
Syntheses of new formyl ester and cyano ester substituted bithiophenes, bifurans and furanothiophenes in good yield are described.

2- Synthesis, DNA Binding, Fluorescence measurements and Antiparasitic Activity of DAPI Related Diamidines.

A novel series of extended DAPI analogues were prepared by insertion of either a carbon-carbon triple bond (16a-d) or a phenyl group (21a,b and 24) at position-2. The new amidines were evaluated in vitro against both Trypanosoma brucei rhodesiense (T. b. r.) and Plasmodium falciparum (P. f.). Five compounds (16a, 16b, 16d, 21a, 21b) exhibited IC50 values against T. b. r. of 9 nM or less which is two to nine folds more effective than DAPI. The same five compounds exhibited IC50 values against P. f. of 5.9 nM or less which is comparable to that of DAPI. The fluorescence properties of these new molecules were recorded, however; they do not offer any advantage over that of DAPI.

3- 1H-Benzimidazole-2-acetonitriles as Synthon in Fused Benzimidazole Synthesis

This review summarizes the methods for preparing 1H-benzimidazole-2-acetonitriles and their reactions in the past years, some of which have been applied to the synthesis of biologically active molecules. The main reactions are divided into several groups according to some types of the fused benzimidazoles.

4- Synthesis and Antiprotozoal Activity of 2,5-Bis[amidinoaryl]thiazoles

Abstract: Seven novel diamidino 2,5-bis(aryl)thiazoles (5a-5g) were synthesized and evaluated against Trypanosoma brucei rhodesiense (T. b. r.) and Plasmodium falciparum (P. f). The diamidines were obtained directly from the corresponding bis-nitriles(4a-4g) by the action of lithium bis(trimethylsilyl)amide. The bis-nitriles 4a-4f were synthesized in four steps starting with the Stille coupling of 2-tributyltinthiazole with the appropriate cyanoaryl halide. The bis-nitrile 5g was obtained by the palladium facilitated coupling of the mixed tin-silyl reagent 2-trimethylsilyl-5-trimethylthiazole with 2-bromo-5-cyanopyridine. The amidoxime potential prodrugs were obtained by the reaction of hydroxylamine with the bis-nitriles. O-Methylation of the amidoximes gave the corresponding N-methoxyamidines. The amidoxime potential prodrugs were obtained by the reaction of hydroxylamine with the bis-nitriles. O-Methylation of the amidoximes gave the corresponding N-methoxyamidines. The diamidines showed strong DNA binding affinity as reflected by Tm measurements. Four of the diamidines 5a, 5b, 5d and 5e were highly active in vitro against P. f. giving IC50 values between 1.1 and 2.5 nM. The same four diamidines showed IC50 values between 4 and 6 nM against T. b. r. The selectivity indices ranged from 233 to 9175. One diamidine 5a produced one of four cures at an ip dose of 4x 5mg/kg in the STIB900 mouse model for acute African trypanosomiasis. The amidoxime and N-methoxyamidine of 5a were the only produgs to provide cures (1/4 cures) in the same mouse model on oral dosage at 4x 25 mg/kg.
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2-Amino-4-thiazolidinones: synthesis and reactions

Methods for the synthesis of 2-amino-4-thiazolidinones and their chemical properties are reviewed for the first time. 2-Amino-4-thiazolidinones are synthetically versatile substrates, as they can be used for the synthesis of a large variety of biologically active compounds, such as thiazolodihydropyrazoles, thiazolotriazines, and thiazolotetrahydropyrimidones, and as a raw material for drug synthesis. The high reactivity of amino and active methylene groups next to the carbonyl of the thiazolidin ring represents useful targets for many organic reactions.

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DNA Minor Groove Induced Dimerization of Heterocyclic Cations: Compound Structure, Binding Affinity, and Specificity for a TTAA Site

