7902 J. Med. Chem. 2010, 53, 7902–7917
DOI: 10.1021/jm100762r

Journal of Medicinal Chemistry Perspective

Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore

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Received June 23, 2010

Introduction

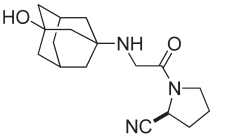
Over 30 nitrile-containing pharmaceuticals are prescribed for a diverse variety of medicinal indications with more than 20 additional nitrile-containing leads in clinical development. Trends identifying the roles of the nitrile in medical agents have emerged as the number of nitrile-containing pharmaceuticals has increased. Coupled with the increasing number of nitrile-containing agents have been structural advances that provide insight into the binding of small molecule inhibitors. X-ray crystallography in particular is providing key insight into small molecule−protein interactions through an increasing number of structures with inhibitors bound in the active site. Augmenting the available interactions with current nitrile-containing pharmaceuticals are details from clinical candidates no longer under development. The present review surveys this range of medicinally active nitriles by focusing on the roles of the CN unit.

The prevalence of nitrile-containing pharmaceuticals and the continued stream of potential agents in the clinic attest to the biocompatibility of the nitrile functionality.[1] The nitrile group is not particularly electrophilic toward free nucleophiles, even glutathione,[2] unless activated by adjacent structural elements such as electron withdrawing groups.[3] A caveat is the highly orchestrated activation−electrophilic additions such as those being exploited in several aminonitriles for diabetes and osteoporosis treatments that feature a reversible electrophilic attack (vide infra).

The nitrile group is quite robust and, in most cases, is not readily metabolized.[4] Metabolically, the nitrile group in most nitrile-containing drugs is passed through the body unchanged.[5] In cases of drug metabolism prior to elimination, the formation of glucuronides,[6] conjugation with glutathione,[7] N-dealkylation,[8] N-acetylation,[9] hydrolysis,[6a−d] and oxidation[10] typically occurs at sites remote from the nitrile and without modification of the nitrile group.

Release of cyanide from aromatic or fully substituted carbons is not observed,[11] whereas alkylnitriles bearing an adjacent proton can be oxidized in the liver to cyanohydrins with subsequent cyanide release.[12] Mandelonitrile, a cyanohydrin produced by ingesting almonds or some fruit pits, releases cyanide as the main degradation pathway and is responsible for the toxicity of cyanogenic glycosides.[13] The potential oxidation and cyanide ejection likely explains why only four of the bioactive nitriles in the review contain an adjacent C−H bond. Epoxidation of alkenenitriles and ring opening can potentially liberate cyanide, but the epoxidation is synthetically difficult[14] and metabolism at other sites appears more likely given the success of several alkenenitrile-containing pharmaceuticals.

Vildagliptin (**1**) is a recently released aminonitrile-containing antidiabetic drug in which the nitrile bearing carbon is not fully substituted (Figure 1).[15] Perhaps because of a concern for cyanide release, the metabolism has been closely examined in humans. The main metabolite comes from hydrolysis of the nitrile which likely stems from the covalent intermediate formed from this carboxyl transition structure analogue. Nitrile hydrolysis is rather rare and, when observed, is a very minor metabolic pathway.[16]



Vildagliptin (**1**)

Figure 1. Aminonitrile vildagliptin.

Nitriles are unusual functionalities by virtue of the short, polarized triple bond.[17] The linear, rodlike geometry has a cylindrical diameter of 3.6 Å for the π-system[18] resulting in a minuscule steric demand along the axis. For comparison, the C≡N unit is essentially 8 times smaller than a methyl group![19] Several crystal structures show the nitrile projecting into narrow clefts to make polar interactions or hydrogen bonds in sterically congested environments.[20]

Nitriles often play a key role as hydrogen bond acceptors.[17,21] Several crystal structures show hydrogen bonding between the nitrile nitrogen and amino acids or to water which in turn is bound to the protein backbone. Many hydrogen bonds are between the nitrile and serine or arginine as expected for these hydrogen bond donors. In other clinical candidates, the strong dipole facilitates polar interactions in which the nitrile acts as a hydroxyl or carboxyl isostere.

The review is structured according to the nature of the nitrile-bearing substituent. As the number of nitrile-containing drug leads is vast, the review has focused on launched nitrile-containing pharmaceuticals and currently active clinical candidates. Most nitrile-containing pharmaceuticals are aromatics with aliphatic-, alkene-, and nitrogen-bearing nitriles being progressively less frequent. Within each class, the bioactive nitriles are collated according to common structural elements

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 Published on Web 08/30/2010

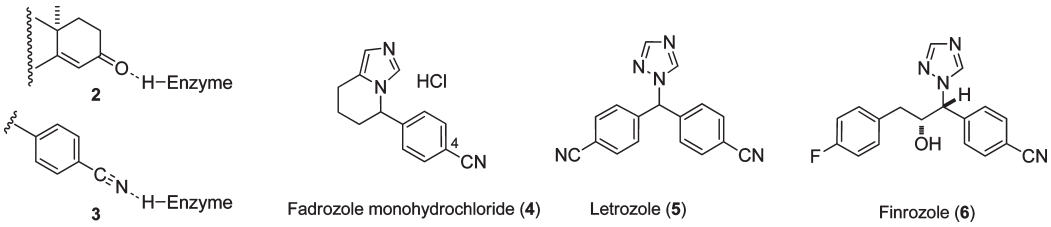


Figure 2. Nitrile-containing aromatase and aldolase inhibitors.

and mode of action. The hope is that this survey will allow greater deployment of this versatile functionality within drug leads.

Arylnitrile-Containing Pharmaceuticals

By far the largest class of nitrile-containing drugs is comprised of an aromatic core with a nitrile substituent. In many cases the nitrile functions as a ketone bioisostere with the nitrile engaging in nonspecific, polar interactions. In other instances the nitrile is relatively remote from the recognition site and may polarize the aromatic π-system to optimize $\pi-\pi$ interactions. Para-substituted arylnitriles are common, possibly because the excellent inductive properties of the nitrile group more strongly polarize the aromatic ring, making aromatics less susceptible to oxidative metabolism.

