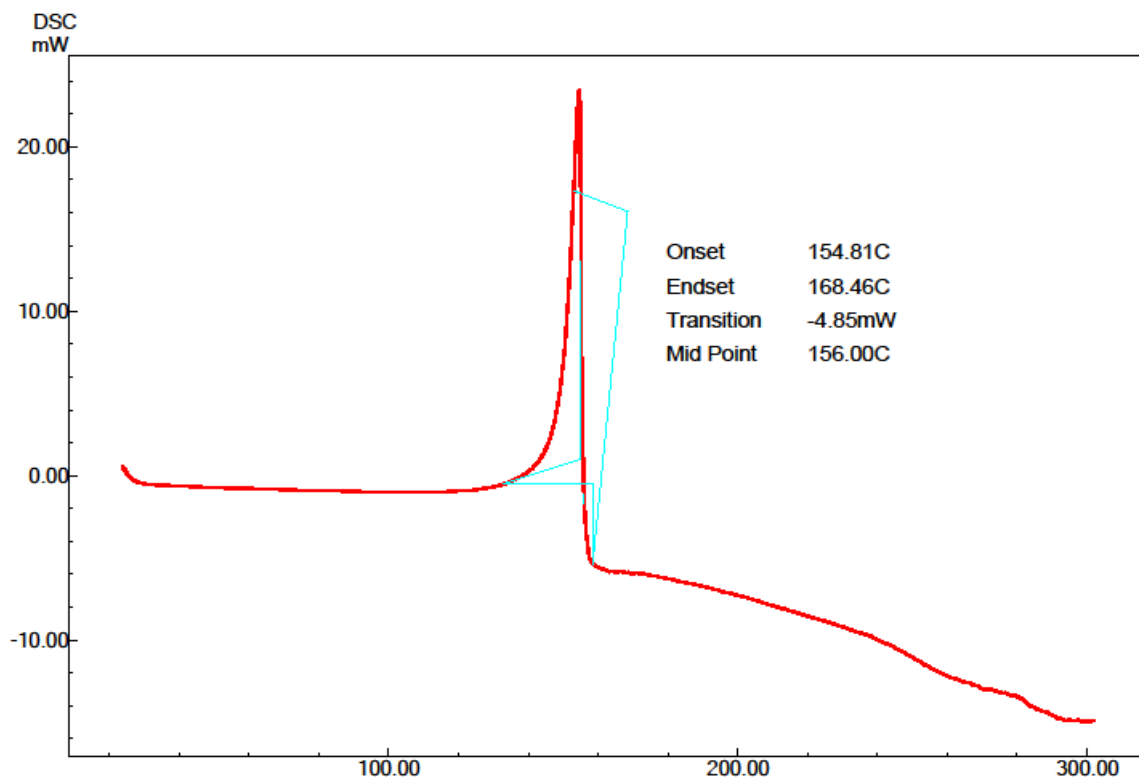
HRMS

Acquisition Parameter

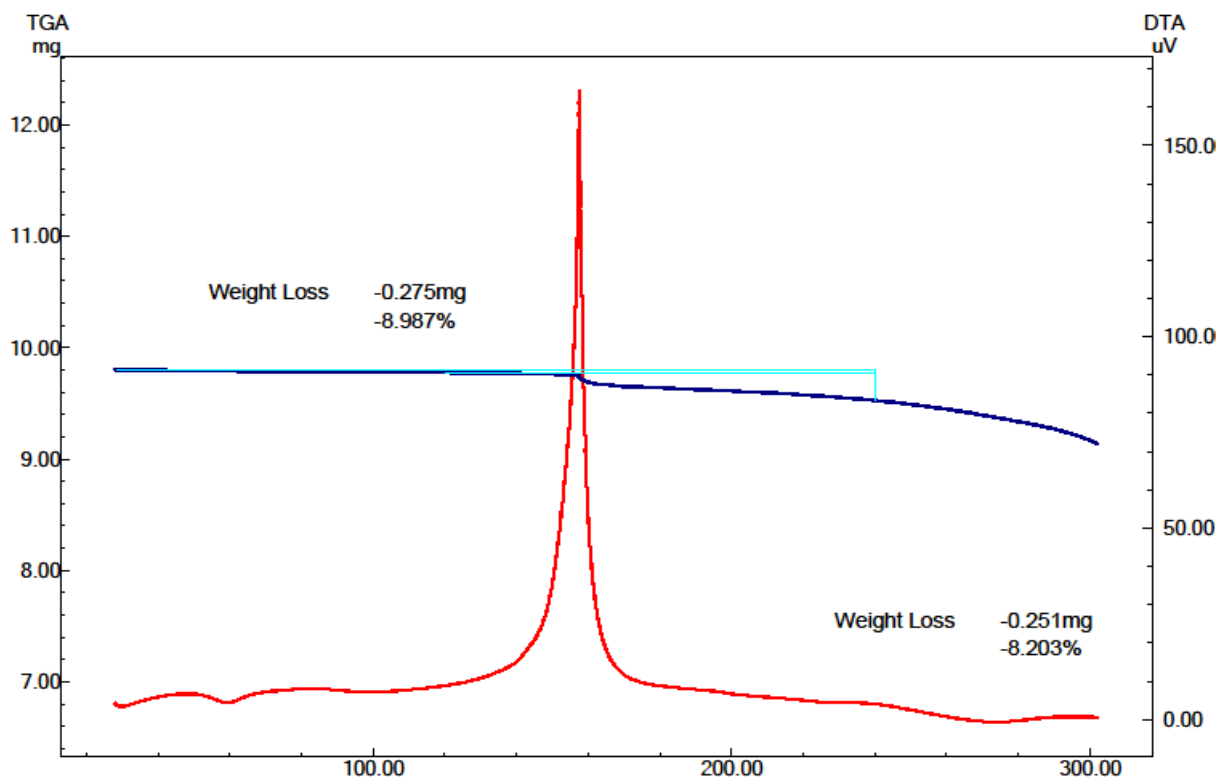
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1500 m/z	Set Collision Cell RF	100.0 Vpp	Set Divert Valve	Waste



