Review

N-Pyrrylarylsulfones with High Therapeutic Potential

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Abstract: This review illustrates the various studies made to investigate the activity of N-pyrrylarylsulfone containing compounds as potential antiviral, anticancer and SNC drugs. A number of synthetic approaches to obtain tetracyclic, tricyclic and non-cyclic compounds, and their biological activity with regard to structure–activity relationships (SARs) have been reviewed. The literature reviewed here may provide useful information on the potential of N-pyrrylarylsulfone pharmacophore as well as suggest concepts for the design and synthesis of new N-pyrrylarylsulfone based agents.

Keywords: sulfonamide; heterocycle; polycyclic compound; therapeutic agent

1. Introduction

Sulfonamide is the basis of several groups of drugs [1]. Intense interest focused on sulfonamide drugs after the discovery in 1935 that the activity of red dye Prontosil [2,3] was attributed to breakdown product sulfanilamide (1). The antibacterial sulfonamides work as competitive inhibitors of the dihydropteroate synthase, an enzyme involved in folate synthesis [4]. The simple 1 was cheaper than Prontosil, had fewer unwanted effects and did not impart the typical red color to the skin. Nowadays, sulfonamides have been replaced by other antibacterial drugs such as β-lactam antibiotics, with some important exception; for example, sulfamethoxazole (2) is used for treatment of urinary and respiratory-tracts infections [5]. Sulfa molecules have been chemically manipulated to obtain drug for the treatment of leprosy, fluid accumulation and diabetes. The modern era of drug treatment of leprosy began in 1937 when the sulfa drug dapsone (3) [6] proved to be highly effective. For more than six decades, 3 remained first line drug to treat leprosy. Since 1980s, 3 has been administered in combination with rifampicin and clofazimine for treatment of leprosy [7]. Chlorothiazide (4) is a carbonic anhydrase inhibitor which was introduced in 1958 as a diuretic drug and is used to treat hypertension and edema [8,9]. Before the discovery of 4, mercurial drugs associated with severe toxicity were the only available drugs to treat fluid retention. Few years later, in 1962, another sulfonamide, furosemide (5), was discovered as diuretic drug and is used to treat fluid retention and for the treatment of high blood pressure [10]. Tolbutamide (6), the first sulfonylurea anti-diabetic drug, was approved in the United States in 1957 for the treatment of type 2 diabetics [11]. Even though since 1964 there were concerns that sulfonylurea antidiabetic drugs may increase cardiovascular risk, the current literature does not confirm the detrimental risk profile of sulphonylureas compared with other anti-diabetic drugs [12]. Ethoxyzolamide (7) is a carbonic anhydrase inhibitor used in the treatment of glaucoma and duodenal ulcers, and as a diuretic [13]. Other sulfa drug examples include antivirals agents, such HIV-1 non-nucleoside reverse transcriptase and protease inhibitors [14–18], HCV NS3/4A protease [19] and NS5B polymerase inhibitors [20]; antibiotics, such mafenide, approved by the FDA in 1948 [21]; and nonsteroidal anti-inflammatory drug such celecoxib, a COX-2 selective inhibitor [22] (Chart 1).
After reduction of 15 (CGP-361A) (polycyclic pyrrole-containing systems with potential therapeutic effects such as anticancer (leukemia and lymphoma), anti-microbial (bacteria, malaria, protozoa, and fungi) and central nervous system agents (antipsychotic and anxiolytic) (for example, pyrrolnitrin (8) [24], tolmetin (9) [25], isamoltane (CGP-361A) (10) [26], porphobilinogen (11) [27], and atorvastatin (12) [28]). Recently, VU0410150 (13), a pyrrylarylsulfone containing compound, has been discovered as mGluR4-positive allosteric modulator and evaluated as potential drug for treatment for Parkinson’s disease [29,30]. In the past decades, numerous N-pyrrylarylsulfones have been synthesized by our research group in several drug discovery projects. In this work, attempt has been made to review various N-pyrrylarylsulfone based compounds to discuss the synthetic approaches and the biological activity with regard to structure–activity relationships (SARs).

2. Pyrrolo[1,2-b]-s-triazolo[3,4-d][1,2,5]benzothiadiazepine 5,5-dioxide

Tetracyclic systems, for example mianserin, aptazepine and bretazenil, have been widely investigated as psychotic drugs. The synthesis of pyrrolobenzothiadiazepine anellated withazole ring started as a development of a previous research project on tetra-anellated heterocycles [31–33]. Pyrrolo[1,2-b]-s-triazolo[3,4-d][1,2,5]benzothiadiazepine 5,5-dioxide (14) was synthesized by reaction of 2-nitrobenzensulfonyl chloride with ethyl pyrrole-2-carboxylate in the presence of potassium tert-butoxide and 18-crown-6 to provide 2-ethoxycarbonyl-1-(2-nitrobenzenesulfonyl)-1H-pyrryl(15).