Several substituted benzonitriles have been developed as selective inhibitors of the aromatase enzyme for the treatment of estrogen-dependent diseases. Placement of the nitrile in the para position is essential for inhibition. There is general agreement that the nitrile mimics the carbonyl group of androst-4-ene-3,17-diones by functioning as a hydrogen bond acceptor (cf. **2** and **3**, Figure 2).[22] **4** (fadrozole monohydrochloride), marketed by Novartis as Afema, was one of the first nonsteroidal aromatase inhibitors[23] for treatment of breast cancer.[24] Structure–activity relationships identified the efficacy of electron withdrawing groups at C-4 with bromine and nitrile groups being best.[25] Subsequent development by Novartis identified **5** (letrozole) as a more potent oral aromatase inhibitor for the adjuvant treatment of hormonally responsive breast cancer.[26] Recently the crystallographic structure of enzyme-bound androstenedione was determined which may aid in designing future members of this class of inhibitors.[27]

Structurally related to **4** and **5** is **6** (finrozole) which functions as both an aromatase[28] and aldosterone inhibitor.[29] Interest in **6** was stimulated by the implication of aldosterone's role in several pathogenic diseases and in regulating sodium and potassium balance, extracellular fluid volume, and blood pressure. The nitrile group of **6** mimics the steroidal carbonyl by acting as a hydrogen bond acceptor. Separation of the most active finrazole enantiomer was achieved using monoclonal antibodies with a recent crystal structure showing the nitrile interacting with main chain phenylalanine and histidine residues.[30]

Among the numerous nonsteroidal androgen receptor antagonists[31] is **7** (bicalutamide, Figure 3). Launched by AstraZeneca for the treatment of advanced prostate cancer,[32] **7** has good oral bioavailability with minimal activity toward other steroid receptors. The crystal structure of the stronger-binding[33] *R*-enantiomer shows the nitrile participating in a hydrogen bond to arginine and to a water molecule bound in the active site.[34] The hydrogen bonding and positioning of **7** show the nitrile mimicking the 3-keto functionality of dihydrotestosterone.

Several androgen receptor antagonists are in various stages of clinical trials for a variety of indications. Effort to use structurally related antagonists for the topical treatment of acne and hair loss led to the development of **8** (RU-58841),[35] which was later superseded by **9** (PF-0998425).[36] Like **7**, the nitrile of **9** interacts with an arginine residue and has polar interactions with glutamine and leucine at the binding site.[36]

An excellent example of the equivalency of complex arylnitriles and steroids is apparent in the comparative cocrystal structures of the human progesterone ligand binding domain with **10** (progesterone, Figure 4a) and **11** (tanaproget, Figure 4b). **11** is one of a potentially new class[37] of nonsteroidal contraceptives in clinical trials.[38] The key interaction with Gln 725 and Arg 766 is a hydrogen bond to the enone carbonyl of **10** which is exceptionally well mimicked by a similar interaction with the nitrile group of **11**.[39] Hydrogen bonding to the nitrile explains the superior efficacy of this functionality over other electron withdrawing groups within this small binding pocket.

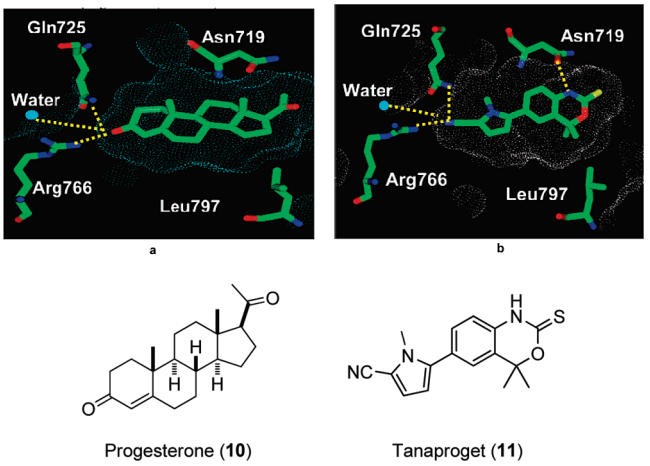


Figure 4. Cocrystallizations in the human progesterone ligand binding domain.[38]

Inhibition of farnesyltransferase has become an important target for preventing oncogenesis by disrupting cell signaling. **12** (BMS-214662) is a farnesyltransferase inhibitor[40] that

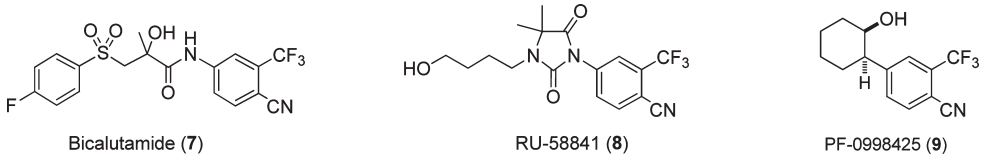


Figure 3. Nonsteroidal receptor antagonists in which nitriles function as carbonyl bioisosteres.

entered early clinical trials[41] for chronic myeloid leukemia (Figure 5).[42] Crystallization of **12** complexed with mammalian farnesyltransferase shows aromatic π-interactions within a deep hydrophobic cleft that are critical for binding.[43] No specific interactions of the nitrile were identified, but for **12** the nitrile group improves pharmacokinetic properties. Solubility studies revealed that the nitrile substituent in **12** was nearly 10-fold more soluble than the corresponding bromo analogue.[44]

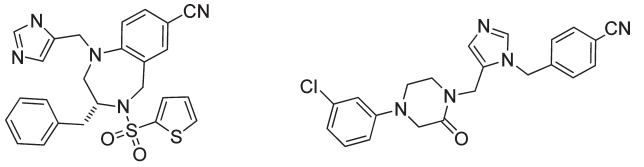


Figure 5. Nitrile-containing farnesyltransferase inhibitors.

13 (L-778,123) is a dual inhibitor of farnesyltransferase and geranylgeranyltransferase which entered phase I trials for the treatment of pancreatic cancer, non-small-cell lung cancer, and head and neck cancer.[45] Two crystal structures of bound **13** show polar interactions of the nitrile nitrogen with glutamine and arginine in the two enzymes.[46]

14 (neratinib) is an irreversible epidermal growth factor receptor (EGFR[a]) inhibitor currently in phase II trials for patients with breast cancer[47] and non-small-cell lung cancer (Figure 6).[48] The related antineoplastic agent **15** (pelitinib, EKB-569) entered phase I clinical trials for treating solid tumors[49] and cancers resistant to treatment with gefitinib or erlotinib.[50] Crystallization of **14** in a mutant kinase confirms the irreversible inhibition through Michael addition of cysteine to the enamide.[51] The structure reveals a polar interaction between the nitrile and a key methionine residue postulated as being critical for the remarkable selectivity exhibited over vascular epidermal growth factor receptor-2 (VEGFR-2). **15** also acts as an irreversible Michael acceptor.[52] **16** (bosutinib, SKI-606) is a kinase inhibitor in phase III clinical trials for treating chronic myelogenous leukemia in patients resistant to other tyrosine kinase inhibitors.[53] Docking studies identified a key hydrogen bond between threonine and the nitrile nitrogen of **16** which is a common motif in these kinase inhibitors.[54]

Early structure−activity relationships for the neratinib family of kinase inhibitors was guided by recognition that the quinazoline-based inhibitors functioned through a water-bound hydrogen bond bridged to a proximal threonine residue (**17**, Figure 7). Modeling indicated that substitution of the azomethine−water aggregate for a sp^2-CN unit, **18**, would displace water and allow direct hydrogen bonding between the nitrile and the amino acid.[55] This strategy was successfully applied to quinazoline analogues[56] leading to identification of **14**[50] and **15**.[57] Crystallographically guided lead optimization led to a similar substitution in quinazoline and benztriazine inhibitors of scytalone dehydratase.[58]

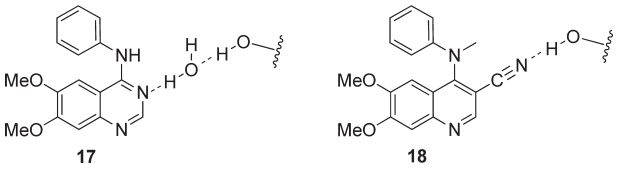


Figure 7. Nitrile-substituted cyanoquinoline as an azomethine−water bioisostere.