With the increasing number and variations of genome sequences available, control of gene expression with synthetic, cell-permeable molecules is within reach. The variety of sequence-specific binding agents is, however, still quite limited. Many minor groove binding agents selectivity recognize AT over GC sequences but have less ability to distinguish among different AT sequences. The goal with this article is to develop compounds that can bind selectively to different AT sequences. A number of studies indicate that AATT and TTAA sequences have significantly different physical and interaction properties and different requirements for minor groove recognition. Although it has been difficult to get minor groove binding at TTAA, DB293, a phenylâ€“furanâ€“benzimidazole diamidine, was found to bind as a strong, cooperative dimer at TTAA but with no selectivity over AATT. In order to improve selectivity, we made modifications to each unit of DB293. Binding affinities and stoichiometries obtained from biosensorsurface plasmon resonance experiments show that DB1003, a furanâ€“furanâ€“ benzimidazole diamidine, binds strongly to TTAA as a dimer and has selectivity (KTAA/KAATT=6). CD and DNase I footprinting studies confirmed the preference of this compound for TTAA. In summary, (i) a favorable stacking surface provided by the pi system, (ii) H-bond donors to interact with TA base pairs at the floor of the groove provided by a benzimidazole (or indole) â€“NH and amidines, and (iii) appropriate curvature of the dimer complex to match the curvature of the minor groove play important roles in differentiating the TTAA and AATT minor grooves.

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Synthesis and antimicrobial activity of certain benzimidazole and fused benzimidazole derivatives

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Induced topological changes in DNA complexes: influence of DNA sequences and small molecule structures

Heterocyclic diamidines are compounds with antiparasitic properties that target the minor groove of kinetoplast DNA. The mechanism of action of these compounds is unknown, but topological changes to DNA structures are likely to be involved. In this study, we have developed a polyacrylamide gel electrophoresis-based screening method to determine topological effects of heterocyclic diamidines on four minor groove target sequences: AAAAA, TTTAA, AAATT and ATATA. The AAAAA and AAATT sequences have the largest intrinsic bend, whereas the TTTAA and ATATA sequences are relatively straight. The changes caused by binding of the compounds are sequence dependent, but generally the topological effects on AAAAA and AAATT are similar as are the effects on TTTAA and ATATA. A total of 13 compounds with a variety of structural differences were evaluated for topological changes to DNA. All compounds decrease the mobility of the ATATA sequence that is consistent with decreased minor groove width and bending of the relatively straight DNA into the minor groove. Similar, but generally smaller, effects are seen with TTTAA. The intrinsically bent AAAAA and AAATT sequences, which have more narrow minor grooves, have smaller mobility changes on binding that are consistent with increased or decreased bending depending on compound structure.

Synthesis and antiviral activity of benzimidazolyland triazolyl-1,3,5-triazines

A novel series of 1,3,5-triazine analogs was successfully synthesized through conjugation with benzimidazole or 1,2,4-triazole derivatives via a methylenethio linker. The new analogs were in vitro evaluated against HSV-1 in Vero cells; among these analogs, two compounds exhibited good effect in inhibiting HSV-1 replication (for compound 5p: EC50 = 3.5 lg/ml, SI = 358; for compound 5r: EC50 = 5.0 lg/ml, SI = 300) in comparison to acyclovir.

Exploration of larger central ring linkers in furamidine analogues: Synthesis and evaluation of their DNA binding, antiparasitic and fluorescence properties
The effects of replacing the central furan ring of furamidine with indole and benzimidazole on their DNA binding affinity, antiparasitic activity and fluorescence are reported. The bis-cyanophenylindoles required to make the corresponding amidines were prepared by sequential Stille and/or Suzuki coupling reactions. The bis-cyanophenylbenzimidazoles were obtained by coupling 4-cyanobenzaldehydes with the appropriate cyano substituted phenylenediamine. The bis-nitriles were converted to the diamidines by reaction with Li[N(Si(CH3)3)]2 or by Pinner methodology. Specifically, we have prepared new series of 2,6- and 2,5-diaryl indoles (6a,b, 12 and 17aâ€“d) and the related benzimidazoles (24, 30 and 35). The new compounds bind in the DNA minor groove in DNA AT base pair sequences and eight of the ten new analogues exhibit DTm values comparable to or higher than that of furamidine. Six of ten of the new compounds exhibit lower IC50 values against Trypanosoma brucei rhodesiense (T. b. r.) and eight of ten exhibit lower IC50 values against Plasmodium falciparum (P. f.) than furamidine. Four of the ten show greater efficacy than furamidine in the rigorous T. b. r. STIB900 mouse model for African trypanosomiasis. Generally, the fluorescence properties of the new analogues are similar to that of DAPI.