After reduction of 15 to amino derivative 16, the product was cyclized to lactam 17 in the presence of 2-hydroxypyridine as a bifunctional catalyst. Treatment of 17 with di-4-morpholinylphosphinic chloride (18) in the presence of sodium hydride afforded phosphinyloxyimine 19 which was transformed into 14 by reaction with formylhydrazine (Scheme 1) [34].
11-ethoxycarbonyl-10,11-dihydropyrrolo[1,2-b]pyrrole with ethyl glyoxylate via a Pictet-Spengler type condensation gave 10,10-dioxide (28 via diketo intermediate 3). 2-Methyl-1,3,4,14b-tetrahydro-2H-benzothiadiazepine-11-acetic acid bis methylamide 5,5-dioxide (20) was reduced with lithium aluminum hydride (26) and debenzylated to 27 with hydrogen over Pd/C. Finally, 27 was converted to 21 via reductive amination using formaldehyde in the presence of hydrogen (Scheme 2) [35].

![Scheme 1. Synthesis of 14.](image1)

**Scheme 1. Synthesis of 14.**

3. 2-Methyl-1,3,4,14b-tetrahydro-2H-pyrazino[2,1-d]pyrrolo[1,2-b][1,2,5]benzothiadiazepine 10,10-dioxide

Studies on tetracyclic analogs of mianserin as antidepressant drugs led to the development of the pyrrole analog aptazepine and the strictly related isoaptazepine and 10-methyl-10-azaaptazepine (20). Pursuing this research project, 2-methyl-1,3,4,14b-tetrahydro-2H-pyrazino[2,1-d]pyrrolo[1,2-b][1,2,5]benzothiadiazepine 10,10-dioxide (21) (taiaptazepine) was designed as new putative core for central nervous system (CNS) active drugs. The synthesis of 21 is depicted in Scheme 2. Reaction of 1-(2-aminobenzensulfonyl)pyrrole with ethyl glyoxylate via a Pictet-Spengler type condensation gave 11-ethoxycarbonyl-10,11-dihydropyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide (22). Reaction of 22 with bromoacetyl bromide afforded the corresponding bromoacetyl derivative 23 which reacted with benzylamine (24) and subsequently thermally cycled to 25. Compound 25 was reduced with lithium aluminum hydride (26) and debenzylated to 27 with hydrogen over Pd/C. Finally, 27 was converted to 21 via reductive amination using formaldehyde in the presence of hydrogen (Scheme 2) [35].

![Scheme 2. Synthesis of 21, and structure of 10-methyl-10-azaaptazepine (20).](image2)

**Scheme 2. Synthesis of 21, and structure of 10-methyl-10-azaaptazepine (20).**

It is worthwhile mentioning that direct cyclization of 24 in the presence of excess of methylamine via diketo intermediate 28, failed due the formation 11-carboxy-10,11-dihydropyrrolo[1,2-b][1,2,5]benzothiadiazepine-11-acetic acid bis methylamide 5,5-dioxide (29). Intramolecular cyclization of 29...
in the presence of 2-hydroxypyridine led exclusively to the spiro derivative 30. It should be noted that treatment of 24 with sodium hydrogen carbonate gave lactam 31, which might be the intermediate of the conversion of 24 to 29 (Scheme 3) [36].

Scheme 3. Chemical transformation of 24.

Compounds 21 and 22 were enantioseparated by enantioselective HPLC, and the absolute configuration of the pure enantiomers was established by circular dichroism (CD) spectroscopy. The in vitro binding affinities for several CNS receptors (DA1, DA2, DA3, 5-HT1A, 5-HT2A, 5-HT2C, 5-HT3, α1NA, α2NA and muscarinic receptors) showed that both enantiomers of derivative 21, (−)-(R)-21 and (+)-(S)-21, showed higher affinities than the (−)-(R)-22 and (+)-(S)-22 counterparts, with exception of α1NA for which (+)-(S)-22 was superior. Compound (+)-(S)-21 showed good affinities for 5-HT1A, 5-HT2A, 5-HT2C, and α1NA receptors but only moderate affinities for DA1, DA2 and 5-HT3 receptors. Compared to the reference compounds mirtazepine, mianserine and 5-methoxymianserin, this compound showed higher affinity of the 5-HT1A subtype, and different general pharmacological profile [37].