DSC

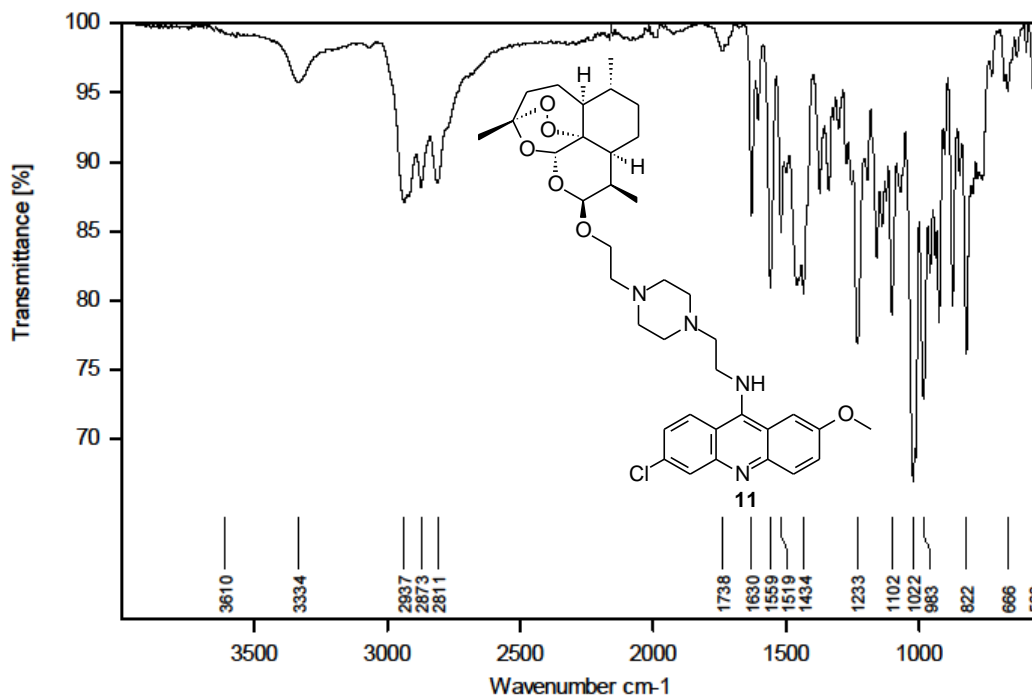


TGA

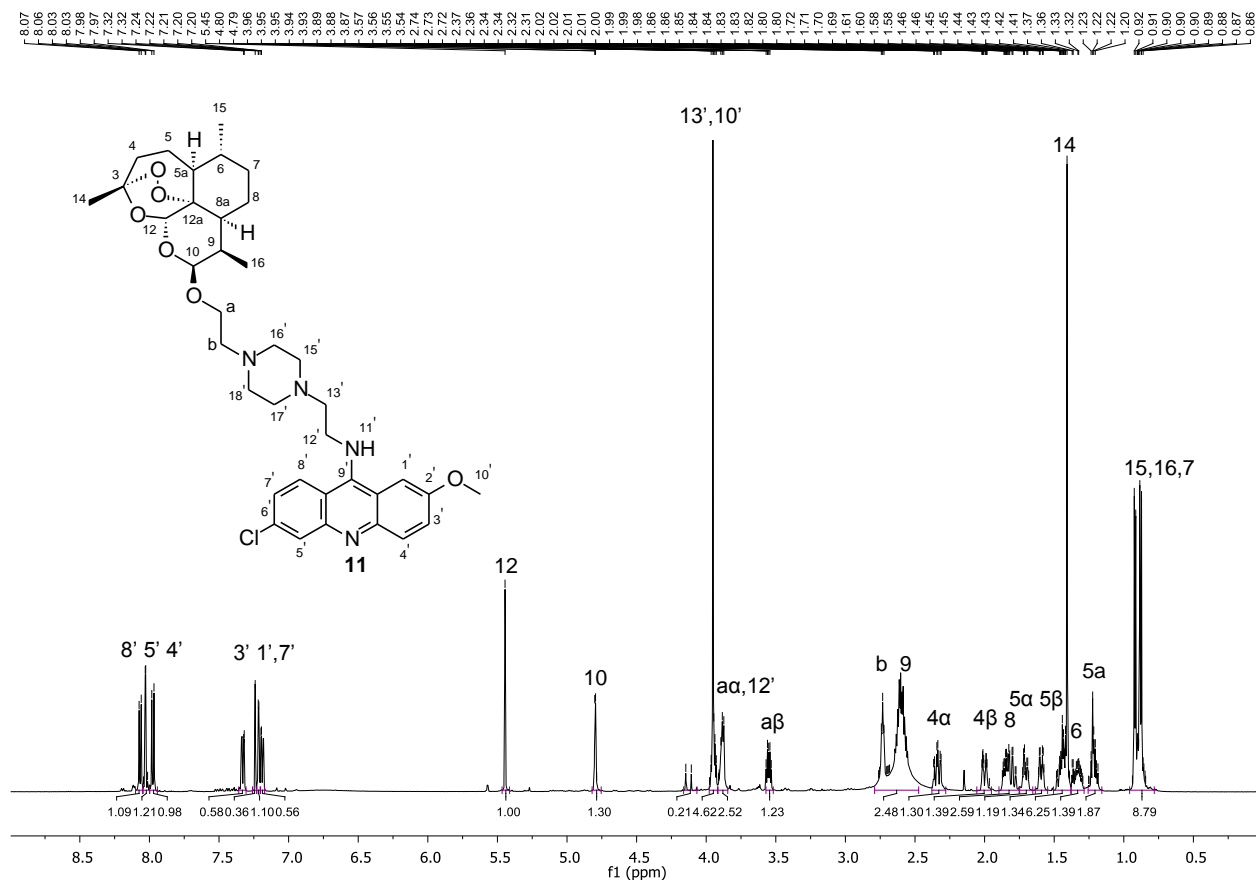


Compound 11:

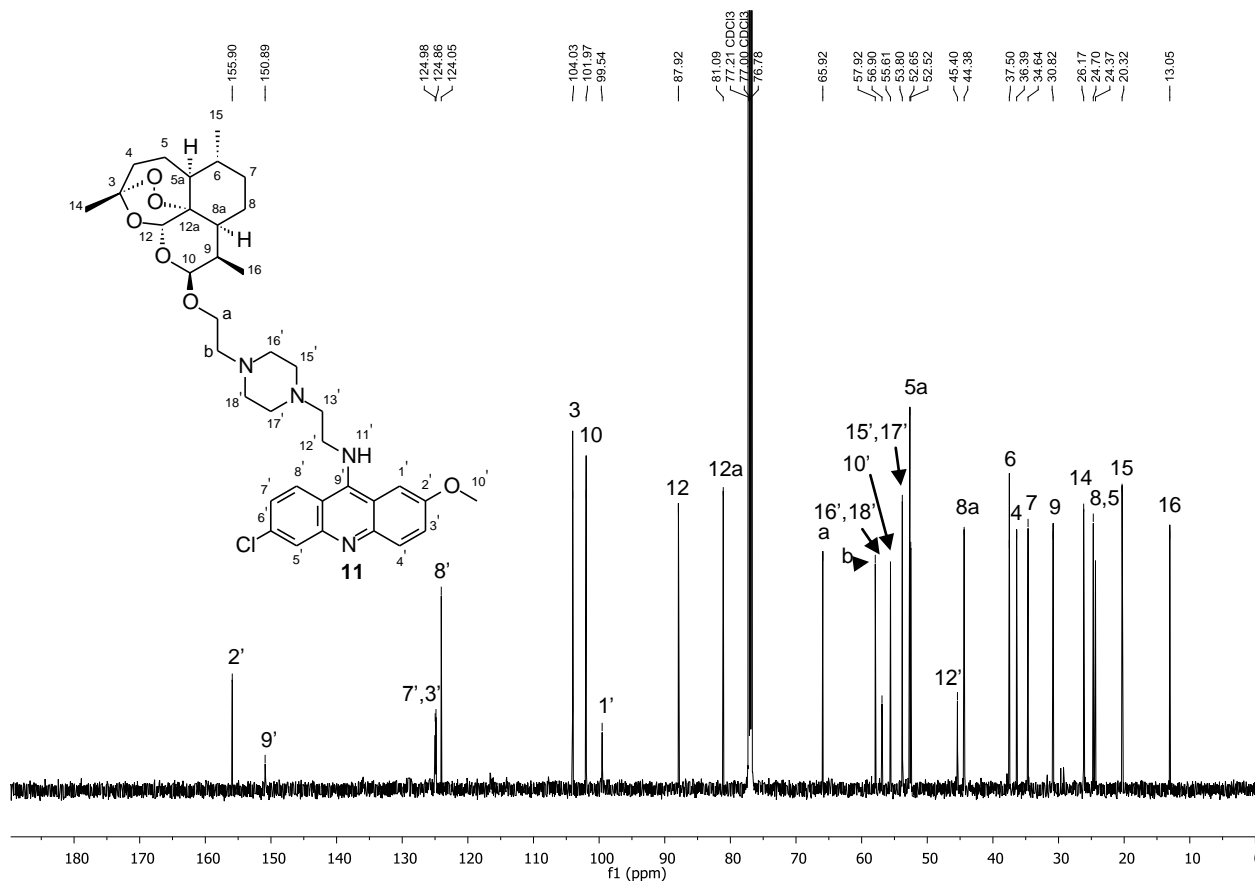
IR



^1H NMR



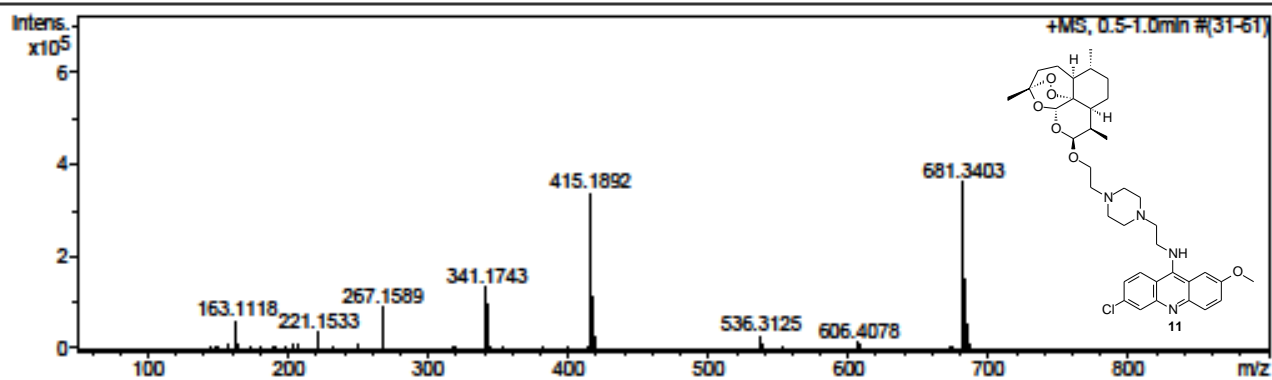
¹³C NMR



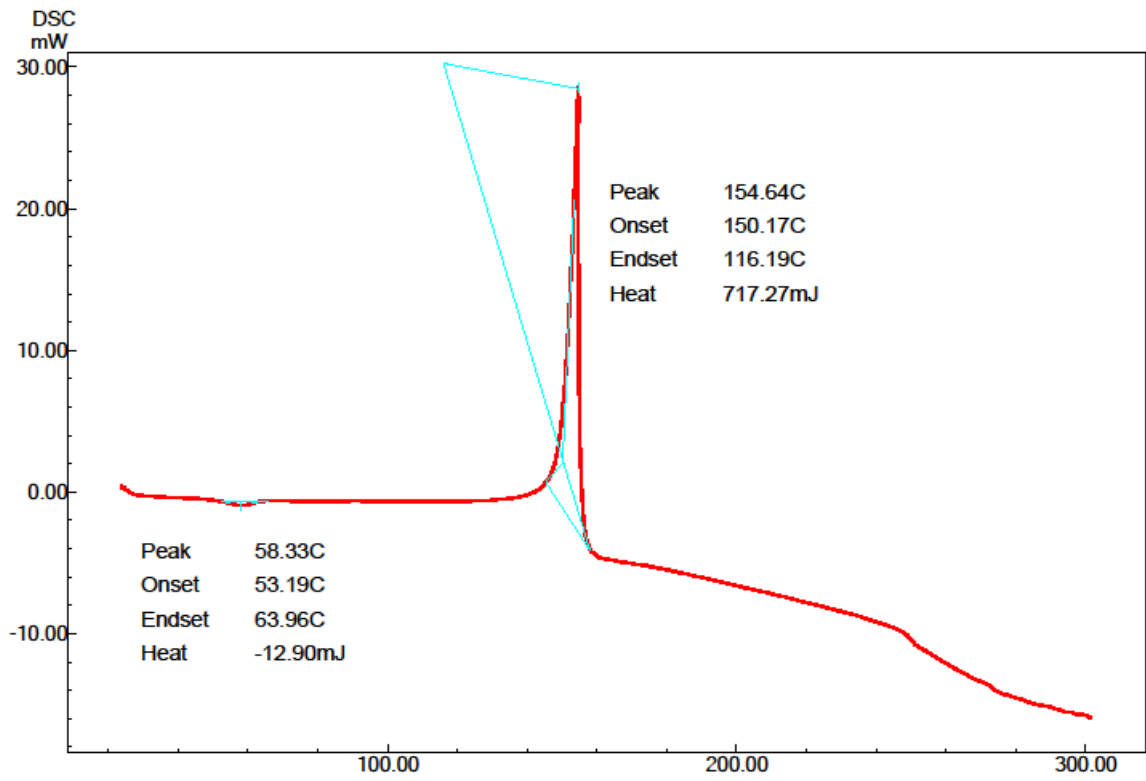
HRMS

Acquisition Parameter

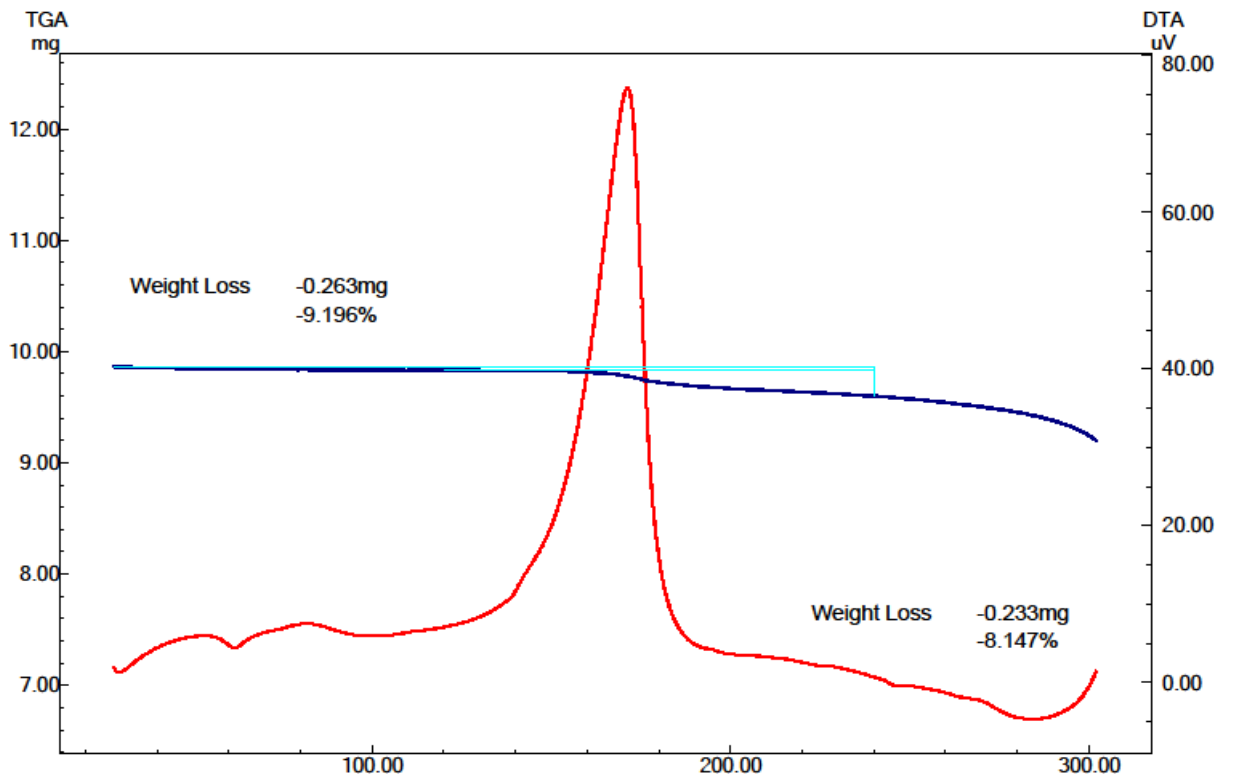
Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1500 m/z	Set Collision Cell RF	100.0 Vpp	Set Divert Valve	Waste



DSC



TGA



APPENDIX B: GUIDE FOR AUTHORS



EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES

Official Journal of the [European Federation for Pharmaceutical Sciences \(EUFEPS\)](#)

AUTHOR INFORMATION PACK

TABLE OF CONTENTS

• Description	p.1
• Audience	p.1
• Impact Factor	p.1
• Abstracting and Indexing	p.2
• Editorial Board	p.2
• Guide for Authors	p.4



ISSN: 0928-0987

DESCRIPTION

The *European Journal of Pharmaceutical Sciences* is the official journal of the [European Federation for Pharmaceutical Sciences \(EUFEPS\)](#). The journal publishes research reports, review articles and scientific commentaries on all aspects of the pharmaceutical sciences with strong emphasis on originality and scientific quality. [The Editors](#) welcome articles in this multidisciplinary field, ranging from drug discovery, over drug delivery to drug development. More specifically, the Journal publishes reports in **medicinal chemistry, pharmacology, drug absorption and metabolism, pharmacokinetics and pharmacodynamics, pharmaceutical and biomedical analysis, drug delivery** including **gene delivery, drug targeting, pharmaceutical technology, pharmaceutical biotechnology** and clinical **drug evaluation**. Scientific commentaries and review articles are generally by invitation only or by consent of the Editors. Proceedings of scientific meetings may be published as special issues or supplements to the Journal. Manuscripts submitted to the Journal are only accepted on the understanding that (a) they are subject to editorial review (generally by two independent referees); (b) they have not been, and will not be, published in whole or in part in any other journal; (c) the recommendations of the Declarations of Helsinki and Tokyo, for humans, and the European Community guidelines as accepted principles for the use of experimental animals have been adhered to.