19 (milrinone), marketed as Primacor, is a phosphodiesterase inhibitor used for treating heart failure,[59] particularly when conventional treatment with vasodilators and diuretics is ineffective (Figure 8).[60] **19** shares some structural homology with thyroxine and stimulates the myocardial membrane in a similar manner to the hormone. **20** (Olprinone) is a structurally related phosphodiesterase inhibitor used for heart failure which both enhances myocardial contraction and acts as a vasodilator.[61] X-ray crystallography of human transthyretin with **20** shows the cyanopyridone ring bound in the hormone pocket.[62] The nitrile binds deeper in the position occupied by iodine while binding closer and tighter to the amino acids lining the channel. Replacing the nitrile with an amino group maintains activity but with fewer contacts to residues in the binding pocket. A bromine substituent fits better in the same pocket, suggesting that the nitrile has a similar polarizing influence but with greater hydrophilicity.[63] The interchange of nitrile and iodine or bromine as nonclassical isosteres[64] in imidazoles,[65] has been observed during lead optimization of other inodilators.[66]

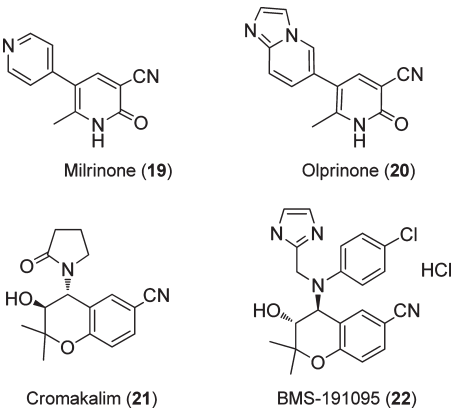


Figure 8. Nitrile-containing cardiovascular agents.

21 (cromakalim) is a potassium-dependent ATP channel opener used to treat hypertension.[67] This "first generation" treatment lacks specificity which led to the search for selective agents with decoupled anti-ischemic and vasorelaxant activity.[68] Of the numerous analogues pursued, **22** (BMS-191095) is particularly promising with over 4000-fold improved selectivity

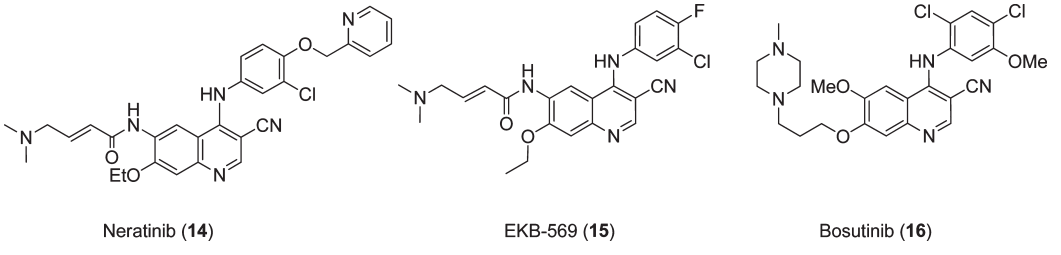


Figure 6. Nitrile-containing kinase inhibitors.

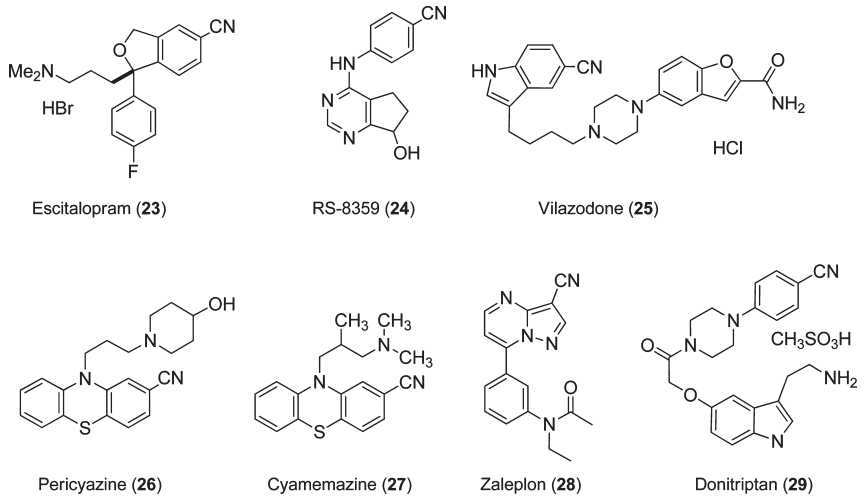


Figure 9. Nitrile-containing CNS drugs.

for the ischemic myocardium than **21**.[69] The receptor is assumed to have a π-interaction to the aromatic core and hydrogen bonding with the nitrile.[70] Replacement of the aromatic nitrile by iodine affords an equipotent analogue, again indicating some similarity between nitrile and halogen groups.[71] The hydrogen bonding, however, is not as critical as in previous examples because replacing the nitrile with iodine maintains the potency. Structure−activity series within cromakalim-type potassium ion channel openers have shown that the cyanophenyl ring can be replaced with an N-6 pyridyl ring indicative of hydrogen bonding analogous to that observed in cyanoquinolines (cf. Figure 7).[67a,71]

Several phenyl-substituted nitriles have been developed for treatment of mood disorders (Figure 9). Although the receptors are usually known, in most instances the precise binding, in terms of interactions, is not well understood. (±)-**23** (citalopram) is a selective serotonin reuptake inhibitor prescribed for depression which has recently been superseded by the more efficacious single enantiomer **23** (escitalopram).[72] Molecular modeling suggests that the two enantiomers bind in the human serotonin transporter with opposite orientations of the aromatic groups and with an interaction between the nitrile and a phenylalanine residue.[73] **24** (RS-8359) is a selective and reversible monoamine oxygenase inhibitor under examination for treatment of depression.[74] Clinical studies[75] demonstrate different efficacies for the two enantiomers of **24** and an in vivo epimerization through oxidation and reduction of the benzylic alcohol.[76]

25 (vilazodone) is a dual-acting serotonergic antidepressant that has completed phase III clinical trials.[77] During screening of a series of analogues the most efficacious leads contained electron withdrawing groups, with the nitrile or fluorine substituents being the most potent. Computed molecular electrostatic potentials and dipole moments showed a strong homology suggesting that the nitrile can function as a fluorine bioisostere.[78] Electrostatic mapping performed during the development of the muscarinic agonist, sabcomeline, generated similar electrostatic potential maps for the respective imidoyl nitrile, fluoride, and chloride, again suggesting the nitrile as a halogen bioisostere.[79]

[a]Abbreviations: EGFR, epidermal growth factor receptor; VEGFR-2, vascular epidermal growth factor receptor 2; GABA, γ-aminobutyric acid; 5-HT_{1B}, 5-hydroxytryptamine receptor 1B; NNRTI, non-nucleoside reverse transcriptase inhibitor; DPP IV, dipeptidyl peptidase IV; MDR, multidrug resistance; ADME, absorption, distribution, metabolism, and excretion.