4. Imidazo[5,1-d]pyrrolo[1,2-b][1,2,5]benzothiadiazepine 9,9-dioxide

Imidazo[5,1-d]pyrrolo[1,2-b][1,2,5]benzothiadiazepine 9,9-dioxide (32) was synthesized as a new benzothiadiazepine tetracyclic ring of pharmaceutical interest. The synthesis of 32 was achieved by a simple procedure involving the anellation of pyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide (33) at the 10,11-azomethine bond by cycloaddition with tosylmethyl isocyanide (TosMIC) in the presence of butyl lithium. Alternatively, 32 could be prepared starting from addition reaction of nitromethane to the azomethine bond of 33 to provide 34 which was reduced to amino 35 with of hydrogen at high pressure in the presence of nickel/Raney as a catalyst. Treatment of 35 with triethyl orthoformate furnished the dihydro derivative 36 which was oxidized to 32 with manganese dioxide (Scheme 4) [38].

Scheme 4. Synthesis of 32.
5. **5H-pyrrolo[1,2-b][1,2,5]benzothiadiazepin-11(10H)-one 5,5-dioxide**

5H-pyrrolo[1,2-b][1,2,5]benzothiadiazepin-11(10H)-one 5,5-dioxide (PBTD) derivatives, analogs of compound 17 described in Scheme 1, were synthesized as a novel class of HIV-1-specific non-nucleoside reverse transcriptase inhibitors (NNRTIs). In general, the newly synthesized compounds were non-cytotoxic for MT-4 cells at concentrations up to 300 μM. Maximum antiviral activity was obtained with compounds 37a-h bearing the chlorine atom at position 7 and the alkyl/alkenyl group at position 10 of the pyrrolo[1,2-b][1,2,5]benzothiadiazepine ring (Table 1). Compounds 37a and 37b (EC₅₀ ≈ 1.0 and 0.5 μM, respectively) showed the highest potency and selectivity (SI of >300 and >600, respectively) [39].

| Compound | R          | HIV-1 IIIb |
|----------|------------|------------|
|          |            | CC₅₀ b (μM) | EC₅₀ c (μM) | SI d |
| 37a      | H          | >300       | 1.0        | >300 |
| 37b      | Me         | >300       | 0.5        | >600 |
| 37c      | Et         | 283        | 2.4        | 118  |
| 37d      | Propyl     | 126        | 14         | 9    |
| 37e      | Isopropyl  | >300       | Nd  e       | -    |
| 37f      | Allyl      | >300       | 3.7        | >81  |
| 37g      | Crotyl     | >300       | 4.1        | >73  |
| 37h      | Dimethylallyl | >300     | 129        | >2   |

* Data are mean values of two to three independent experiments each one in triplicate.  
** CC₅₀: cytotoxic concentration (μM) to induce 50% death of noninfected cells, as evaluated with the MTT method in MT-4 cells.  
*** EC₅₀ (HIV-1, IIIb): effective concentration (μM) to inhibit by 50% HIV-1 (IIIb strain) induced cell death, as evaluated with the MTT method in MT-4 cells.  
**** SI: selectivity index calculated as CC₅₀/EC₅₀ ratio.  
***** Nd, no data.

Crystal structure [40] of 37a showed that the aromatic moieties adopted a dihedral angle of 114.4°, a value that was very near to the optimal value of the butterfly-like conformation reported by the Schaefer’s model [41].

6. **Pyrrolo[1,2-b][1,2,5]benzothiadiazepine Acetic Acid 5,5-dioxide**

The PBTD scaffold has been exploited in several antiviral research programs. A series of pyrrolo[1,2-b][1,2,5]benzothiadiazepine acetic acid derivatives was synthesized by reaction of 1-(2-amino-benzenesulfonyl)pyrrole with ethyl 3,3-diethoxypropionate in aqueous acetic acid to furnish ethyl 10,11-dihydro-pyrrolo[1,2-b][1,2,5]benzothiadiazepine-11-acetic acid 5,5-dioxide (38). Ester 38 was N-acylated in the presence of triisobutylamine to afford ethyl 10,11-dihydro-10-(4-methylbenzoyl) pyrrolo[1,2-b][1,2,5]benzothiadiazepine-11-acetate 5,5-dioxide (39) which was hydrolyzed into the corresponding acetic acid 40. Alternatively, alkaline hydrolysis of 38 furnished acid 41 which was transformed into azetidone 42 by treatment with trifluoroacetic anhydride (Scheme 5). Derivatives 38 and 42 showed significant inhibition of HIV-1 with EC₅₀ = 19.5 and 18 μM, respectively) [42].

Replacement of the pyrrole ring of PBTD with the indole (43) resulted in weaker antiretroviral compounds [39]. On the other hand, the 5H-indolo[3,2-b][1,5]benzothiazepine isomers (e.g., 44), were endowed with anti-HIV-1 activity in the low micromolar range of concentrations [43]. In addition, 1H-pyrrolo[2,3-b][1,5]benzothiazepine (e.g., 45), 1H-pyrrolo[3,2-b][1,5]benzothiazepine (e.g., 46) [44] and 9H-pyrrolo[2,1-b][1,3,6]benzothiazacocin-11(1H)-one 4,4-dioxide derivatives (47) [45] were
synthesized as new heterocyclic systems mimicking the structural features of the PBTDs scaffold (Chart 2).