The Trypanocidal Activity of Amidine Compounds Does Not Correlate with Their Binding Affinity to Trypanosoma cruzi Kinetoplast DNA

Due to limited efficacy and considerable toxicity, the therapy for Chagasâ€™ disease is far from being ideal, and thus new compounds are desirable. Diamidines and related compounds such as arylimidamides have promising trypanocidal activity against Trypanosoma cruzi. To better understand the mechanism of action of these heterocyclic cations, we investigated the kinetoplast DNA (kDNA) binding properties and trypanocidal efficacy against T. cruzi of 13 compounds. Four diamidines (DB75, DB569, DB1345, and DB829), eight arylimidamides (DB766, DB749, DB889, DB709, DB613, DB1831, DB1852, and DB2002), and one guanylylhydrazone (DB1080) were assayed in thermal denaturation (Tm) and circular dichroism (CD) studies using whole purified T. cruzi kDNA and a conserved synthetic parasite sequence. The overall CD spectra using the whole kDNA were similar to those found for the conserved sequence and were indicative...
of minor groove binding. Our findings showed that some of the compounds that exhibited the highest trypanocidal activities (e.g., DB766) caused low or no change in the Tm measurements. However, while some active compounds, such as DB766, induced profound alterations of kDNA topology, others, like DB1831, although effective, did not result in altered Tm and CD measurements. Our data suggest that the strong affinity of amidines with kDNA per se is not sufficient to generate and trigger their trypanocidal activity. Cell uptake differences and possibly distinct cellular targets need to be considered in the final evaluation of the mechanisms of action of these compounds.

12-

**Unusual Regioselective Reactions of 2,4-Bis(methylsulfanyl)pyrimidine under Modified Suzuki and Stille Cross-Coupling Conditions**

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13-

**Pyrazole-3(4)-carbaldehyde: synthesis, reactions and biological activity**

This review deals with synthesis and reactions of pyrazole-3(4)-carbaldehydes as well as their biological activity. The data on the methods of synthesis, chemical reactions, and biological activity of these heterocycles published over the last years are reviewed here for the first time.

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**SYNTHETIC ACCESSES TO AZOLYLTHIAZOLES**

Published data over the last years on the methods of synthesis and biological applications of azolylthiazoles are reviewed here for the first time till 2011. The review was classified according to the type of azole ring linked to thiazole.

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**Water-Mediated Binding of Agents that Target the DNA Minor Groove**

Small molecule complexes with DNA that incorporate linking water molecules are rare, and the DB921-DNA complex has provided a unique and well-defined system for analysis of water-mediated binding in the context of a DNA complex. DB921 has a benzimidazole-biphenyl system with terminal amidines that results in a linear conformation that does not possess the appropriate radius of curvature to match the minor groove shape and represents a new paradigm that does not fit the classical model of minor groove interactions. To better understand the role of the bound water molecule observed in the X-ray crystal structure of the DB921 complex, synthetic modifications have been made in the DB921 structure, and the interactions of the new compounds with DNA AT sites have been
evaluated with an array of methods, including DNase I footprinting, biosensor-surface plasmon resonance, isothermal titration microcalorimetry, and circular dichroism. The interaction of a key compound, which has the amidine at the phenyl shifted from the para position in DB921 to the meta position, has also been examined by X-ray crystallography. The detailed structural, thermodynamic, and kinetic results provide valuable new information for incorporation of water molecules in the design of new lead scaffolds for targeting DNA in chemical biology and therapeutic applications.

The efficacy of novel arylimidamides against Trypanosoma Cruzi in vitro

The present study aimed to determine the in vitro biological efficacy and selectivity of 7 novel AIAs upon bloodstream trypomastigotes and intracellular amastigotes of Trypanosoma cruzi. The biological activity of these aromatic compounds was assayed for 48 and 24 h against intracellular parasites and bloodstream forms of T. cruzi (Y strain), respectively. Additional assays were also performed to determine their potential use in blood banks by treating the bloodstream parasites with the compounds diluted in mouse blood for 24 h at 4 °C. Toxicity against mammalian cells was evaluated using primary cultures of cardiac cells incubated for 24 and 48 h with the AIAs and then cellular death rates were determined by MTT colorimetric assays. Our data demonstrated the outstanding trypanocidal effect of AIAs against T. cruzi, especially DB1853, DB1862, DB1867 and DB1868, giving IC50 values ranging between 16 and 70 nanomolar against both parasite forms. All AIAs presented superior efficacy to benznidazole and some, such as DB1868, also demonstrated promising activity as a candidate agent for blood prophylaxis. The excellent anti-trypanosomal efficacy of these novel AIAs against T. cruzi stimulates further in vivo studies and justifies the screening of new analogues with the goal of establishing a useful alternative therapy for Chagas disease.