Benefits to authors

We also provide many author benefits, such as free PDFs, a liberal copyright policy, special discounts on Elsevier publications and much more. Please click here for more information on our [author services](#).

Please see our [Guide for Authors](#) for information on article submission. If you require any further information or help, please visit our support pages: <http://support.elsevier.com>

AUDIENCE

Pharmaceutical and Biopharmaceutical Scientists, Medicinal Chemists, Pharmacologists, Analytical Chemists, Clinical Pharmacologists, Pharmaceutical Engineers

IMPACT FACTOR

2012: 2.987 © Thomson Reuters Journal Citation Reports 2013

ABSTRACTING AND INDEXING

BIOSIS
Beilstein Database
CAB Abstracts
Chemical Abstracts
Current Contents/Life Sciences
EMBASE
International Pharmaceutical Abstracts
MEDLINE®
Natural Products Update/Royal Society of Chemistry
S.E.F. Editoriale
Science Citation Index
Scopus

EDITORIAL BOARD

Editor-in-Chief

M. Brandl, Dept. of Physics and Chemistry, University of Southern Denmark, Campusvej 55, DK-5230 Odense M, Denmark, **Email:** mmb@sdu.dk

Section Editors

C. Altomare, Università degli Studi di Bari, Bari, Italy
S. Auriola, University of Eastern Finland, Kuopio, Finland
R. Bodmeler, Freie Universität Berlin, Berlin, Germany
H. Derendorf, University of Florida, Gainesville, FL, USA
J. Filipović-Grčić, University of Zagreb, Zagreb, Croatia
B. Gander, Eidgenössische Technische Hochschule (ETH) Zürich, Zürich, Switzerland
U. Hilgenfeldt, Ruprecht-Karls-Universität Heidelberg, Heidelberg, Germany
J. Kuntsche, University of Southern Denmark, Odense M, Denmark
E. Mastrobattista, Utrecht University, Utrecht, Netherlands

Editorial Board

L.J. Aarons, University of Manchester, Manchester, UK
F. Ahsan, Texas Tech School of Pharmacy, Amarillo, TX, USA
J.M. Aiache, University of Clermont-Ferrand, Clermont-Ferrand, France
M.J. Alonso, Universidade de Santiago de Compostela, Santiago de Compostela, Spain
P. Artursson, Uppsala Universitet, Uppsala, Sweden
A. Avdeef, in-ADME Research, New York, NY, USA
M. Bermejo Sanz, Miguel Hernández University, San Juan de Alicante, Spain
O.J. Bjerrum, University of Copenhagen, Copenhagen, Denmark
H.H. Blume, Socratec R&D, Oberursel, Germany
J.A. Bouwstra, Leiden/Amsterdam Center for Drug Research (LACDR), Leiden, Netherlands
D. Brayden, University College Dublin, Dublin, Ireland
C.M. Caramella, Università degli Studi di Pavia, Pavia, Italy
M.C. Davies, University of Nottingham, Nottingham, UK
S.C. De Smedt, Universiteit Gent, Gent, Belgium
M. Eichelbaum, Dr. Margarete Fischer-Bosch Inst., Stuttgart, Germany
A. Fahr, Friedrich-Schiller-Universität Jena, Jena, Germany
E. Fattal, PhD, Université Paris-Sud (Paris XI), Châtenay-Malabry, France
M. Finel, University of Helsinki, Helsinki, Finland
H. W. Frjllink, Rijksuniversiteit Groningen, Groningen, Netherlands
G. Golomb, Hebrew University of Jerusalem, Jerusalem, Israel
R.H. Guy, University of Bath, Bath, UK
J. Hirvonen, University of Helsinki, Helsinki, Finland
P. Honkakoski, University of Eastern Finland, Kuopio, Finland
L. Illum, IDentity / Cosmas-Damian Ltd., Nottingham, UK
G. Imanidis, Universität Basel, Basel, Switzerland
K.-I. Inul, Kyoto Pharmaceutical University, Kyoto, Japan
H.E. Junginger, Marburg, Germany
M.O. Karlsson, Uppsala Universitet, Uppsala, Sweden
J. Kopecek, University of Utah, Salt Lake City, UT, USA
R. Kostianen, University of Helsinki, Helsinki, Finland
J. Kreuter, Goethe-Universität Frankfurt, Frankfurt, Germany

R.S. Langer, Massachusetts Institute of Technology, Cambridge, MA, USA
V.H.L. Lee, Chinese University of Hong Kong, Shatin, N.T., Hong Kong
C.-M. Lehr, Helmholtz-Institute for Pharmaceutical Research and Saarland University, Saarbrücken, Germany
H. Lennernäs, Uppsala Universitet, Uppsala, Sweden
P. Macheras, University of Athens, Athens, Greece
U. Massing, KTB Klinik für Tumorbologie, Freiburg, Germany
J.W. McGinity, University of Texas at Austin, Austin, TX, USA
C.R. Middaugh, University of Kansas, Lawrence, KS, USA
S. Mitragotri, University of California at Santa Barbara, Santa Barbara, CA, USA
C. O'Driscoll, University College Cork, Cork, Ireland
O. Pelkonen, University of Oulu, Oulu, Finland
F. Podczek, University College London (UCL), London, UK
J.E. Polli, University of Maryland, Baltimore, MD, USA
J.P. Remon, Universiteit Gent, Gent, Belgium
J.S. Remy, Université de Strasbourg, Illkirch, France
R.C. Rowe, University of Bradford, Bradford, West Yorkshire, UK
W. Sadée, Ohio State University, Columbus, OH, USA
E.H. Schacht, Universiteit Gent, Gent, Belgium
C. Selch-Larsen, University of Copenhagen, Copenhagen, Denmark
J. Siepmann, Université Lille Nord de France, Lille, France
E. B. Souto, Fernando Pessoa University, Porto, Portugal
S. Spampinato, Università di Bologna, Bologna, Italy
G. Storm, Utrecht University, Utrecht, Netherlands
Y. Sugiyama, University of Tokyo, Tokyo, Japan
F.C. Szoka, University of California at San Francisco (UCSF), San Francisco, CA, USA
Y. Takakura, Kyoto University, Kyoto, Japan
G.T. Tucker, University of Sheffield, Sheffield, UK
K. Uekama, Kumamoto University, Kumamoto, Japan
K. Ulbrich, Academy of Sciences of the Czech Republic, Prague, Czech Republic
A. Urtti, University of Helsinki, Helsinki, Finland
H. van de Waterbeemd, Saint Andre, France
M.R. Vert, Université Montpellier, Montpellier, France
E. Wagner, PhD, Ludwig-Maximilians-Universität München (LMU), München, Germany
M. Yliperttula, University of Helsinki, Helsinki, Finland

GUIDE FOR AUTHORS

INTRODUCTION

Manuscripts submitted to the journal are accepted on the understanding that: (1) they are subject to editorial review, (2) they have not been and will not be published in whole or in part in any other journal and (3) the recommendations of the Declarations of Helsinki and Tokyo, for humans, and the European Community guidelines as accepted principles for the use of experimental animals, have been adhered to. *The European Journal of Pharmaceutical Sciences* will, therefore, only consider manuscripts that describe experiments which have been carried out under approval of an institutional or local ethics committee.

Types of Paper

Research articles

Review articles

The manuscript of a review article should be arranged as described for research articles but according to the following sections: title page, abstract and keywords (Indexing terms, normally 3-6 items), Introduction, Specific sections determined by the author, Conclusions, Acknowledgements, References, Figure legends and Figures, Tables. Sections ranging from the Introduction to the Conclusions should be numbered. Subdivisions within a section should also be numbered within that section: 2.1., 2.2., 2.3. etc. All pages should be numbered consecutively, the title page being p.1.

Commentaries and Mini-reviews

One page suggestions for comprehensive reviews, commentaries or mini-reviews should be sent to the Editor-in-Chief at ejps@sdu.dk for consideration. Please see detailed information on commentaries and mini-reviews below.

