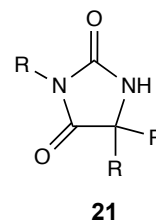
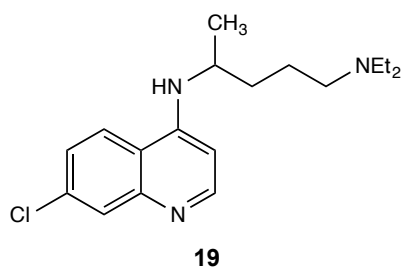
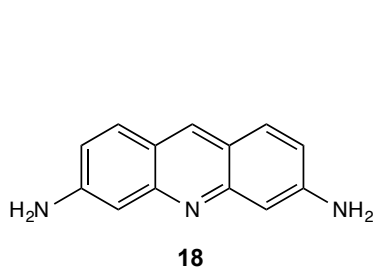
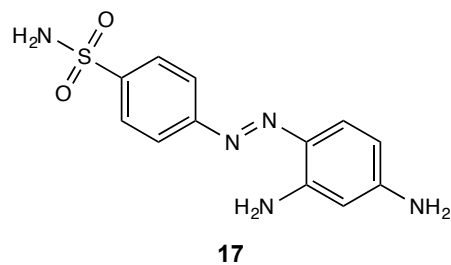
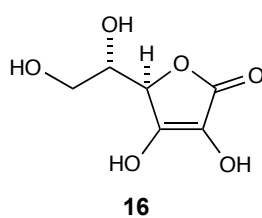
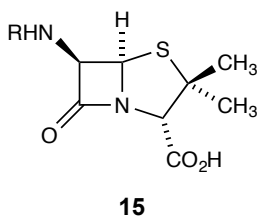
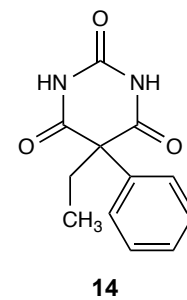
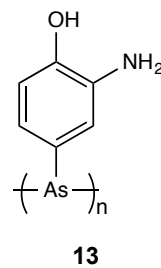
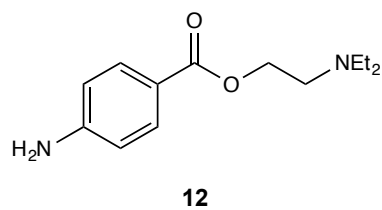
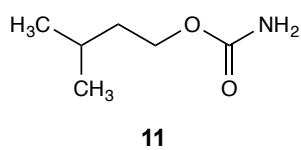
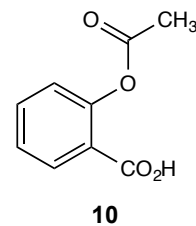