Heterocyclic dications as a new class of telomeric g-quadruplex targeting agents

Small molecules that can induce and stabilize G-quadruplex DNA structures represent a novel approach for anti-cancer and anti-parasitic therapy and extensive efforts have been directed towards discovering lead compounds that are capable of stabilizing quadruplexes. The purpose of this study is to explore conformational modifications in a series of heterocyclic dications to discover structural motifs that can selectively bind and stabilize specific G-quadruplexes, such as those present in the human telomere. The G-quadruplex has various potential recognition sites for small molecules; however, the primary interaction site of most of these ligands is the terminal tetrads. Similar to duplex-DNA groove recognition, quadruplex groove recognition by small molecules offers the
potential for enhanced selectivity that can be developed into a viable therapeutic strategy. The compounds investigated were selected based on preliminary studies with DB832, a bifuryl-phenyl diamidine with a unique telomere interaction. This compound provides a paradigm that can help in understanding the optimum compound-DNA interactions that lead to quadruplex groove recognition. DNA recognition by the DB832 derivatives was investigated by biophysical experiments such as thermal melting, circular dichroism, mass spectrometry and NMR. Biological studies were also performed to complement the biophysical data. The results suggest a complex binding mechanism which involves the recognition of grooves for some ligands as well as stacking at the terminal tetrads of the human telomeric G-quadruplex for most of the ligands. These molecules represent an excellent starting point for further SAR analysis for diverse modes of quadruplex recognition and subsequent structure optimization for drug development.

18-

2-Chloroquinoline-3-carbaldehydes: synthesis, reactions and applications

This review summarizes the synthetic methods, reactions and biological applications of 2-chloroquinoline-3-carbaldehydes during the period from 1999 to 2011. The reactions are subdivided in groups that cover reactions at the chloro or aldehyde substituent and reactions which involve both groups. Most reaction types have been successfully applied and used in the production of biological active compounds.

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In Vitro and In Vivo Investigation of the Efficacy of Arylimidamide DB1831 and Its Mesylated Salt Form - DB1965 - against Trypanosoma cruzi Infection

Chagas disease is caused by infection with the intracellular protozoan parasite Trypanosoma cruzi. At present, nifurtimox and benznidazole, both compounds developed empirically over four decades ago, represent the chemotherapeutic arsenal for treating this highly neglected disease. However, both drugs present variable efficacy depending on the geographical area and the occurrence of natural resistance, and are poorly effective against the later chronic stage. As a part of a search for new therapeutic opportunities to treat chagasic patients, pre-clinical studies were performed to characterize the activity of a novel arylimidamide (AIA - DB1831 (hydrochloride salt) and DB1965 (mesylate salt)) against T.cruzi. These AIAs displayed a high trypanocidal effect in vitro against both relevant forms in mammalian hosts, exhibiting a high selectivity index and a very high efficacy (IC50 value/48 h of 5â€“40 nM) against intracellular parasites. DB1965 shows high activity in vivo in acute experimental models (mouse) of T.cruzi, showing a similar effect to benznidazole (Bz) when compared under a scheme of 10 daily consecutive doses with 12.5 mg/kg. Although no parasitological cure was observed after treating with 20 daily
consecutive doses, a combined dosage of DB1965 (5 mg/kg) with Bz (50 mg/kg) resulted in parasitaemia clearance and 100% animal survival. In summary, our present data confirmed that aryimidamides represent promising new chemical entities against T. cruzi in therapeutic schemes using the AIA alone or in combination with other drugs, like benznidazole.

**Evaluation of Arylimidamides DB1955 and DB1960 as Candidates against Visceral Leishmaniasis and Chagas Disease â€“ In Vivo Efficacy, Acute Toxicity, Pharmacokinetics and Toxicology Studies**