Commentaries (Guidance)

The definition of a Commentary for EJPS is three-fold. Firstly, it can be an argued piece of provocative scientific writing purporting to take a balanced position on a controversial pharmaceutical science topic. A second option is for the author to approach the topic from a particular viewpoint on one side of an argument. A third option is to provide a topical update on a hot topic in Pharmaceutical Sciences and this can be more informative than controversial.

Commentaries will be commissioned by the editors in advance or invited from non-commissioned authors if they wish to initially submit a one page summary of the intended Commentary to the editors in advance. All manuscripts will be assessed by 2-3 independent referees.

The journal is looking for a stimulating and provoking essays, with referenced material, but without an extensive reference list. Commentaries can contain one summary figure and/or table and should have no more than 30 references to preferably recent peer-reviewed material. The word count should be approximately 2,000 words maximum.

The commentary should have a short abstract summary of 150 to 200 words and 4-5 key words should be included, The text should be broken down into 4-5 numbered sections beginning with an Introduction and ending with a Conclusions section. A model of the structures is to be found in *Eur. J. Pharm. Sci.* 19, 1-11 by R.D. Combes

Mini-review (Guidance)

Mini-reviews are thought provoking reviews of contemporary pharmaceutical research. Themes are as described in the Scope of the Journal section.

Mini-reviews will usually be commissioned by the editors in advance, but contributions are invited from non-commissioned authors if they wish to initially submit a one page summary of the intended review to the editors in advance. All manuscripts will be assessed by 2-3 independent referees.

The structure of the mini-review is as follows: a title page followed by a 200-300 word abstract with 4-5 key words. The text is then divided into numbered sections finishing with a Summary section. References should be kept to a maximum of 60 and should be mostly to recent peer-reviewed material. There is a combined maximum of 5 figures / tables. Authors are encouraged to submit their original unpublished work as part of the review if appropriate. The total length of the review should be a maximum of 4,000 words.

BEFORE YOU BEGIN

Ethics in publishing

For information on Ethics in publishing and Ethical guidelines for journal publication see <http://www.elsevier.com/publishingethics> and <http://www.elsevier.com/journal-authors/ethics>.

Conflict of interest

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. See also <http://www.elsevier.com/conflictsofinterest>. Further information and an example of a Conflict of Interest form can be found at: http://help.elsevier.com/app/answers/detail/a_id/286/p/7923.

Submission declaration

Submission of an article implies that the work described has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis or as an electronic preprint, see <http://www.elsevier.com/postingpolicy>), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder.

Changes to authorship

This policy concerns the addition, deletion, or rearrangement of author names in the authorship of accepted manuscripts:

Before the accepted manuscript is published in an online issue: Requests to add or remove an author, or to rearrange the author names, must be sent to the Journal Manager from the corresponding author of the accepted manuscript and must include: (a) the reason the name should be added or removed, or the author names rearranged and (b) written confirmation (e-mail, fax, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed. Requests that are not sent by the corresponding author will be forwarded by the Journal Manager to the corresponding author, who must follow the procedure as described above. Note that: (1) Journal Managers will inform the Journal Editors of any such requests and (2) publication of the accepted manuscript in an online issue is suspended until authorship has been agreed.

After the accepted manuscript is published in an online issue: Any requests to add, delete, or rearrange author names in an article published in an online issue will follow the same policies as noted above and result in a corrigendum.

Article transfer service

This journal is part of our Article Transfer Service. This means that if the Editor feels your article is more suitable in one of our other participating journals, then you may be asked to consider transferring the article to one of those. If you agree, your article will be transferred automatically on your behalf with no need to reformat. More information about this can be found here: <http://www.elsevier.com/authors/article-transfer-service>.

Copyright

This journal offers authors a choice in publishing their research: Open Access and Subscription.

For Subscription articles

Upon acceptance of an article, authors will be asked to complete a 'Journal Publishing Agreement' (for more information on this and copyright, see <http://www.elsevier.com/copyright>). An e-mail will be sent to the corresponding author confirming receipt of the manuscript together with a 'Journal Publishing Agreement' form or a link to the online version of this agreement.

Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the Publisher is required for resale or distribution outside the institution and for all other derivative works, including compilations and translations (please consult <http://www.elsevier.com/permissions>). If excerpts from other copyrighted works are included, the author(s) must obtain written permission from the copyright owners and credit the source(s) in the article. Elsevier has preprinted forms for use by authors in these cases: please consult <http://www.elsevier.com/permissions>.

For Open Access articles

Upon acceptance of an article, authors will be asked to complete an 'Exclusive License Agreement' (for more information see <http://www.elsevier.com/OAauthoragreement>). Permitted reuse of open access articles is determined by the author's choice of user license (see <http://www.elsevier.com/openaccesslicenses>).

Retained author rights

As an author you (or your employer or institution) retain certain rights. For more information on author rights for:

Subscription articles please see <http://www.elsevier.com/journal-authors/author-rights-and-responsibilities>.

Open access articles please see <http://www.elsevier.com/OAauthoragreement>.

Role of the funding source

You are requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement then this should be stated. Please see <http://www.elsevier.com/funding>.

Funding body agreements and policies

Elsevier has established agreements and developed policies to allow authors whose articles appear in journals published by Elsevier, to comply with potential manuscript archiving requirements as specified as conditions of their grant awards. To learn more about existing agreements and policies please visit <http://www.elsevier.com/fundingbodies>.

Open access

This journal offers authors a choice in publishing their research:

Open Access

- Articles are freely available to both subscribers and the wider public with permitted reuse
- An Open Access publication fee is payable by authors or their research funder

Subscription

- Articles are made available to subscribers as well as developing countries and patient groups through our access programs (<http://www.elsevier.com/access>)
- No Open Access publication fee

All articles published Open Access will be immediately and permanently free for everyone to read and download. Permitted reuse is defined by your choice of one of the following Creative Commons user licenses:

Creative Commons Attribution (CC BY): lets others distribute and copy the article, to create extracts, abstracts, and other revised versions, adaptations or derivative works of or from an article (such as a translation), to include in a collective work (such as an anthology), to text or data mine the article, even for commercial purposes, as long as they credit the author(s), do not represent the author as endorsing their adaptation of the article, and do not modify the article in such a way as to damage the author's honor or reputation.

Creative Commons Attribution-NonCommercial-ShareAlike (CC BY-NC-SA): for non-commercial purposes, lets others distribute and copy the article, to create extracts, abstracts and other revised versions, adaptations or derivative works of or from an article (such as a translation), to include in a collective work (such as an anthology), to text and data mine the article, as long as they credit the author(s), do not represent the author as endorsing their adaptation of the article, do not modify the article in such a way as to damage the author's honor or reputation, and license their new adaptations or creations under identical terms (CC BY-NC-SA).

Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND): for non-commercial purposes, lets others distribute and copy the article, and to include in a collective work (such as an anthology), as long as they credit the author(s) and provided they do not alter or modify the article.

To provide Open Access, this journal has a publication fee which needs to be met by the authors or their research funders for each article published Open Access.

Your publication choice will have no effect on the peer review process or acceptance of submitted articles.

The publication fee for this journal is **\$3000**, excluding taxes. Learn more about Elsevier's pricing policy: <http://www.elsevier.com/openaccesspricing>.

Language (usage and editing services)

Please write your text in good English (American or British usage is accepted, but not a mixture of these). Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the English Language Editing service available from Elsevier's WebShop (<http://webshop.elsevier.com/languageediting/>) or visit our customer support site (<http://support.elsevier.com>) for more information.

Informed consent and patient details

Studies on patients or volunteers require ethics committee approval and informed consent, which should be documented in the paper. Appropriate consents, permissions and releases must be obtained where an author wishes to include case details or other personal information or images of patients and any other individuals in an Elsevier publication. Written consents must be retained by the author and copies of the consents or evidence that such consents have been obtained must be provided to Elsevier on request. For more information, please review the *Elsevier Policy on the Use of Images or Personal Information of Patients or other Individuals*, <http://www.elsevier.com/patient-consent-policy>. Unless you have written permission from the patient (or, where applicable, the next of kin), the personal details of any patient included in any part of the article and in any supplementary materials (including all illustrations and videos) must be removed before submission.