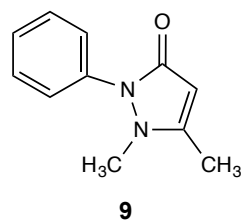
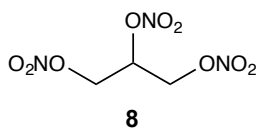
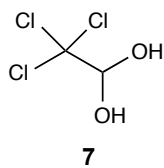
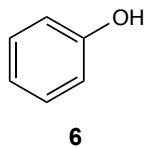
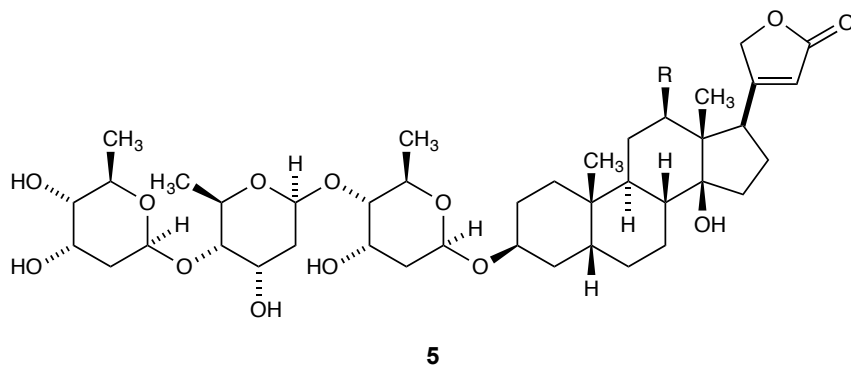
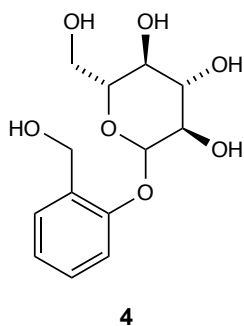
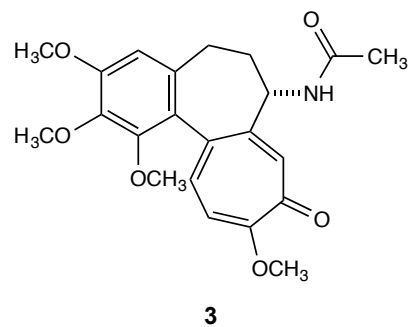
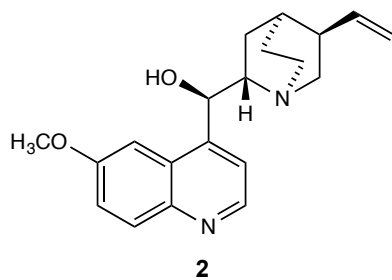
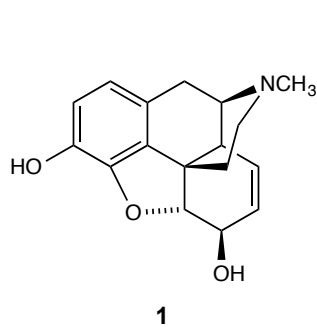
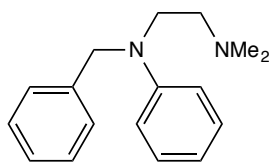