26 (pericyazine) is a phenothiazine antipsychotic thought to act on several receptors in the brain but for which no specific binding is available.[80] **27** (cyamemazine) is an antipsychotic widely used in France to minimize withdrawal symptoms after drug addiction.[81] The mechanism of cyamemazine's anxiolytic action, and therefore the role of the functional groups, is unknown.

28 (zaleplon) is a non-benzodiazepine hypnotic drug used for treating insomnia.[82] Binding assays show that **28** selectively binds to $GABA_A$ receptors containing the α_1 subunit, though the exact interactions are currently unknown.[83] **29** (donitriptan) is a 5-HT_{1B} agonist[84] that entered phase II trials for the treatment of migraines.[85]

A series of nitrile-containing aromatics, some containing two nitriles, are ushering in a potentially revolutionary approach for treating AIDS.[86] **30** (etravirine) is the first of this new type of non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV to be launched (Figure 10).[87] **31** (dapivirine)[88] and **32** (rilpivirine) are among the many etravirine analogues under development, with **32** being touted as among "the most potent anti-HIV agent(s) ever discovered."[89] The nitrile groups of **32** project deep into the binding pocket with the flexible pyrimidine allowing conformational mobility and potency, even with several mutation-induced changes of the binding pocket.[90] Crystallographic analyses of HIV-1 inhibitor complexes indicate that one nitrile binds to a water molecule that bridges to amino acids on the main chain.[91]

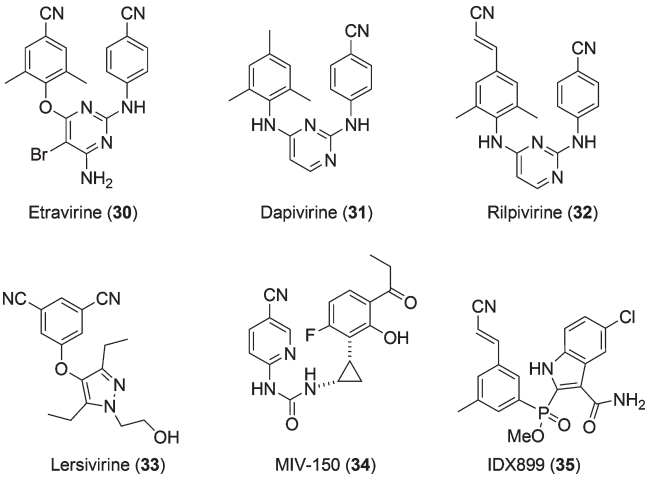


Figure 10. Nitrile-containing anti-HIV agents.

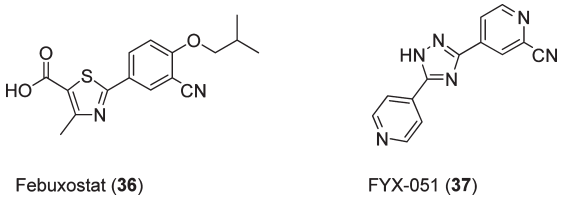


Figure 11. Nitrile-containing xanthine oxidase inhibitors.

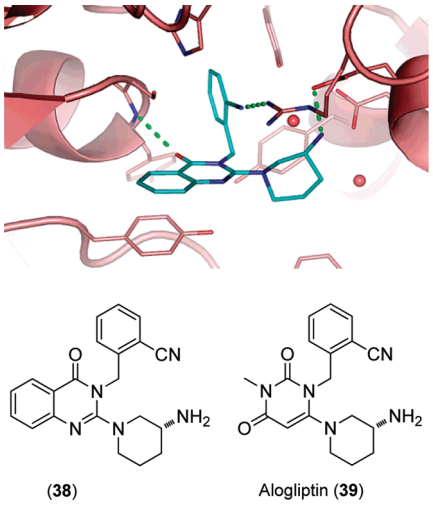


Figure 12. Nitrile-containing DPP IV inhibitors.[103]

33 (lersivirine, UK-453,061) is a novel NNRTI currently in phase II clinical trials.[92] Structural optimization identified the nitrile and the corresponding chloride as being equipotent, with the nitrile being much less lipophilic and more metabolically stable.[93] **34** (MIV-150) was developed as an NNRTI but is not suitable as an antiviral therapy because of poor systemic absorption after oral administration.[94] Exploiting the poor absorption, **34** is now being evaluated as a vaginal microbicide.[95] Early pharmacokinetics and oral bioavailability of ^{14}C-labeled **35** (IDX899) in humans are promising with further clinical studies in progress.[96]

36 (febuxostat) is a non-purine xanthine oxidase inhibitor used to treat gouty arthritis (Figure 11).[97] X-ray crystallography suggests hydrogen bonding between the nitrile, a bound water, and amino acids, which positions **36** in the channel leading to the molybdenum active site.[98] In the more potent inhibitor **37** (FYX-051) with better binding affinity,[99] the nitrile has a direct hydrogen bond with an arginine residue.[100]

39 (alogliptin) is a noncovalent inhibitor of dipeptidyl peptidase IV (DPP IV) in phase III clinical trials for the treatment of diabetes (Figure 12, bottom right).[101] **39** exhibits a 10 000 times greater preference for DPP IV over the related peptidase DPP VIII and has therapeutic advantages over existing DPP IV inhibitors.[102] The inhibitor design was based on docking the cyanoaryl ring of a substituted quinazolinone (**38**) into a hydrophobic pocket augmented with hydrogen bonding between the nitrile and an arginine residue.[103] X-ray crystallography of a cocrystal structure of **38** in the active site of DPP IV is consistent with the design motif, clearly showing a hydrogen bond from arginine to the nitrile (Figure 12, top). Optimizations to minimize hERG activity and maximize the metabolic half-life led to **39** which presumably has analogous enzyme interactions.

Unfortunately no information is available for the role of the nitrile in medications **40**−**47** (Figure 13). **40** (lodoxamide) and **41** (lodoxamide ethyl) are histamine inhibitors used as ocular anti-inflammatory agents.[104] Structurally related **42** (TYB-2285) entered phase II clinical trials in Japan for asthma and atopic dermatitis.[105] **43** (strontium ranelate) is prescribed to promote bone formation[106] through a dual-action mechanism of preventing bone resorption while stimulating bone formation.[107] **44** (ravuconazole) is a recently released broad spectrum antifungal agent[108] for which molecular modeling suggests that the cyanophenyl ring participates in π-stacking in the target lanosterol 14-demethylase.[109] **45** (isavuconazole) is a structural isomer in advanced clinical trials as a broad-spectrum azole antifungal agent.[110] **46** (NO-1886, ibrolipim) is a lipoprotein lipase activator that entered phase II trials in Japan for the potential treatment of hyperlipidemia.[111] **47** (epanolol) is a β blocker used for angina pectoris.[112] Although the exact role of the nitrile is unknown in these agents, a reasonable speculation is that the nitrile was installed to balance the electronics of the aromatic rings and/or to reduce potential for oxidative metabolism.