Submission

Submission to this journal proceeds totally online and you will be guided stepwise through the creation and uploading of your files. The system automatically converts source files to a single PDF file of the article, which is used in the peer-review process. Please note that even though manuscript source files are converted to PDF files at submission for the review process, these source files are needed for further processing after acceptance. All correspondence, including notification of the Editor's decision and requests for revision, takes place by e-mail removing the need for a paper trail.

Referees

Please submit, with the manuscript, the names, addresses and e-mail addresses of three potential referees. Note that the editor retains the sole right to decide whether or not the suggested reviewers are used.

Additional Information

Editorial review: All manuscripts are generally submitted to 2-3 referees who are chosen for their ability to evaluate the work. Supplementary material may be included to facilitate the review process. Authors may request that certain referees should not be chosen. Members of the editorial board will usually be called upon for advice when there is disagreement among the referees or between referees and authors, or when the editors believe that the manuscript has not received adequate consideration by the referees.

All referees' comments must be responded to, and suggested changes be made. The author should detail the changes made in response to the referees' comments and suggestions in an accompanying letter. If the author disagrees with some changes, the reason, supported by data, should be given. The editors may refuse to publish manuscripts from authors who persistently ignore referees' comments. Handwritten additions or corrections will not be accepted. Only complete retyping of the pages affected by revision is acceptable. A revised manuscript should be received by the editorial office no later than 2 months after the editorial decision was sent to the author(s); otherwise it will be processed as a new manuscript.

PREPARATION

Use of word processing software

It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier: <http://www.elsevier.com/guidepublication>). Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork.

To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

LaTeX

If the LaTeX file is suitable, proofs will be produced without rekeying the text. The article should preferably be written using Elsevier's document class 'elsarticle', or alternatively any of the other recognized classes and formats supported in Elsevier's electronic submissions system, for further information see <http://www.elsevier.com/wps/find/authorsview.authors/latex-ees-supported>.

The Elsevier 'elsarticle' LaTeX style file package (including detailed instructions for LaTeX preparation) can be obtained from the Quickguide: <http://www.elsevier.com/latex>. It consists of the file: elsarticle.cls, complete user documentation for the class file, bibliographic style files in various styles, and template files for a quick start. For information about reference management please go to the document at http://cdn.elsevier.com/assets/pdf_file/0011/109388/elsdoc.pdf and click on the section 'bibliography'.

Article structure

Subdivision - numbered sections

Divide your article into clearly defined and numbered sections. Subsections should be numbered 1.1 (then 1.1.1, 1.1.2, ...), 1.2, etc. (the abstract is not included in section numbering). Use this numbering also for internal cross-referencing: do not just refer to 'the text'. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods

Provide sufficient detail to allow the work to be reproduced. Methods already published should be indicated by a reference: only relevant modifications should be described.

Results

Results should be clear and concise.

Text, tables and figures must show minimal overlap, and must be internally consistent.

Discussion

This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions

The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Appendices

If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

Essential title page information

- **Title.** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.

• **Author names and affiliations.** Where the family name may be ambiguous (e.g., a double name), please indicate this clearly. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.

• **Corresponding author.** Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. **Ensure that phone numbers (with country and area code) are provided in addition to the e-mail address and the complete postal address. Contact details must be kept up to date by the corresponding author.**

• **Present/permanent address.** If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Abstract

A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

Graphical abstract

A Graphical abstract is mandatory for this journal. It should summarize the contents of the article in a concise, pictorial form designed to capture the attention of a wide readership online. Authors must provide images that clearly represent the work described in the article. Graphical abstracts should be submitted as a separate file in the online submission system. Image size: please provide an image with a minimum of 531 × 1328 pixels (h × w) or proportionally more, but should be readable on screen at a size of 200 × 500 pixels (at 96 dpi this corresponds to 5 × 13 cm). Bear in mind readability after reduction, especially if using one of the figures from the article itself. Preferred file types: TIFF, EPS, PDF or MS Office files. See <http://www.elsevier.com/graphicalabstracts> for examples.

Keywords

Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Chemical compounds

You can enrich your article by providing a list of chemical compounds studied in the article. The list of compounds will be used to extract relevant information from the NCBI PubChem Compound database and display it next to the online version of the article on ScienceDirect. You can include up to 10 names of chemical compounds in the article. For each compound, please provide the PubChem CID of the most relevant record as in the following example: Glutamic acid (PubChem CID:611). The PubChem CIDs can be found via <http://www.ncbi.nlm.nih.gov/pccompound>. Please position the list of compounds immediately below the 'Keywords' section. It is strongly recommended to follow the exact text formatting as in the example below:

Chemical compounds studied in this article

Ethylene glycol (PubChem CID: 174); Plitidepsin (PubChem CID: 44152164); Benzalkonium chloride (PubChem CID: 15865)

More information is available at: <http://www.elsevier.com/PubChem>.

Abbreviations

Abbreviations are a hindrance for the reader. Use as few abbreviations as possible and write out names of compounds, receptors, etc., in full throughout the text of the manuscript, with the exceptions given below. Unnecessary and nonsense abbreviations are not allowed. Generic names should not be abbreviated. As an example, AMP, HAL, HIST, RAMH, TAM, SST, for amphetamine, haloperidol, histamine, (R)- α -methylhistamine, tamoxifen, somatostatin, are not accepted. Abbreviations which have come to replace the full term (e.g., GABA, DOPA, PDGF, 5-HT, for γ -aminobutyric acid, 3,4-dihydroxyphenylalanine, PDGF, 5-hydroxytryptamine) may be used, provided the term is spelled out in the abstract and in the body of the manuscript the first time the abbreviation is used. Unwieldy chemical names may be abbreviated. As an example, 8-OH-DPAT, DOI, DTG, BAPTA,

for 8-hydroxy-2-(di-*n*-propylamino)tetralin, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane, 1,3-di(2-tolyl)-guanidine, 1,2-bis(*o*-aminophenoxy)ethane-*N,N,N',N'*-tetraacetic acid, are acceptable; however, the full chemical name should be given once in the body of the manuscript and in the abstract, followed in both cases by the abbreviation. Code names may be used, but the full chemical name should be given in the text and in the abstract. *Authors not conforming to these demands may have their manuscripts returned for correction with delayed publication as a result.*

Some abbreviations may be used without definition:

1 ADP, CDP, GDP, IDP 5'-pyrophosphates of adenosine UDPcytidine, guanosine, inosine, uridine AMP etc. adenosine 5'-monophosphate etc. ADP etc. adenosine 5'-diphosphate etc. ATP etc. adenosine 5'-triphosphate etc. CM-cellulosecarboxymethylcellulose CoA and acetyl-CoA coenzyme A and its acyl derivatives DEAE-cellulose O-(diethylaminoethyl)-cellulose DNA deoxyribonucleic acid EGTA ethylene glycol-bis(β -aminoethyl ether)-*N,N,N',N'*-tetraacetic acid FAD flavin-adenine dinucleotide FMN flavin mononucleotide GSH, GSSG glutathione, reduced and oxidized Hepes 4-(2-hydroxyethyl)-1-piperazine-ethanesulphonic acid NAD nicotinamide-adenine dinucleotide NADP nicotinamide-adenine dinucleotide phosphate NMN nicotinamide mononucleotide Pi, PPi orthophosphate, pyrophosphate RNA ribonucleic acid Tris 2-amino-2-hydroxymethylpropane-1,3-diol

Two alternative conventions are currently in use in some cases. For example, for the phosphoinositides there are both the abbreviations recommended by the IUPAC-IUB and those of the Chilton Convention (e.g., PtdIns(4,5)P₂ vs. PIP₂ for phosphatidylinositol 4,5-bisphosphate). The journal will accept either of these forms but not their combination.