APPENDIX 1 Some Important Events in Medicinal Chemistry

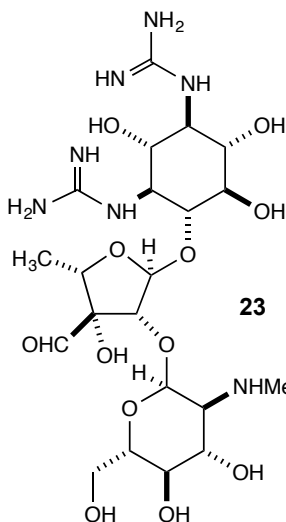
- 1670 Bacteria were first identified by van Leeuwenhoek.
- 1803 Serturmer first isolated morphine **1** in an impure form from the opium poppy.
- 1817 Runge isolated quinine **2** from cinchona bark.
- 1820 Pelletier and Caventon isolated colchicine **3** from the crocus for use in gout.
- 1829 Leroux isolated salicin **4** from willow bark.
- 1833 Morphine **1** isolated and purified on a commercial scale by Macfarlane & Co.
- 1842 Diethyl ether was first used as an anaesthetic by Long.
- 1841 Homolle and Quevenne isolated impure digitoxin **5** (R = H) from foxgloves.
- 1844 Wells used nitrous oxide as an anaesthetic in dentistry.
- 1847 Simpson first used trichloromethane (chloroform, CHCl₃) as an anaesthetic.
- 1867 Lister pioneered the use of phenol **6** as an antiseptic in surgery.
- 1868 Liebreich discovered the sleep-producing properties of chloral hydrate **7**.
- 1874 Maclagan used salicin **4** in rheumatic fever.
- 1879 Murrell showed that glyceryl trinitrate **8** could relieve the pain of angina.
- 1884 Knorr and Filehne introduced phenazone **9** as an antipyretic, stimulating interest in synthetic drugs.
- 1891 Ehrlich coined the term *chemotherapy*. He used methylene blue to treat malaria, the first synthetic material to be used to attack a specific disease.
- 1898 Hoffman first synthesised aspirin **10**.
- 1899 Hedonal **11** was prepared as a deliberate replacement for chloral hydrate.
- 1903 Eischom synthesised procaine **12** as a local anaesthetic.
- 1905 Langley published his theory of *receptive substances*.
- 1909 Ehrlich patented salvarsan **13**, the first purely synthetic chemotherapeutic, for use against syphilis.
- 1912 Hauptmann found that phenobarbitone **14** was antiepileptic.
- 1921 Banting and Best first isolated insulin.
- 1923 Gulland and Robinson determined the chemical structure of morphine **1**.
- 1929 Fleming first observed the antibiotic activity of the penicillins **15**.
- 1930 Active principle of foxglove shown to be digoxin **5** (R = OH) by Smith.
- 1931 King first isolated vitamin C **16**.
- 1932 Erlenmeyer espoused the concept of *bioisosterism*, the similar biological activity of different groups.
- 1932 Domagk discovered the antibacterial activity of sulphamidochrysoidine **17**.
- 1934 Proflavine **18** was introduced as an antibacterial agent
- 1934 Chloroquine **19** was found to have antimalarial activity.
- 1934 Cyclopropane **20** was introduced as a general anaesthetic.
- 1935 The first virus was characterised by Stanley.
- 1937 Putman and Merritt introduced the use of hydantoins **21** as anticonvulsants.
- 1940 Florey and Chain developed the commercial scale isolation of penicillins **15**.
- 1942 Nitrogen mustards were found to act as anticancer alkylating agents.
- 1942 Phenbenzamine **22** was introduced as the first anti-histamine agent.
- 1944 Waksman isolated the aminoglycoside antibiotic streptomycin **23**.
- 1945 The structure of the penicillins **15** was confirmed.
- 1945 The antibiotic chlorotetracycline **24** [*American Cyanamid*] was isolated.
- 1945 Woodward and Doering first synthesised quinine **2**.
- 1947 Anti-histamines were shown to be anti-seasickness agents.