7. PBTDs as Chronic Myelogenous Leukemia (CML) Agents

The antitumor activity of pyrrolo[2,1-c][1,4]benzodiazepines (PBDs, e.g., \(48\)) related to anthramycin was extensively studied, as it was documented in Thurston’s review \([46]\). Given the high structural similarity between PBTD and PBD compounds, two PBTDs, \(23\) and its 10-(4-methylbenzoyl) derivative \(49\), were selected for screening of pro-apoptotic and anti-leukemia activity (Chart 3; Tables 2 and 3) \([47]\). PBTD \(23\) was prepared by an improved procedure using dimethoxyacetal of ethyl glyoxylate in absolute ethanol in the presence of 4-toluene sulfonic acid (PTSA). Compound \(23\), prepared as described in Scheme 2, was N-acylated to \(49\) with 4-methylbenzoyl by refluxing in 1-bromo-3-chloropropane in the presence of sodium hydrogen carbonate. PBTDs \(23\) and \(49\) induced apoptosis in K562 cells and caused cell death in BCR-ABL-positive leukemia cells obtained from chronic myeloid leukemia patients who were at onset or were IM-resistant. Apoptotic mechanism studies showed that PBTDs \(23\) and \(49\) activated the caspase activity through two different pathways: both compounds activated caspase-3; \(23\) significantly reduced the procaspase-8; in contrast \(49\) evidenced a decrease of procaspase-9 band. The apoptosis was observed before the expression of BCR-ABL protein and the tyrosine phosphorylation. PBTDs-mediated suppression of K562 cell proliferation was characterized by the appearance of DNA fragmentation and was associated with the poly(ADP-ribose) polymerase (PARP) cleavage. PBTDs \(23\) and \(49\) treatment resulted in caspase-3 activation through down-regulation of Bcl-2 and up-regulation of Bax \([48]\). PBTDs possessed inhibitory activity against mTOR and impeded hyper-phosphorylation of Akt as a feedback of inhibition of mTOR by rapamycin \([49]\). These findings highlighted PBTDs as potential agents for the treatment of CML \([50,51]\).

![Scheme 5. Synthesis of 38 and 42.](image)

![Chart 2. Heterocyclic compounds structurally correlated to PBTD HIV-1 NNRTIs.](image)
Table 2. Apoptotic activity of 23 and 49 in cells from CML patients at onset at 10 μM [46].

| Patient | Sex | Age | Source | % of Apoptosis |
|---------|-----|-----|--------|---------------|
|         |     |     |        | 23 | 49 |
|         |     |     |        | 24 h | 48 h | 24 h | 48 h |
| 1       | M   | 45  | PB a   | 64  | 70  | 77  | 85  |
| 2       | M   | 60  | BM b   | 50  | 70  | 70  | 85  |
| 3       | F   | 73  | PB     | 65  | 79  | 66  | 82  |
| 4       | M   | 83  | BM     | 50  | 70  | 50  | 75  |
| 5       | F   | 46  | PB     | 50  | 70  | 60  | 80  |
| 6       | F   | 27  | PB     | 50  | 70  | 60  | 80  |
| 7       | F   | 45  | PB     | 60  | 80  | 64  | 80  |
| 8       | M   | 35  | PB     | 60  | 80  | 65  | 85  |
| 9       | M   | 66  | PB     | 60  | 80  | 60  | 80  |
| 10      | F   | 38  | PB     | 50  | 70  | 70  | 80  |
| 11      | F   | 65  | PB     | 52  | 71  | 55  | 78  |
| 12      | F   | 27  | PB     | 52  | 73  | 55  | 78  |

a PB: peripheral blood cells. b BM: bone marrow cells.

Table 3. Apoptotic activity of 23 and 49 in cells from CML patients in blast crisis and Imatinib-resistant at onset at 10 μM.

| Patient | Sex | Age | Source | Percent Apoptosis |
|---------|-----|-----|--------|-------------------|
|         |     |     |        |                   |
|         |     |     |        | 23 | 49 |
|         |     |     |        | 24 h | 48 h | 24 h | 48 h |
| 13      | M   | 38  | PB a   | 60  | 80  | 40  | 60  |
| 14      | F   | 70  | PB     | 55  | 78  | 50  | 70  |

a PB: peripheral blood cells.