Arylimidamides (AIAs) have shown outstanding in vitro potency against intracellular kinetoplastid parasites, and the AIA 2,5-bis[2-(2-propoxy)-4-(2-pyridylimino)aminophenyl]furan dihydrochloride (DB766) displayed good in vivo efficacy in rodent models of visceral leishmaniasis and Chagas disease. In an attempt to further increase the solubility and in vivo antikinetoplastid potential of DB766, the mesylate salt of this compound and of the closely related AIA 2,5-bis[2-(2-cyclopentyloxy)-4-(2-pyridylimino)aminophenyl]furan hydrochloride (DB1852) were prepared. These two mesylate salts, designated DB1960 and DB1955, respectively, exhibited dose-dependent activity in the murine model of VL, with DB1960 inhibiting liver parasitemia by 51% at an oral dose of 100 mg/kg/day — 5 and DB1955 reducing liver parasitemia by 57% when given by the same dosing regimen. In a murine T. cruzi model, DB1960 decreased the parasitemia levels that peaked at 8 days post infection by 46% when given orally at 100 mg/kg/day 5 — 1, while DB1955 had no effect on peak parasitemia levels when administered by the same dosing regimen. Distribution studies revealed that these compounds accumulated to micromolar levels in the liver, spleen, and kidney, but to a lesser extent in the heart, brain, and plasma. A 5-day repeat-dose toxicology study with DB1960 and DB1955 was also conducted in female BALB/c mice, with the compounds administered orally at 100, 200 and 500 mg/kg/day. In the high dose groups, DB1960 resulted in changes in serum chemistries, causing statistically significant increases in serum BUN, LDH, AST, and ALT levels, and a 21% decrease in body weight was observed in this group. These changes were consistent with microscopic findings in the liver and kidney of the treated animals. The incidences of observed clinical signs (hunched posture, tachypnea, tremors and ruffled fur) were more frequent
in DB1960 treated groups than those treated with DB1955. However, histopathological examination of tissue samples indicated that both compounds caused adverse effects at all dose levels.

**Suzuki-Miyaura Coupling Reactions of 3,5-Dichloro-1, 2, 4-thiadiazole**

3,5-Dichloro-1, 2, 4-thiadiazole was allowed to react with different aryl boronic acids under different Suzuki-Miyaura coupling conditions: at room temperature 5-aryl-3-chloro-1, 2, 4-thiadiazoles were obtained and at toluene reflux temperature the products were 3,5-diaryl-1, 2, 4-thiadiazoles. Sequential coupling reactions lead to 3,5-diaryl-1, 2, 4-thiadiazoles with non-identical aryl groups. The structure of 3-methoxy-5-(4-methoxyphenyl) -1, 2, 4-thiadiazole was established from X-ray crystallographic data.

**Synthesis, DNA binding and antileishmanial activity of low molecular weight bis-arylimidamides**

The effects of reducing the molecular weight of the antileishmanial compound DB766 on DNA binding affinity, antileishmanial activity and cytotoxicity are reported. The bis-arylimidamides were prepared by the coupling of aryl S-(2-naphthylmethyl)thioimidates with the corresponding amines. Specifically, we have prepared new series of bis-arylimidamides which include 3a, 3b, 6, 9a, 9b, 9c, 13, and 18. Three compounds 9a, 9c, and 18 bind to DNA with similar or moderately lower affinity to that of DB766, the rest of these compounds either show quite weak binding or no binding at all to DNA. Compounds 9a, 9c, and 13 were the most active against L. amazonensis showing IC50 values of less than 1 μM, so they were screened against the intracellular L. donovani, showing outstanding activity with IC50 values of 25-79 nM. Despite exhibiting little in vitro cytotoxicity these three compounds were quite toxic to mice.

**Antileishmanial Bis-arylimidamides: DB766 Analogs Modified in the Linker Region and Bis-arylimidamide Structure-activity Relationships**

Analogs of the lead antileishmanial bis-arylimidamide DB766 were prepared that possess unsymmetrical substitutions on the diphenylfuran linker, and an additional compound was synthesized that contains isopropoxy groups meta to the central furan. These agents all displayed nanomolar in vitro potency against intracellular Leishmania with selectivity indexes >100 compared to J774 macrophages. While the unsymmetrical analogs were toxic to mice when given ip at 30 mg/kg/day, the compound bearing the meta isopropoxy groups was well tolerated by mice and showed activity in a murine model of visceral leishmaniasis when administered ip at 30 mg/kg/day for five days.
Targeting the DNA-binding activity of the human ERG transcription factor using new heterocyclic dithiophene diamidines

Direct modulation of gene expression by targeting oncogenic transcription factors is a new area of research for cancer treatment. ERG, an ETS-family transcription factor, is commonly over-expressed or translocated in leukaemia and prostate carcinoma. In this work, we selected the di-(thiophene-phenylamidine) compound DB1255 as an ERG/DNA binding inhibitor using a screening test of synthetic inhibitors of the ERG/DNA interaction followed by electrophoretic mobility shift assays (EMSA) validation. Spectrometry, footprint and biosensor-surface plasmon resonance analyses of the DB1255/DNA interaction evidenced sequence selectivity and groove binding as dimer.