- 1947 Isoproterenol **25** [*Boehringer-Ingelheim*] was introduced as a bronchodilator.
- 1949 Lithium ions Li^+ were shown to control manic depression.
- 1952 6-Mercaptopurine **26** [*Wellcome*] was shown to have anti-leukaemic activity.
- 1952 Reserpine **27** [*Ciba*] shown to be antihypertensive and tranquilising.
- 1952 Chlorpromazine **28** [*Smith, Kline & French / Rhone-Poulenc*] introduced as an anti-psychotic agent.
- 1952 Isoniazid **29** [*Hoffmann-LaRoche*] was introduced as an anti-tubercular agent.
- 1952 The first synthesis of morphine **1** was achieved.
- 1952 Erythromycin **30** was isolated and shown to have broad-spectrum antibiotic activity.
- 1953 Potassium phenoxymethyl penicillin **31** marketed as the first orally-active penicillin.
- 1953 The structure of DNA was announced.
- 1957 The growth-retarding effects of interferon on viruses was discovered.
- 1957 Imipramine **32** [*Geigy*] found to be an anti-depressant.
- 1957 Chlorothiazide **33** was introduced as a diuretic in congestive heart failure.
- 1958 The anti-psychotic haloperidol **34** [*Janssen*] was discovered.
- 1959 Aminopenicillanic acid **15** (R = H) [*Beechams*] used as a source of semi-synthetic penicillins.
- 1959 Idoxuridine **35** was introduced as the first anti-viral agent
- 1959 Enovid **36** was approved for use as the first oral contraceptive.
- 1959 The *Journal of Medicinal Chemistry* was founded by Beckett and Burger.
- 1960 Chlorodiazepoxide **37** was marketed as an anxiolytic.
- 1961 Tranylcypromine **38** [*Smith, Kline & French*] introduced as anti-depressant.
- 1962 Statistical, regression and molecular orbital analyses were applied to medicinal chemistry by a number of workers, principally Hansch.
- 1963 Valproic acid **39** was found to be an anti-convulsant.
- 1963 Indomethacin **40** [*Merck*] introduced as an anti-inflammatory agent.
- 1964 Cephaloridine **41** [*Eli Lilly / Glaxo*], the first orally active cephalosporin, marketed.
- 1964 Propranolol **42** [*ICI*] was introduced as a β -adrenergic blocker.
- 1964 Ibuprofen **43** [*Boots*] was introduced as an anti-pyretic.
- 1965 Tetramisole **44** [*Janssen*] was introduced as a broad spectrum anthelmintic.
- 1966 Allopurinol **45** [*Wellcome*] was marketed as an anti-gout agent.
- 1967 Salbutamol **46** [*Glaxo*] found to be a lung-specific bronchodilator.
- 1967 Cotzias pioneered the use of L-dopa **47** as therapy for Parkinsonism.
- 1967 Intal **48** [*Fisons*] was introduced as the first prophylactic anti-allergy agent.
- From 1970 onwards many new therapeutic agents were introduced by the major pharmaceutical companies — a few examples are listed below.*
- 1971 Tamoxifen **49** [*ICI*] was introduced for the treatment of breast cancer.
- 1976 Cimetidine **50** [*Smith, Kline & French*] was introduced as the first histamine H-2 antagonist.
- 1977 Acyclovir **51** [*Wellcome*] introduced for the treatment of viral herpes infections.
- 1978 Cyclosporin A **52** [*Sandoz*] introduced as an immunosuppressant, revolutionising transplant surgery.
- 1978 Ranitidine **53** [*Glaxo*] introduced as a histamine H-2 antagonist. Ten years later it became the biggest selling drug of all time.
- 1980 Captopril **55** [*Squibb*] the first ACE inhibitor, introduced as an anti-hypertensive.
- 1987 AZT **56** [*Wellcome*] introduced as the first anti-AIDS agent.
- 1988 The first biotechnology products appear including; α -interferon, human insulin, and human growth factor.