8. Pyrryl Aryl Sulfones

Diarylsulfones emerged as a chemical class of HIV-1 NNRTIs. The presence of the nitro group at position 2 of the phenyl ring and the sulfur bridging atom as sulfur dioxide are fundamental structural characteristics for their activity. The antiviral activity of 2-nitrophenyl phenyl sulfone (50, NPPS) [52] prompted the synthesis of a series of 41 pyrryl aryl sulfones (PAS) and some related derivatives [53]. Pyrryl 2-nitrophenyl sulfone (51) was straightforwardly prepared by nucleophilic substitution reaction between 2-nitrobenzenesulfonyl chloride and pyrrole in the presence of n-tetrabutylammonium hydrogen sulfate (TBAS) as a phase transfer catalyst. On the other hand, alkaline hydrolysis of 2-ethoxycarbonylpyrrole (16) [34] afforded the acid 52 which was transformed into 53 by reaction with ethyl chloroformate in the presence of 4-methylmorpholine followed by treatment of the intermediate mixed anhydride with glycine ethyl ester (Scheme 6).
Ester 55 was prepared by treating the corresponding acid 54 [54] with oxalyl chloride and then with anhydrous ethanol. Reaction of 1-(2-aminobenzenesulfonyl)pyrrole [35] with methyl malonyl chloride in the presence of triethylamine led to amide 56 which in turn was methylated to 57 or 58 with one or two equivalents of methyl chloride, respectively, in the presence of potassium carbonate (Scheme 6). Compound 16, a 2-nitrophenyl 1-pyrrol sulfone bearing the 2-ethoxycarbonyl function, showed the highest anti HIV-1 activity (Table 4).

### Table 4. Anti-HIV-1 Activity of PASs 16 and 51–58.

| Compound | HIV-1 IIIb |
|----------|------------|
|          | CC<sub>50</sub> (μM) | EC<sub>50</sub> (μM) | SI |
| 16       | >308       | 15.08        | >20 |
| 51       | 36.55      | >36.55       | -   |
| 52       | >337.5     | >337.5       | -   |
| 53       | >262.2     | >262.2       | -   |
| 54       | >333       | >333         | -   |
| 55       | 255        | >255         | -   |
| 56       | >370       | 63           | >5.8|
| 57       | >279       | >279         | -   |
| 58       | >285       | >285         | -   |
| NPPS     | -          | 1.4          | -   |

<sup>a</sup> Data are mean values of two to three independent experiments each one in triplicate; <sup>b</sup> CC<sub>50</sub>: cytotoxic concentration (μM) to induce 50% death of non-infected cells, as evaluated with the MTT method in MT-4 cells; <sup>c</sup> EC<sub>50</sub> (HIV-1, IIIb): effective concentration (μM) to inhibit by 50% HIV-1 (IIIb strain) induced cell death, as evaluated with the MTT method in MT-4 cells; <sup>d</sup> SI: selectivity index calculated as CC<sub>50</sub>/EC<sub>50</sub> ratio.

The importance of the diaryl sulfone moiety for the design of new anti-HIV-1 agents was further confirmed by the synthesis of new series of PAS and indolyl aryl sulfones [55,56]. The amino-PAS
derivatives were synthesized as follows. Alkylation of the 2-amino group was achieved by reaction of 59a and 59b with the appropriate aldehyde in the presence of sodium cyanoborohydrate; carboxamides were obtained by heating with an acyl chloride in pyridine (Scheme not shown). It was reported that the 4-chloroaniline moiety or the related 5-chloro-2-pyridylamine represented the key feature of highly potent HIV-1 NNRTIs, for example 8-Cl-TIBO [57], 7-Cl-PBTD [37] [39] (Table 1), 3,3-dialkyl-3,4-dihydroquinoxaline-2-((1H)thione [58], oxoquinoline [59], and PETT [60]. In the case of PAS derivatives, the 4-chloroaniline moiety worked as a pharmacophore only when the sulfonyl group was near to the amino group. The nature of the pharmacophore could not be modified without affecting the anti-HIV-1 activity. The highest anti-HIV-1 activity of compounds 59a and 59b was also associated with the presence of the alkoxy carbonyl group at position 2 of the pyrrole ring. Alkylation of aniline nitrogen completely abolished the activity (data not shown), whereas acylation led to weakly active compounds (Table 5). The ability to inhibit the recombinant reverse transcriptase (rRT) of HIV-1 is depicted in Table 6. When tested against the rRT form HIV-1 mutants resistant to nevirapine (Y181C) and TIBO (L1001I), the compounds showed activity at 10-fold higher concentrations.