Abbreviations of units of measurements and other terms are as follows:

Units of mass

1 kilogram kg gram g milligram mg microgram μ g nanogram ng mole (gram-molecule) mol millimole mmol micromole μ mol nanomole nmol picomole pmol femtomole fmol equivalent eq

Units of time

1 hour h minute min second s millisecond ms microsecond μ s

Units of volume

1 litre l millilitre ml microlitre μ l

Units of length

1 metre m centimetre cm millimetre mm micrometre μ m nanometre nm

Units of concentration

1 molar (mol/l) M millimolar mM micromolar μ M nanomolar nM picomolar pM

Units of heat, energy, electricity

1 joule J degree Celsius (centigrade) °C coulomb C ampere A volt V ohm Ω siemens S

Units of radiation

1 curie Ci counts per minute cpm disintegrations per minute dpm becquerel Bq

Miscellaneous

1 gravity g dissociation constant *K*_d median doses LD₅₀, ED₅₀ probability *P* routes of drug administration i.v., i.p., s.c., i.m. square centimetre cm² standard deviation S.D. standard error of the mean S.E.M. Svedberg unit of sedimentation coefficient S Hill coefficient *n*/*H*

The isotope mass number should appear before the atomic symbol, e.g., [3H]noradrenaline, [14C]choline. Ions should be written: Fe³⁺, Ca²⁺, Mg²⁺. The term absorbance (A) is preferred to extinction or optical density. For abbreviations not included in this list consult: *Units, Symbols and Abbreviations, A Guide for Biological and Medical Authors and Editors*, 1994 (The Royal Society of Medicine, London), ISBN 0-905958-78-0, or *Scientific Style and Format. The CBE Manual for Authors, Editors, and Publishers*, 6th edn. (Cambridge University Press, Cambridge), ISBN 0-521-47154-0.

Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g. lab technicians, statisticians, colleagues providing help preparing the manuscript).

Nomenclature and Units

Only generic and chemical names of drugs should be used, although a proprietary equivalent may be indicated once, in parentheses. *Pharmacological and Chemical Synonyms*, E.E.J. Marler, 9th edn. (Elsevier, Amsterdam, 1990) may be consulted.

The nomenclature of chemical substances should be consistent, clear and unambiguous, and should conform to the usage of the American Chemical Society and the convention recommended by the International Union of Pure and Applied Chemistry (IUPAC). When in doubt, writers should consult the indexes of *Chemical Abstracts*; the various reports and pamphlets of the American Chemical Society Committee on Nomenclature, Spelling and Pronunciation; and from the International Union of Biochemistry and Molecular Biology (IUBMB): *Biochemical Nomenclature and Related Documents* (Portland Press, London).

When drugs, which are mixtures of stereoisomers are used, the fact that they have a composite nature and the implication of this for interpretation of the data and drawing of conclusions should be made clear. The use of the appropriate prefix is essential. Use of the generic name alone without prefix would be taken to refer to agents with no stereoisomers. The nomenclature of the various isomers and isomeric mixtures can be found in: (i) *IUPAC, Nomenclature of Organic Chemistry*, eds. J. Rigaudy and S.P. Klesney (Pergamon Press, London), 1979, p. 481; (ii) *Signs of the times: the need for a stereochemically informative generic name system*, Simonyi, M., J. Gal and B. Testa, 1989, *Trends Pharmacol. Sci.* 10, 349. For nomenclature of peptides, see *Neuropeptides*, Vol. 1, 1981, p. 231.

The nomenclature of receptors and their subtypes should conform to the *TIPS 1995 Receptor & Ion Channel Nomenclature Supplement (Trends Pharmacol. Sci. Receptor Nomenclature Supplement 1995)*. Copies of this supplement are available from the publisher (Elsevier Trends Journals, Oxford Fulfilment Centre, P.O. Box 800, Kidlington, Oxford OX5 1DX, UK. Tel.: (44-1865) 843-699; Fax: (44-1865) 843-911).

The trivial name of the enzyme may be used in the text, but the systematic name and classification number according to *Enzyme Nomenclature*, rev. edn. (Academic Press, New York, NY, 1984) should be quoted the first time the enzyme is mentioned.

Database linking

Elsevier encourages authors to connect articles with external databases, giving their readers one-click access to relevant databases that help to build a better understanding of the described research. Please refer to relevant database identifiers using the following format in your article: Database: xxxx (e.g., TAIR: AT1G01020; CCDC: 734053; PDB: 1XFN). See <http://www.elsevier.com/databaselinking> for more information and a full list of supported databases.

GenBank accession numbers

Gene accession numbers refer to genes or DNA sequences about which further information can be found in the databases at the National Center for Biotechnical Information (NCBI) at the National Library of Medicine. Authors wishing to enable other scientists to use the accession numbers cited in their papers via links to these sources, should reference this information in the following manner:

For each and every accession number cited in an article, authors should type the accession number in **bold, underlined text**. Letters in the accession number should always be capitalised. (See Example 1 below.) This combination of letters and format will enable Elsevier's typesetters to recognize the relevant texts as accession numbers and add the required link to GenBank's sequences.

Example 1: "GenBank accession nos. **AI631510**, **AI631511**, **AI632198**, and **BF223228**), a B-cell tumor from a chronic lymphatic leukemia (GenBank accession no. **BE675048**), and a T-cell lymphoma (GenBank accession no. **AA361117**)".

Authors are encouraged to check accession numbers used very carefully. **An error in a letter or number can result in a dead link.**

In the final version of the **printed article**, the accession number text will not appear bold or underlined (see Example 2 below).

Example 2: "GenBank accession nos. AI631510, AI631511, AI632198, and BF223228), a B-cell tumor from a chronic lymphatic leukemia (GenBank accession no. BE675048), and a T-cell lymphoma (GenBank accession no. AA361117)".

In the final version of the **electronic copy**, the accession number text will be linked to the appropriate source in the NCBI databases enabling readers to go directly to that source from the article (see Example 3 below).

Example 3: "GenBank accession nos. AI631510, AI631511, AI632198, and BF223228), a B-cell tumor from a chronic lymphatic leukemia (GenBank accession no. BE675048), and a T-cell lymphoma (GenBank accession no. AA361117)".

Formulas and equations

Structural chemical formulas, process flow diagrams and complicated mathematical expressions should be very clearly presented. All subscripts, superscripts, Greek letters and unusual characters must be identified. Structural chemical formulas and process flow diagrams should be prepared in the same way as graphs.

Present simple formulae in the line of normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by exp. Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

Footnotes

Footnotes should be used sparingly. Number them consecutively throughout the article, using superscript Arabic numbers. Many wordprocessors build footnotes into the text, and this feature may be used. Should this not be the case, indicate the position of footnotes in the text and present the footnotes themselves separately at the end of the article. Do not include footnotes in the Reference list.

Table footnotes

Indicate each footnote in a table with a superscript lowercase letter.

Artwork

Image manipulation

Whilst it is accepted that authors sometimes need to manipulate images for clarity, manipulation for purposes of deception or fraud will be seen as scientific ethical abuse and will be dealt with accordingly. For graphical images, this journal is applying the following policy: no specific feature within an image may be enhanced, obscured, moved, removed, or introduced. Adjustments of brightness, contrast, or color balance are acceptable if and as long as they do not obscure or eliminate any information present in the original. Nonlinear adjustments (e.g. changes to gamma settings) must be disclosed in the figure legend.

Electronic artwork

General points

- Make sure you use uniform lettering and sizing of your original artwork.
- Embed the used fonts if the application provides that option.
- Aim to use the following fonts in your illustrations: Arial, Courier, Times New Roman, Symbol, or use fonts that look similar.

- Number the illustrations according to their sequence in the text.
- Use a logical naming convention for your artwork files.
- Provide captions to illustrations separately.
- Size the illustrations close to the desired dimensions of the printed version.
- Submit each illustration as a separate file.

A detailed guide on electronic artwork is available on our website:

<http://www.elsevier.com/artworkinstructions>

You are urged to visit this site; some excerpts from the detailed information are given here.

Formats

If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply 'as is' in the native document format.

Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

EPS (or PDF): Vector drawings, embed all used fonts.

TIFF (or JPEG): Color or grayscale photographs (halftones), keep to a minimum of 300 dpi.

TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings, keep to a minimum of 1000 dpi.

TIFF (or JPEG): Combinations bitmapped line/half-tone (color or grayscale), keep to a minimum of 500 dpi.

Please do not:

- Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors;
- Supply files that are too low in resolution;
- Submit graphics that are disproportionately large for the content.

Color artwork

Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF), or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color on the Web (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. **For color reproduction in print, you will receive information regarding the costs from Elsevier after receipt of your accepted article.** Please indicate your preference for color: in print or on the Web only. For further information on the preparation of electronic artwork, please see <http://www.elsevier.com/artworkinstructions>.