α-Arylacetonitriles

α-Arylacetonitrile drugs contain the nitrile on a quaternary carbon adjacent to an aromatic ring. Positioning the nitrile on a fully substituted carbon prevents oxidation at the nitrile-bearing carbon and thereby prevents cyanide release.[113] **48** (anastrazole), **49** (verapamil), and **50** (gallopamil) are widely prescribed and are among the best-studied nitrile-containing pharmaceuticals (Figure 14). The blockbuster drug **48**, marketed by Astra-Zeneca under the trade name Arimidex, is considered the drug of choice for treating estrogen-dependent

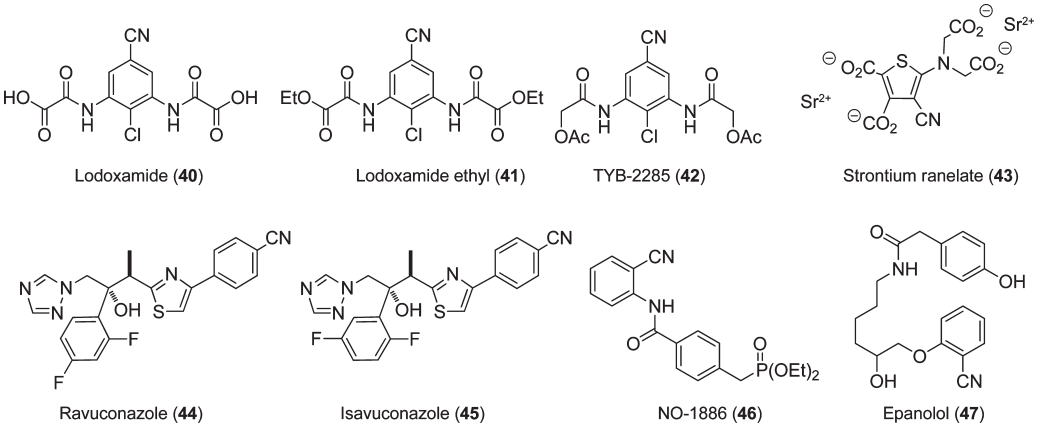


Figure 13. Miscellaneous arylnitrile-containing inhibitors.

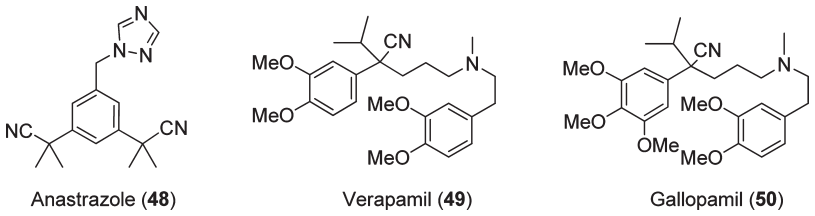


Figure 14. Most widely prescribed nitrile-containing pharmaceuticals.

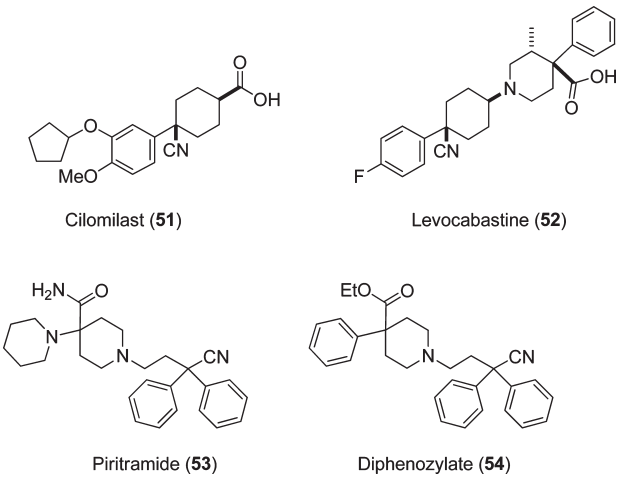


Figure 15. Bioactive quatarnary arylacetonitriles.

breast cancer.[114] Docking of **48** into the human aromatase homology model reveals a potential hydrogen bonding interaction of the two nitriles with an adjacent serine residue.[115]

49 is a calcium channel antagonist used as an antiarrhythmic agent to treat angina.[116] **49** relaxes blood vessels so the heart does not have to pump as hard and simultaneously increases the supply of blood and oxygen to the heart which reduces chest pain. **50** is a methoxy derivative of **48** having a 10-fold increase in potency.[117] Molecular modeling suggests that the polar nitrile group of these inhibitors, which is required for activity,[118] engages in a strong dipole interaction with the enzyme-bound calcium through the nitrile nitrogen.[119]

49 blocks the drug efflux pump P-glycoprotein and is often employed as a standard to gauge reversal of multidrug resistance (MDR). Strategies to modify verapamil into more potent and selective MDR agents highlight the necessity of the nitrile group.[120]

51 (cilomilast, Ariflo) was developed as a phosphodiesterase inhibitor (DPP4) for use as an anti-inflammatory and antiasthmatic agent (Figure 15).[121] **51**[122] completed phase III trials with less than ideal results, leaving the drug's fate in question. Numerous analogues, particularly with more rigid scaffolds,[123] have been developed to optimize activity and minimize nausea, diarrhea, and headache symptoms associated with this class of inhibitors.[124] A cocrystal structure with **51** bound in the phosphodiesterase reveals an interaction of the nitrile with methionine and leucine residues.[125] As with many of these polar interactions, slight movement of the protein may allow intimate hydrogen bonding. **52** (levocabastine) is a selective second-generation H_1-receptor antagonist used for allergic conjunctivitis.[126] The precise interaction of **52** with the receptor is not known.

53 (piritramide, Figure 15) is a synthetic opioid, almost equipotent with morphine, which is prescribed for treating postoperative pain.[127] Structurally related **54** (diphenoxylate, lomotil) is used to treat diarrhea.[128] **54** is rapidly hydrolyzed to the corresponding acid, difenoxin, which slows intestinal contractions and peristalsis, allowing the body to remove water and return the intestine to normal function.

Alkenenitrile-Containing Pharmaceuticals

Drugs containing the unsaturated nitrile functionality are conjugated either with additional electron withdrawing groups or with heteroatoms (Figure 16). Often the nitrile is positioned adjacent to a hydrogen bond donor or acceptor, implying an electronic role for the nitrile group. Conjugation of the nitrile with an additional electron withdrawing group facilitates Michael additions[129] as in **55** (entacapone).