Table 5. Anti-HIV-1 activity of amino-PAS 59a–h against the WT strain a.

| Compound | R1           | R2                          | HIV-1 III B |
|----------|--------------|------------------------------|-------------|
|          |              | CC50 b (µM) | EC50 c (µM) | SI d        |
| 59a      | 2-NH2-5-Cl   | 2-COOEt       | >300        | 0.18 ± 0.05 | >2140  |
| 59b      | 2-NH2-5-Cl   | 2-COOEt       | >300        | 0.14 ± 0.05 | >2140  |
| 59c      | 2-NO2        | 2-COOEt       | >300        | 15 ± 1.5    | >20    |
| 59d      | 2-Cl         | 2-COOEt       | 141         | 25 ± 2.5    | 5      |
| 59e      | 2-NH2-5-Cl   | 2-COOEt       | 100         | 0.40 ± 0.05 | 250    |
| 59f      | 2-NHCHO-5-Cl | 2-COOEt       | >300        | 1.0 ± 0.3   | >300   |
| 59g      | 2-NHCOOMe-5-Cl| 2-COOEt     | ≥300        | 1.0 ± 0.3   | ≥300   |
| 59h      | 2-NHCOOEt    | 2-COOEt       | >300        | 1.0 ± 0.3   | >300   |
| NVP      |              | >10000        | 0.60 ± 0.4  | >167       |

a Data are mean values of two to three independent experiments each one in triplicate; b CC50: cytotoxic concentration (µM) to inhibit 50% death of non-infected cells, as evaluated with the MTT method in MT-4 cells; c EC50 (HIV-1, III B): effective concentration (µM) to inhibit by 50% HIV-1 (III B strain) induced cell death, as evaluated with the MTT method in MT-4 cells; d SI: selectivity index calculated as CC50/EC50 ratio; e NVP: nevirapine.

Table 6. Anti-HIV-1 activity of PAS 59a–h against the rRT.

| Compound | IC50 ± SD (µM) a |
|----------|-----------------|
|          | WT IIIB | Y181C | L1001 |
| 59a      | 0.45 ± 0.09    | 6.9 ± 2.3 | 7.4 ± 1.2 |
| 59b      | 0.40 ± 0.05    | 7.5 ± 1.4 | 8.5 ± 1.0 |
| 59c      | 0.40 ± 0.14    | 5.0 ± 1.5 | 10 ± 3.1 |
| 59d      | 0.27 ± 0.10    | 8.0 ± 2.0 | 14 ± 1.2 |
| 59e      | 0.90 ± 0.12    | 14 ± 2.5 | >20    |
| 59f      | >20            | >20     | >20    |
| 59g      | >20            | >20     | >20    |
| 59h      | >20            | >20     | >20    |
| NVP      | 0.60 ± 0.1     | >20     | 3.5 ± 0.18 |

a Compound concentration required to inhibit the HIV rRT activity by 50%. SD: standard deviation.

Compound 59b was selected as lead compound for an antiviral project based on molecular modeling studies. Using the three-dimensional structure of HIV-1 RT cocryostallized with α-APA
(alpha-anilinophenyl acetamide) derivative R95845, a model of RT/59b complex was derived using previously developed SARs. The experimentally determined RT bound conformations of α-APA R90385 [61] served as basis to select conformations of 59b for docking studies. By scanning the rotatable bonds of the crystal structure of 59b, a low energy conformation was identified and this compound superimposable on α-APA R95845 about the aromatic rings and the COOEt/COMe and SO2/CONH2 groups. Inspection of the RT/59b complex revealed a region of the HIV-1 NNBS (non-nucleoside binding site) delimited by Tyr181, Tyr188 and Trp229 side chains, which could be filled by substituents at position 4 of the pyrrole ring. Among the compounds synthesized, 60 (EC50 = 42 nM; IC50 = 50 nM) was the most potent PAS derivative (Table 7). Compared with 59b, it showed three- and eight-fold improvement in cell-based and enzyme assays, respectively [62].

Table 7. Anti-HIV-1 activity of PAS 60 in MT-4 cells and against rRT. a

| Compound | CC50 b (µM) | HIV-1 IIIb | IC50 e (µM) |
|----------|-------------|------------|-------------|
|          | EC50 c (µM) | SI d       |             |
| 60       | 240         | 0.042      | 5333        |
| NVP f    | >200        | 0.35       | >571        |
|          |             |            | 0.64        |

a Data are mean values of two to three independent experiments each one in triplicate; b CC50: cytotoxic concentration (µM) to induce 50% death of non-infected cells, as evaluated with the MTT method in MT-4 cells; c EC50 (HIV-1, IIIb): effective concentration (µM) to inhibit by 50% HIV-1 (IIIb strain) induced cell death, as evaluated with the MTT method in MT-4 cells; d SI: selectivity index calculated as CC50/EC50 ratio; e Compound concentration required to inhibit the HIV rRT activity by 50%; f NVP: nevirapine.