Please note: Because of technical complications which can arise by converting color figures to 'gray scale' (for the printed version should you not opt for color in print) please submit in addition usable black and white versions of all the color illustrations.

Figure captions

Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

Tables

Number tables consecutively in accordance with their appearance in the text. Place footnotes to tables below the table body and indicate them with superscript lowercase letters. Avoid vertical rules. Be sparing in the use of tables and ensure that the data presented in tables do not duplicate results described elsewhere in the article.

References

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication and a copy of the title page of the relevant article must be submitted.

Reference links

Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please

note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is encouraged.

Web references

As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

References in a special issue

Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

Reference management software

This journal has standard templates available in key reference management packages EndNote (<http://www.endnote.com/support/enstyles.asp>) and Reference Manager (<http://refman.com/support/rmstyles.asp>). Using plug-ins to wordprocessing packages, authors only need to select the appropriate journal template when preparing their article and the list of references and citations to these will be formatted according to the journal style which is described below.

Reference formatting

There are no strict requirements on reference formatting at submission. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume number/book chapter and the pagination must be present. Use of DOI is highly encouraged. The reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct. If you do wish to format the references yourself they should be arranged according to the following examples:

Reference style

Text: All citations in the text should refer to:

1. *Single author:* the author's name (without initials, unless there is ambiguity) and the year of publication;
2. *Two authors:* both authors' names and the year of publication;
3. *Three or more authors:* first author's name followed by 'et al.' and the year of publication.

Citations may be made directly (or parenthetically). Groups of references should be listed first alphabetically, then chronologically.

Examples: 'as demonstrated (Allan, 2000a, 2000b, 1999; Allan and Jones, 1999). Kramer et al. (2010) have recently shown'

List: References should be arranged first alphabetically and then further sorted chronologically if necessary. More than one reference from the same author(s) in the same year must be identified by the letters 'a', 'b', 'c', etc., placed after the year of publication.

Examples:

Reference to a journal publication:

Van der Geer, J., Hanraads, J.A.J., Lupton, R.A., 2010. The art of writing a scientific article. *J. Sci. Commun.* 163, 51–59.

Reference to a book:

Strunk Jr., W., White, E.B., 2000. *The Elements of Style*, fourth ed. Longman, New York.

Reference to a chapter in an edited book:

Mettam, G.R., Adams, L.B., 2009. How to prepare an electronic version of your article, in: Jones, B.S., Smith, R.Z. (Eds.), *Introduction to the Electronic Age*. E-Publishing Inc., New York, pp. 281–304.

Journal abbreviations source

Journal names should be abbreviated according to the

List of title word abbreviations: <http://www.issn.org/2-22661-LTWA-online.php>.

Video data

Elsevier accepts video material and animation sequences to support and enhance your scientific research. Authors who have video or animation files that they wish to submit with their article are strongly encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed. All submitted files should be properly labeled so that they directly relate to the video file's content. In order to ensure that your video or animation material is directly

usable, please provide the files in one of our recommended file formats with a preferred maximum size of 50 MB. Video and animation files supplied will be published online in the electronic version of your article in Elsevier Web products, including ScienceDirect: <http://www.sciencedirect.com>. Please supply 'stills' with your files: you can choose any frame from the video or animation or make a separate image. These will be used instead of standard icons and will personalize the link to your video data. For more detailed instructions please visit our video instruction pages at <http://www.elsevier.com/artworkinstructions>. Note: since video and animation cannot be embedded in the print version of the journal, please provide text for both the electronic and the print version for the portions of the article that refer to this content.

AudioSlides

The journal encourages authors to create an AudioSlides presentation with their published article. AudioSlides are brief, webinar-style presentations that are shown next to the online article on ScienceDirect. This gives authors the opportunity to summarize their research in their own words and to help readers understand what the paper is about. More information and examples are available at <http://www.elsevier.com/audioslides>. Authors of this journal will automatically receive an invitation e-mail to create an AudioSlides presentation after acceptance of their paper.

Supplementary data

Elsevier accepts electronic supplementary material to support and enhance your scientific research. Supplementary files offer the author additional possibilities to publish supporting applications, high-resolution images, background datasets, sound clips and more. Supplementary files supplied will be published online alongside the electronic version of your article in Elsevier Web products, including ScienceDirect: <http://www.sciencedirect.com>. In order to ensure that your submitted material is directly usable, please provide the data in one of our recommended file formats. Authors should submit the material in electronic format together with the article and supply a concise and descriptive caption for each file. For more detailed instructions please visit our artwork instruction pages at <http://www.elsevier.com/artworkinstructions>.

Submission checklist

The following list will be useful during the final checking of an article prior to sending it to the journal for review. Please consult this Guide for Authors for further details of any item.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:

- E-mail address
- Full postal address
- Phone numbers

All necessary files have been uploaded, and contain:

- Keywords
- All figure captions
- All tables (including title, description, footnotes)

Further considerations

- Manuscript has been 'spell-checked' and 'grammar-checked'
- References are in the correct format for this journal
- All references mentioned in the Reference list are cited in the text, and vice versa
- Permission has been obtained for use of copyrighted material from other sources (including the Web)
- Color figures are clearly marked as being intended for color reproduction on the Web (free of charge) and in print, or to be reproduced in color on the Web (free of charge) and in black-and-white in print
- If only color on the Web is required, black-and-white versions of the figures are also supplied for printing purposes

For any further information please visit our customer support site at <http://support.elsevier.com>.

AFTER ACCEPTANCE

Use of the Digital Object Identifier

The Digital Object Identifier (DOI) may be used to cite and link to electronic documents. The DOI consists of a unique alpha-numeric character string which is assigned to a document by the publisher upon the initial electronic publication. The assigned DOI never changes. Therefore, it is an ideal medium for citing a document, particularly 'Articles in press' because they have not yet received their full bibliographic information. Example of a correctly given DOI (in URL format; here an article in the journal *Physics Letters B*):

<http://dx.doi.org/10.1016/j.physletb.2010.09.059>

When you use a DOI to create links to documents on the web, the DOIs are guaranteed never to change.

Online proof correction

Corresponding authors will receive an e-mail with a link to our ProofCentral system, allowing annotation and correction of proofs online. The environment is similar to MS Word: in addition to editing text, you can also comment on figures/tables and answer questions from the Copy Editor. Web-based proofing provides a faster and less error-prone process by allowing you to directly type your corrections, eliminating the potential introduction of errors.

If preferred, you can still choose to annotate and upload your edits on the PDF version. All instructions for proofing will be given in the e-mail we send to authors, including alternative methods to the online version and PDF.

We will do everything possible to get your article published quickly and accurately - please upload all of your corrections within 48 hours. It is important to ensure that all corrections are sent back to us in one communication. Please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility. Note that Elsevier may proceed with the publication of your article if no response is received.

Offprints

The corresponding author, at no cost, will be provided with a PDF file of the article via e-mail or, alternatively, 25 free paper offprints. The PDF file is a watermarked version of the published article and includes a cover sheet with the journal cover image and a disclaimer outlining the terms and conditions of use. For an extra charge, more paper offprints can be ordered via the offprint order form which is sent once the article is accepted for publication. Both corresponding and co-authors may order offprints at any time via Elsevier's WebShop (<http://webshop.elsevier.com/myarticleservices/offprints>). Authors requiring printed copies of multiple articles may use Elsevier WebShop's 'Create Your Own Book' service to collate multiple articles within a single cover (<http://webshop.elsevier.com/myarticleservices/offprints/myarticlesservices/booklets>).

Additional information

No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. Because of the rapid advances made in the medical sciences, independent verification of diagnoses and drug doses should be made.

AUTHOR INQUIRIES

For inquiries relating to the submission of articles (including electronic submission) please visit this journal's homepage. For detailed instructions on the preparation of electronic artwork, please visit <http://www.elsevier.com/artworkinstructions>. Contact details for questions arising after acceptance of an article, especially those relating to proofs, will be provided by the publisher. You can track accepted articles at <http://www.elsevier.com/trackarticle>. You can also check our Author FAQs at <http://www.elsevier.com/authorFAQ> and/or contact Customer Support via <http://support.elsevier.com>.

© Copyright 2012 Elsevier | <http://www.elsevier.com>