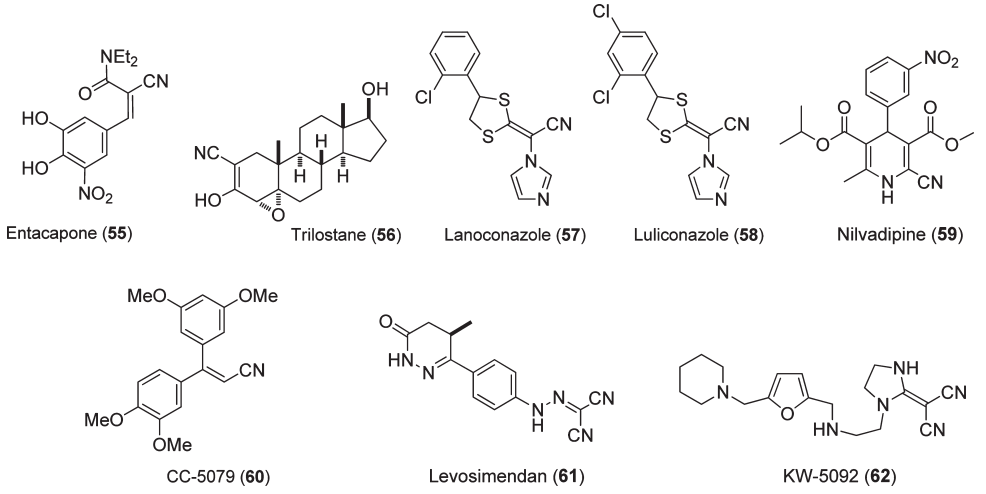


Figure 16. Alkenenitrile-containing pharmaceuticals.

55[130] is a potent inhibitor of catechol-*O*-methyltransferase and used for treating Parkinson's disease by facilitating passage of dopaminergic agents across the blood−brain barrier.[131] Molecular docking reveals a series of hydrogen bonds with the nitrocatechol ring but no specific interactions for the nitrile.[132] **56** (trilostane) is an inhibitor of 3β-hydroxysteroid dehydrogenase that was used to treat Cushing's syndrome in humans but is now licensed only for treating dogs.[133] **56** has been successfully used in treating postmenopausal women for breast cancer[134] by inhibiting 3β-hydroxysteroid dehydrogenase.[135] Molecular modeling and mutant studies demonstrate the necessity of the nitrile group and identifies an interaction with a serine residue as being critical.[136]

57 (lanoconazole)[137] and **58** (luliconazole)[138] are topical antifungal drugs developed and marketed in Japan. Both **57** and **58** inhibit sterol 14α-methylase in fungi,[137] and although they are marketed as racemates, the activity resides in the *S*-enantiomer. A π-interaction is proposed between the enzyme and the dichlorobenzene ring[139] with the dithioalkenenitrile acting as a Michael acceptor.[140] **59** (nilvadipine) is a calcium channel blocker used to treat hypertension and cerebral artery occlusion[141] and recently entered trials to treat Alzheimer's disease.[142] The role of the nitrile is unknown.

Celgene Corp.'s antitumor agent **60** (CC-5079) prevents tubulin polymerization but remains active against multidrug resistant cells.[143] Subsequent assays identified the *Z*-diastereomer as being more active, with molecular modeling suggesting a key hydrogen bond between the nitrile nitrogen and a tyrosine hydroxyl group in tubulin.[144] **61** (levosimendan, Simdax) is a novel inodilator used to manage acute or chronic heart failure.[145] As with many Ca^{2+} sensitization and K^+ channel-mediators, the enzyme−inhibitor interactions are not fully resolved. Development of a related dinitrile inhibitor, **62** (KW-5092), suggests that the dinitrile creates a rigid, polar moiety comparable to a nitro group.[146]

N-Cyanoguanidine Containing Drugs

Several drugs and drug leads contain the *N*-cyanoguanidine functionality.[147] Guanidinium cations interact strongly with carboxylates through lateral (**63**) or terminal (**64**) ionic interactions (Figure 17).[148] In the series of *N*-cyanoguanidine, amidine, and formamidine functionalities the nitrile significantly changes the nitrogen basicity,[149] attenuating the ionization and H-bond acceptor properties.[150] The cyanoguanidine moiety can act as a bioisostere for cyanoamidine,[151] sulfonylguanidine,[152] thiourea,[153] amide, or thioamide[154] functionalities.

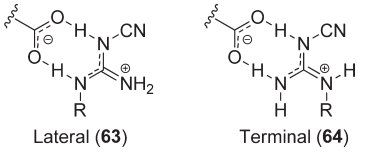


Figure 17. Cyanoguanidine binding motifs.

65 (cimetidine) is a well-studied histamine H_2-receptor antagonist that inhibits the production of acid in the stomach (Figure 18).[155] Originally used to treat heartburn and peptic ulcers, **65** is being examined for several dermatological diseases[156] and as an antitumor agent.[157] **66** (pinacidil) modulates ATP-dependent potassium channels and is used to treat hypertension.[158] **67** (terbogrel), a thromboxane A_2 synthase inhibitor, has a similar cyanoguanidine substitution and is a potential long-term antithrombotic therapy.[159]

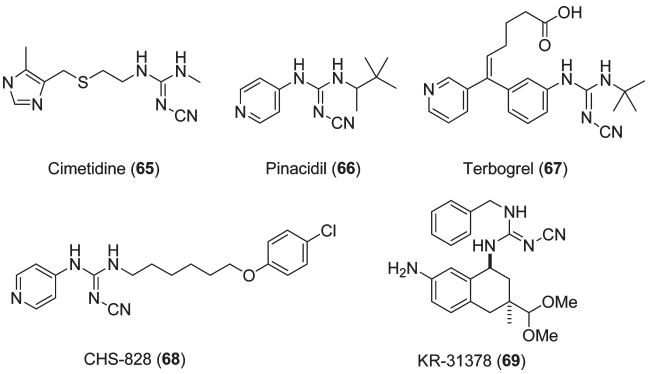


Figure 18. *N*-Cyanoguanidine-containing drugs and drug leads.

68 (CHS-828) is an antineoplastic agent[160] under active development by Gemin X Pharmaceuticals as GMX-1778 (Figure 18).[161] The mechanism by which **68** triggers apoptosis remains to be clarified. **69** (KR-31378) is a potassium ATP channel opener in preclinical trials to protect retinal ganglion cells in glaucoma.[162]

α-Aminonitrile Drugs and Drug Leads

Several aminonitriles have been developed as reversible inhibitors of dipeptidyl peptidase (DPP IV) for treating diabetes.[163] Proline peptidases cleave peptide bonds after a proline residue which, for the hydrolysis of the glucagon-like peptide 1, switches off insulin production to provide a therapeutic approach for type 2 diabetes. **70** (saxagliptin)[164] was recently launched under the name Onglyza, and the structurally related **1**[165] is licensed in Europe. The dinitrile **71** (NVP-DPP728)[166] is in phase II clinical development.