Further studies were conducted to improve the activity of PAS 59b [63]. New PAS derivatives were synthesized by introduction of different alkyl, alkenyl or cycloalkyl substituents at the 2-ester function, along with a small series of 2-carboxamide derivatives, in order to explore the effects of substituents a position of the pyrrole ring. The new derivatives were less potent and sometimes more toxic than the previously reported 59a and 59b. This study confirmed the key role of the 4-chloroanilino moiety and the substituent at the ester function.

Compound 60 was synthesized as depicted in Scheme 7. 5-Chloro-2-nitrobenzenesulfonyl chloride was reacted with 2-ethoxycarbonyl-1H-pyrrole-4-carboxaldehyde in the presence of potassium tert-butoxide and 18-crown-6 to give 61. Sodium borohydride reduction of aldehyde 61 afforded alcohol 62, and the nitro group reduction with iron in glacial acetic acid to provide the amino derivative 60 (Scheme 7).
Three pyrryl heteroaryl sulfones, ethyl 1-[(6-amino-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)sulfonyl]-1H-pyrrrole-2-carboxylate (63), ethyl 1-[(5-amino-1H-benzo[d]imidazol-6-yl)sulfonyl]-1H-pyrrrole-2-carboxylate (64), and ethyl 1-[(6-amino-2H-benzo[d][1,2,3]triazol-5-yl)sulfonyl]-1H-pyrrrole-2-carboxylate (65), were designed as novel HIV-1 NNRTIs using structure-based computational methods (Chart 4) [64]. These compounds inhibited the HIV-1 RT at micromolar concentrations, but were found inactive in the MT-4 cells assay.

![Chart 4. Structure of pyrryl heteroaryl sulfones 63–65.](image)

9. Acylamino Pyrryl Aryl Sulfones

A series of PAS-related compounds bearing acylamino moieties at position 2 of the benzene ring were synthesized as truncated analogs of PBTDs [39]. Furthermore, potent HIV-1 NNRTIs, such as PETT (67) [65] and truncated-TIBO (68) [66] compounds, were designed and synthesized based on the structure of 8-Cl-TIBO (66) [67,68] using a ring-opening strategy. Based on these findings, the same strategy was applied to 7-Cl-PBTD (37a) by breaking the 11,11b bond. The drug design strategy conceived a series of acylamino-PAS (APAS) derivatives, which were synthetized and characterized for their antiviral properties [69] (Chart 5).

![Chart 5. Design of APAS derivatives.](image)

Several APAS derivatives inhibited the HIV-1 replication in MT-4 cells in the 1–2 μM range. Two compounds, 69 and 70, showed activity at submicromolar concentrations with EC₅₀ of 0.4 and 0.5 μM, respectively. Both compounds failed to inhibit the HIV-1 K103N and Y181C mutant strains, similar to that observed for structurally correlated 2-amino-6-[(3,5-dimethyl)sulfonyl]benzonitrile [70]. Although structurally related to the previously reported PAS family, the APAS derivatives were investigated for binding mode in the non-nucleoside binding site of the HIV-1 RT [71]. Derivative 69, the most active among the test APASs, was modeled from the X-ray coordinates of 59b and docked into the HIV-1 NNBS of the RT using the 2-amino-6-[(3,5-dimethyl)sulfonyl]benzonitrile/RT complex [70]. The binding mode of 69 shared similarities with previously reported PASs [62,64]: the ethoxycarbonyl filled the highly hydrophobic region of NNBS, and the 4-chloro-2-methoxycarbonyl moiety took up the H-bond region.

APAS derivatives 69 and 70 were prepared by reacting compound 59b with bromoacetyl bromide 1-bromo-3-chloropropane in the presence sodium hydrogen carbonate to give 2-bromoacetylamino derivative 71. Treatment of 71 with sodium methoxide or thiomethoxide afforded APASs 69 or 70, respectively (Scheme 8).
was identified as 1-amino-6-chloro-(1H-1,2,5-benzothiadiazepine (73), but only a bicyclic derivative that was identified as 1-amino-6-chloro-(1H-pyrrolyl)benzimidazole (74). Structure of 74 was established by NMR spectroscopy and elemental analysis, and was confirmed by crystallographic data. Formation of 74 was hypothesized by extrusion of the sulfur dioxide followed by Smiles rearrangement [73] of 75 to 76. Reduction of nitro group to amino underwent with concomitant cyclization of the intermediate amino derivative 77 to form 74 (Scheme 9). The structure of 74 was confirmed by direct synthesis of 75 and subsequent treatment with iron in acetic acid to provide 74. It is interesting to note that any attempt to obtain 73 from 1-[5-chloro-2-aminophenyl]sulfonyl]-1H-pyrrole-2-carboxyhydrazide (the corresponding amino derivative of 72), by heating in the presence of 2-hydroxypyridine, failed, 37a being the only product of reaction.

Scheme 9. Smile rearrangement of 72 to 74.