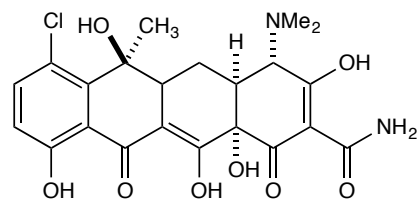




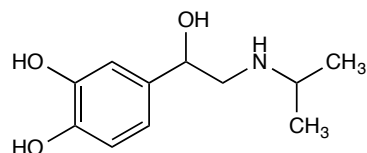
22



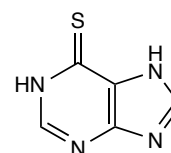
23



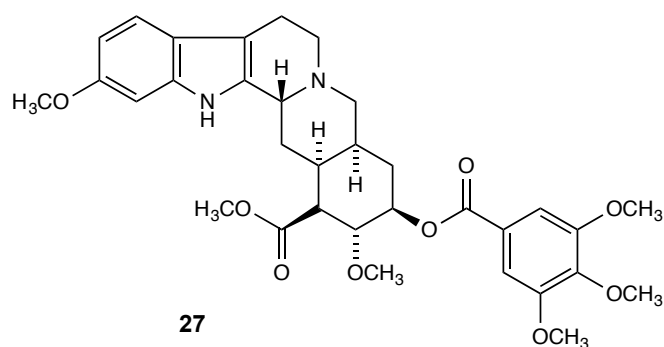
24



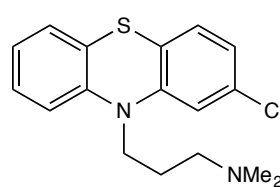
25



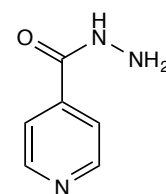
26



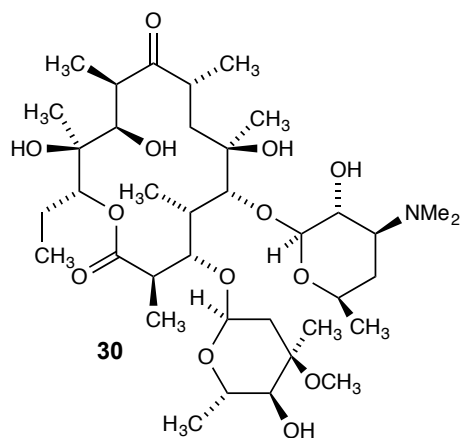
27



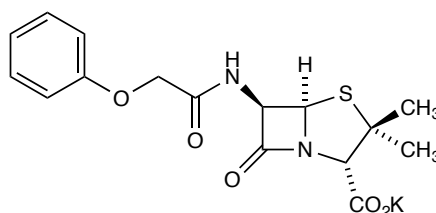
28



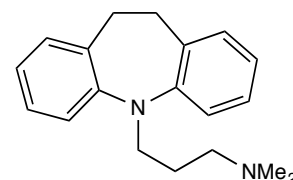
29



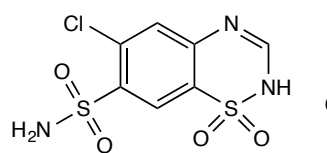
30



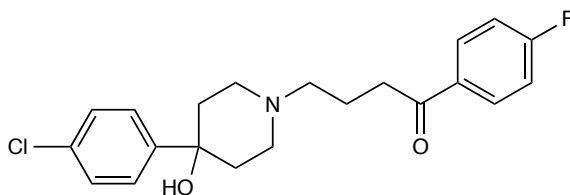
31



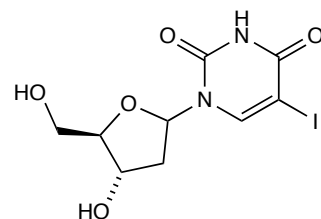
32



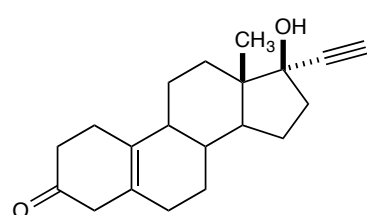
33



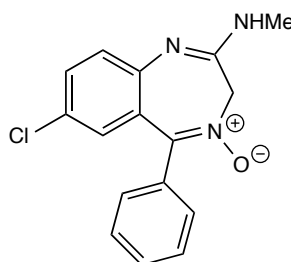
34



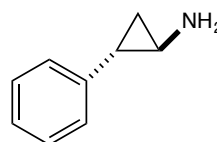
35



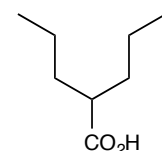
36



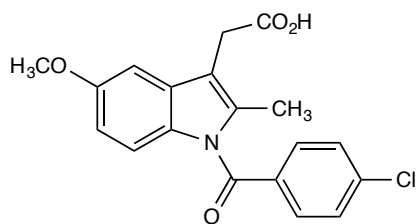