These inhibitors function through attack of a serine residue on the nitrile, resulting in a strong, reversible inhibition with a slow off rate (Figure 19, **72** → **73**).[163] A similar covalent binding occurs in nitrile-based cysteine protease inhibitors[167] for which high selectivity between proteases is possible.[168] Cocrystallization of **70** in DPP IV shows hydrogen bonding between the nitrile nitrogen and asparagines, suggesting a delicate choreography of inhibition in which the aminonitrile binds, becomes activated, and is attacked to form the covalent bond.[169]

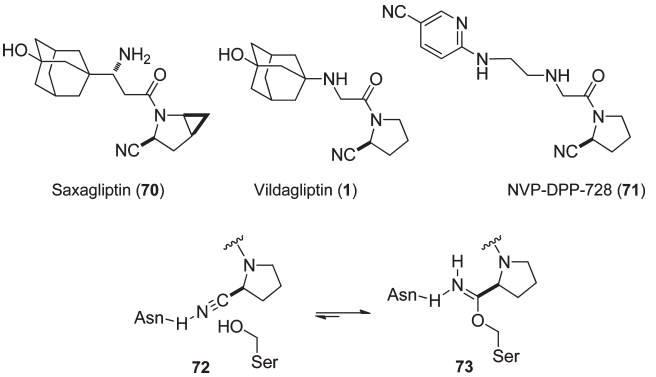


Figure 19. Aminonitrile DPP IV inhibitors.

Several cathepsins, which are cysteine proteases, have been identified as viable drug targets. The search for cathepsin K inhibitors for the treatment of osteoporosis uncovered a series of aminoacetonitrile inhibitors in which the nitrile participates in a reversible, covalent interaction with the active site cysteine residue (Figure 20).[170] Subsequent refinement identified **74** (odanacatib)[171] which is currently in phase III clinical trials.[172]

Significant effort is focused on inhibiting cathepsin S using aminonitrile inhibitors.[173] Aminonitrile **75** is a potent, reversible inhibitor (IC_{50} = 9 nM) whose cocrystallization with cathepsin S shows formation of a reversible thioimidate formed by attack of cysteine, rather than serine, on the nitrile "warhead" (cf. **73**, Figure 19).[174]

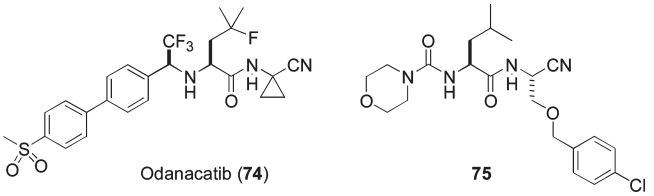


Figure 20. Cathepsin Inhibitors.

Conclusion

Structurally diverse nitrile-containing drugs are in use for a variety of medical treatments. These range from blockbuster drugs such as **48** to numerous candidates currently being pursued in clinical trials. Surveying the interactions of the nitrile within these pharmaceuticals and drug candidates reveals that the biological function of the nitrile group varies considerably. In some instances the nitrile merely polarizes the adjacent electron density, whereas in other cases the nitrile is a key component for molecular recognition.

Recent advances in molecular recognition, through crystallography, NMR, and modeling, are providing an increased understanding of the interactions between small molecule inhibitors and their targets. The survey of nitrile-containing pharmaceuticals and clinical candidates identifies several roles of the nitrile group.

1. One role is as a carbonyl bioisostere. In several nonsteroidal inhibitors arylnitriles function as a carbonyl equivalent. These inhibitors have the advantage of minimizing interference with other steroid receptors and improving bioavailability. The homology is evident in the overlay of progesterone and the nitrile-inhibitor **76** in the progesterone receptor site (Figure 21).[175] The nitrile nitrogen occupies virtually the same position as the carbonyl oxygen of progesterone and engages in the same polar interactions.

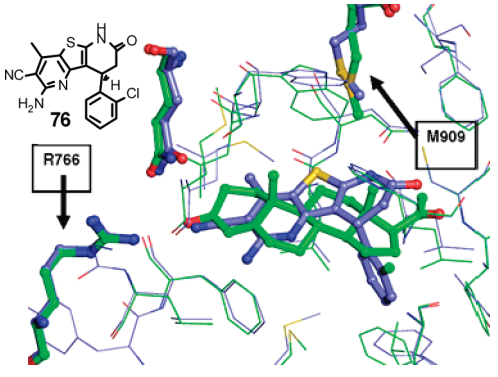
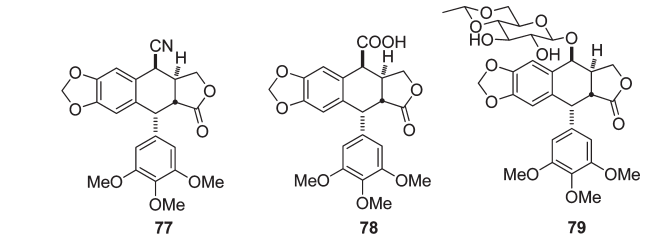


Figure 21. Nitrile inhibitor **76** and progesterone (**10**) overlay. Reprinted with permission from *Bioorganic and Medicinal Chemistry Letters*.[175] Copyright 2009 Elsevier.

2. Another role is as a hydroxyl and carboxyl surrogate. The small, polar nitrile is a strong hydrogen bond acceptor with a significant solvation shell. The combination allows the nitrile to function as hydroxyl and carboxyl surrogates. Hydrogen bonding is particularly common to the protein backbone, amino acid side chains, or water molecules enclosed within the binding domain. The relationship is exemplified by functional group replacements performed using the anticancer drug **79** (etoposide, Figure 22) as a lead structure.[176] Replacing the glycoside with a nitrile **77** was significantly more efficacious than the acid **78**.



	77	78	79
Inhibition of L_{1210} IC_{50}(ng/mL)	3.48	164	155
Inhibition of KB IC_{50}(ng/mL)	155	10,000	308

Figure 22. Comparative nitrile and acid etoposide analogues.

3. The powerful electron-withdrawing nature of the CN unit allows nonspecific dipole interactions with amino acids and metal ions. In cyanoguanidines and related structures, nitrile substitution allows tuning of the guanidine basicity and hydrogen bonding properties.
4. Cyanoquinolines and cyanopyridines (**81**, Figure 23) can act as more potent azomethine−water (**80**) bioisosteres. Interchanging a water-bound quinazoline with a 3-cyano quinoline or pyridine effectively exchanges the mobile hydrogen-bonded pyrimidine−water complex for a direct hydrogen bond between the nitrile and the protein. Expulsion of water from the binding domain adds an additional entropic component to the binding affinity.

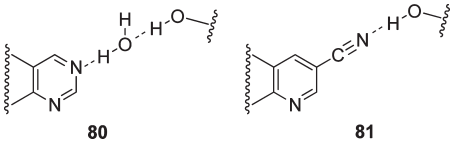


Figure 23. Cyanoquinolines and cyanopyridines as azomethine−water bioisosteres.

5. Carboxyl transition state analogue is another role. Several aminonitriles function as proline peptidases by reversibly forming covalently bound imino esters at the active site. Conversion of the nitrile to the imino ester appears choreographed through activation of the nitrile and addition of serine or cysteine.
6. Halogen bioisostere is another role. The nitrile mimics the polarization of the halides and is often an excellent halogen bioisostere.[177] Being smaller than bromine or iodine, the nitrile is capable of achieving better contact with amino acids lining an active site.
7. The nitrile group improves ADME[178]−toxicology profiles. Computational properties and empirical rules such as Lipinski's rules[179] are routinely employed to guide structure-based drug design. While a potent molecule is essential for drug discovery, ultimately ADME−Tox properties decide which molecule is advanced into clinical trials. During optimization, leads tend to increase in size and lipophilicity[180] which can be

offset by introducing the sterically insignificant nitrile group. Replacing a hydrogen with a nitrile can roughly lower cLogP[181] by half an order of magnitude and nearly an order of magnitude reduction for log *D*.[182] A more dramatic decrease in lipophilicity by over a full order of magnitude for cLogP/log *D* often occurs when replacing a halogen or methyl group by a nitrile.The development of **33** from **82** (capravirine) provides an excellent case study in modulating ADME properties through nitrile substitution.[93] Refining **82** led to the truncated analogue **83** that was evaluated and found to be less potent and more lipophilic. Consistent with the nitrile being a halogen bioisostere, interchanging the chlorine with a nitrile (**83** → **84**) reduced the lipophilicity by an order of magnitude and increased the lipophilic ligand efficiency (LLE).[183] Introduction of a second nitrile led to **33** with similar activity to **82**, 141 mass units smaller, a decreased lipophilicity, and a much improved half-life in human liver microsomes (HLM); 7.5 min for **82** compared to 73 min for **33** (Figure 24).

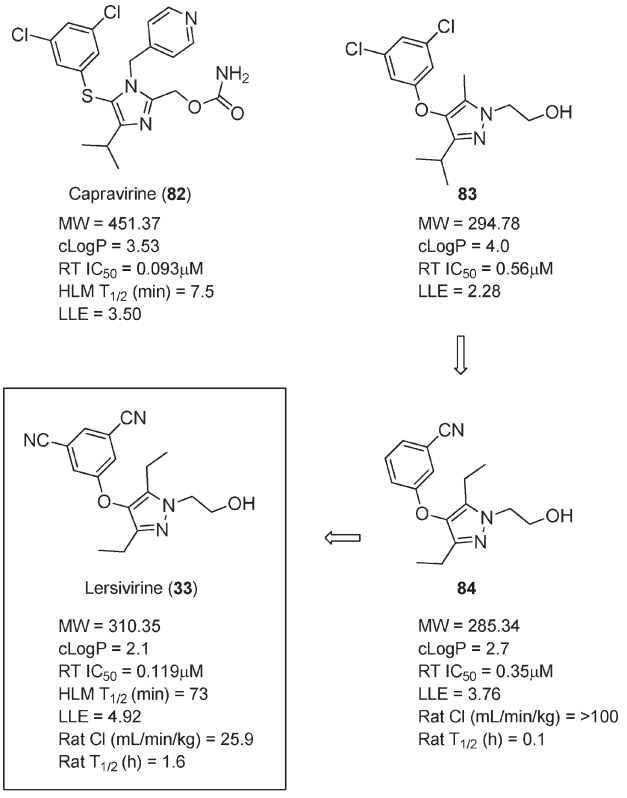


Figure 24. ADME-directed evolution of capravirine (**82**) into lersivirine (**33**).

This review provides a comprehensive survey of the interactions between the nitrile group and a diverse range of bioactive receptors. Collating the nitrile-containing drugs and clinical candidates by their structural similarities reveals at least seven different modes by which nitrile substituents accentuate binding to receptor targets. A greater understanding of these specific functions is likely to facilitate lead optimizations with nitrile-containing candidates and will, optimistically, increase the number of nitrile-containing pharmaceuticals.

Acknowledgment. Financial support for nitrile-based research from the National Science Foundation (Grant 0808996 CHE) and the National Institutes of Health (Grant 2R15AI-051352-03) is gratefully acknowledged. The Center for Advanced Studies, Ludwig Maximilians University (Munich, Germany), and the University of Göteborg, Sweden, are thanked for facilitating the writing of the review by hosting a sabbatical visit (F.F.F.). Critical suggestions from Morten Grøtli and Robert Dancer are gratefully acknowledged.

Biographies

Fraser F. Fleming earned his B.Sc. (Hons.) at Massey University, New Zealand, in 1986 and then pursued a Ph.D. under the direction of Edward Piers at the University of British Columbia, Canada. After graduating in 1990, he moved to Oregon State University for postdoctoral research with James D. White and in 1992 joined the faculty at Duquesne University where he is a Full Professor. His research interests lie broadly in stereochemistry and the reactions of organometallics, particularly for the development of new reactions with nitriles.

Lihua Yao obtained her B.Eng. in Chemical Engineering (2000) at Shanghai University of Engineeering Science, China. From 2000 until 2003, she was a Research Assistant in Shanghai Institute of Organic Chemistry, Chinese Academy Sciences, working on the development of organofluorine methodology. In 2007, she joined Duquesne University, PA, where she is currently working with Fraser Fleming on a transmissive olefination of alkenenitriles.

P. C. Ravikumar obtained his B.Sc. (2000) and M.Sc in Organic Chemistry (2002) from the University of Madras, India. He was awarded a research fellowship from the Council for Scientific and Industrial Research (CSIR), India, for his doctoral research, which he completed in 2006 at the Indian Institute of Science, Bangalore, India, under the guidance of Professor A. Srikrishna. He completed postdoctoral research with Fraser Fleming at Duquesne University, PA (2007−2008), and with Professor Seth B. Herzon at Yale University, CT (2009). He recently accepted an Assistant Professor position at the Indian Institute of Technology, Mandi, India, where he will begin his independent academic career.

Lee Funk received his B.A. in Chemistry from Washington and Jefferson College, PA, followed by a M.S. in Organic Chemistry from Duquesne University, PA. From 2001 through 2008 he worked as a medicinal chemist for Pharmacia (Kalamazoo, MI), Pfizer (La Jolla, CA), and GlaxoSmithKline (Collegeville, PA). As a medicinal chemist, he worked in various therapeutic targets including HCV, oncology, and osteoporosis. In 2008, he transitioned to Mylan's legal Intellectual Property Department. He is currently working as a Senior Scientist performing prior art searches, mapping out patent landscapes, developing invalidity positions, supporting ongoing litigation, and working with R&D scientists to develop noninfringing API/formulations.

Brian C. Shook received a B.S. from the University of Pittsburgh, Johnstown, PA (1996), and a Ph.D. in Synthetic Organic Chemistry from Duquesne University, PA, in 2001 under the guidance of Fraser Fleming. His thesis work included organometallic additions to unsaturated nitriles and the stereoselective cyclizations of nitrile anions to *cis*- and *trans*-decalins. He then pursued a postdoctoral appointment with Robert K. Boeckman, Jr. at the University of Rochester, NY, where he completed the asymmetric total synthesis of bengamide B. In 2002, he joined the Department of Medicinal Chemistry at Johnson & Johnson where he has worked on programs for Parkinson's disease, pain, migraine, and diabetes.

Note Added after ASAP Publication. This manuscript was released ASAP on August 30, 2010 with errors in Figures 10 and 24. The corrected version was posted on September 13, 2010 and again on October 25, 2010.

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