37



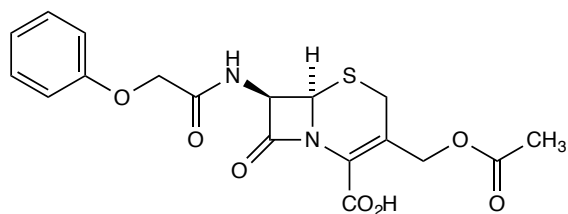
38



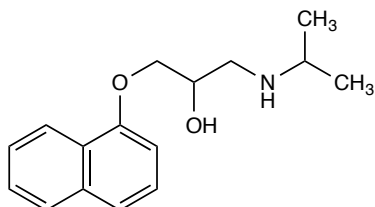
39



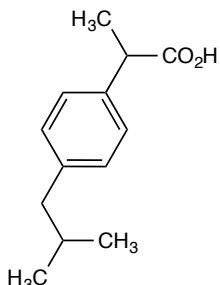
40



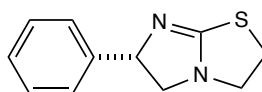
41



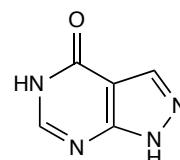
42



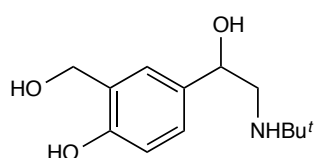
43



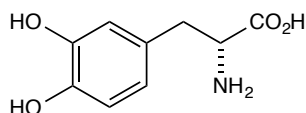
44



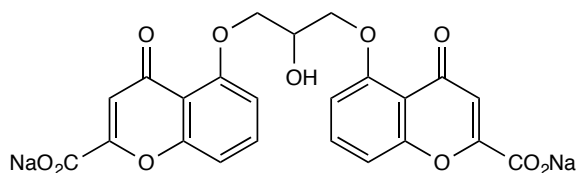
45



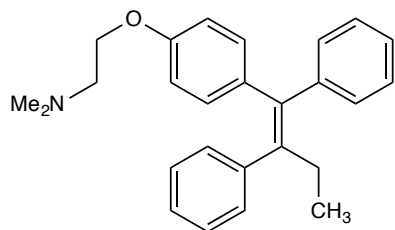
46



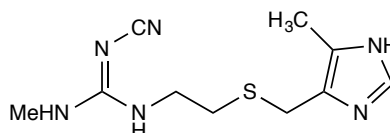
47



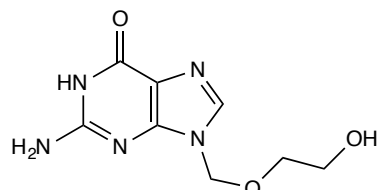
48



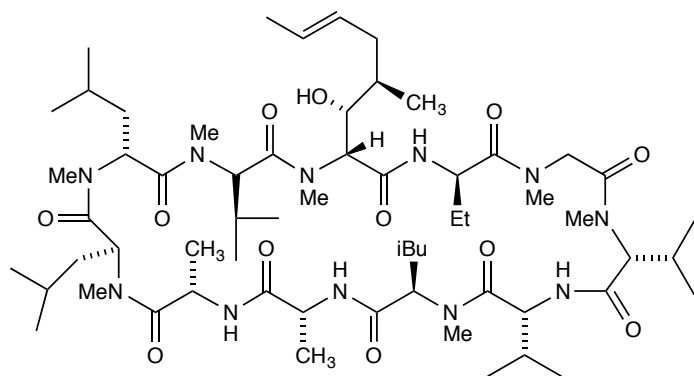
49



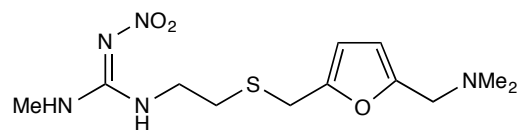
50



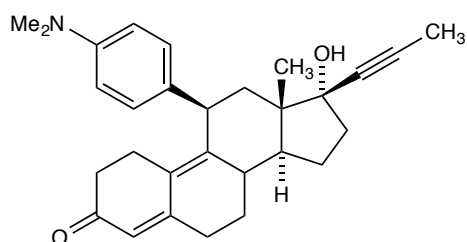
51



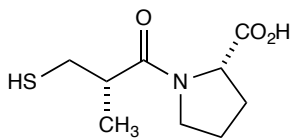
52



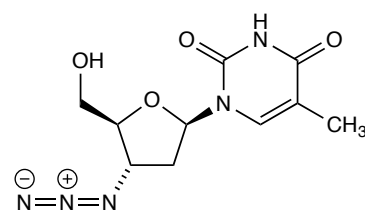
53



54



55



56