11. Structurally Related Compounds

The highly potent anti-HIV-1 activity displayed by Merck carboxamide L-737,126 (78) [74–76] (HIV-1 WT_{IIIB} EC_{50} = 1 nM; HIV-1 RT IC_{50} = 25 nM) prompted the design of new indolylarylsulfone (IAS) analogs. Due to the lack of SAR information, the design of first IAS derivatives was based on PASs’ structural features. In general, 2-ethoxycarbonyl-1-benzenesulfonyl-1H-indoles showed weak antiretroviral activity, with the exception of derivative 79 (HIV-1 WT_{IIIB} EC_{50} = 8.3 μM) bearing the 4-chloroaniline moiety [77]. Indoles bearing the carboxyethyl group at position 3 of the indole were inactive. Moving the 1-benzenesulfonfyl group of 79 to position 3 of the indole gave IAS 80 (HIV-1 WT_{IIIB} EC_{50} = 1.9 μM) that showed 4.3-fold improvement of activity. Replacement of the 2-ester group
with a carboxyamide function, 81 (HIV-1 WT[IIIB EC₅₀ = 0.04 μM] led to a notably increase of both potency and selectivity. SAR studies led to partition the IAS scaffold in three regions: (A) the activity of 78 against HIV-1 mutant strains significantly improved by the presence of two methyl groups at positions 3 and 5 of the 3-phenylsulfonyl moiety (82) [78]; (B) coupling the indole-2-carboxamide with either natural or unnatural amino acids provided potent HIV-1 inhibitors, for example 83–85, against the HIV-1 L100I, K103N, and Y181C strains in CEM cells, with potency comparable to the first line HIV-1 NNRTI efavirenz [79,80]; and (C) the 5-chloro-4-fluoro substitution pattern at the indole ring, compound 86, afforded potent inhibitors of HIV-1 RT WT and RTs carrying the K103N, Y181I, and L100I mutations [81] (Chart 6).

**Chart 6. Structure of indolylsulfones 78–86.**

### 12. Conclusions

*N*-pyrrylarylsulfones display a variety of biological activities. This review illustrates the various studies made to investigate the *N*-pyrrylarylsulfone scaffold as privileged structure to discover putative antiviral, anticancer and SNC drugs. A number of synthetic approaches to obtain tetracyclic pyrrolo[1,2-b]-s-triazolo[3,4-d][1,2,5]benzothiadiazepine 5,5-dioxide, 2-methyl-1,3,4,14b-tetrahydro-2H-pyrazino[2,1-b]pyrrolo[1,2-b][1,2,5]-benzothiadiazepine 10,10-dioxide, imidazo[5,1-d]pyrrolo[1,2-b][1,2,5]benzothia-diazepine 9,9-dioxide, tricyclic 5H-pyrrolo[1,2-b][1,2,5]benzothiazepin-11(10H)-one 5,5-dioxide (PBTD), and non-cyclic pyrryl aryl sulfone and acylamino-PAS (APAS) compounds and their biological activity with regard to structure–activity relationships (SARs) have been reviewed. The literature reviewed here may provide useful information on the potential of *N*-pyrrylarylsulfone pharmacophore as well as suggest concepts for the design and synthesis of new *N*-pyrrylarylsulfone based agents.

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**References**

1. Gerald, M.C. *The Drug Book*; Sterling Education: New York, NY, USA, 2013.
2. Dogmagk, G. Ein Beitrag zur Chemotherapie der bakteriellen Infektionen. *Deutsch. Med. Wochenschr.* 1935, 61, 250–253. [CrossRef]
3. Dogmagk, G. Eine neue Klasse von Desinfektionsmitteln. *Deutsch. Med. Wochenschr.* 1935, 61, 829–832. [CrossRef]
4. Henry, R.J. The mode of action of sulfonamides. *Bacteriol. Rev.* 1943, 7, 175–262. [PubMed]
5. Sulfamethoxazole. DrugBank. Available online: http://www.drugbank.ca (accessed on 17 August 2016).
6. Fromm, E.; Wittmann, J. Derivate des p-nitrophenols. *Ber. Deutsch. Chem. Ges.* 1908, 41, 2264–2273. [CrossRef]
7. Goulart, L.M.; Reis, A.C.; de Rezende, T.M.; Borges, A.S.; Ferreira, M.S.; Nishioka, S.A. Aplastic anaemia associated with multidrug therapy (dapsone, rifampicin and clofazimine) in a patient with lepromatous leprosy. *Lepr. Rev.* 2005, 76, 167–169. [PubMed]
8. Brown, A.; Captain, B. 50 years of thiazides: Should thiazide diuretics be considered third-line hypertension treatment? *Am. J. Ther.* 2011, 18, e244–e254. [CrossRef] [PubMed]
9. Fregly, M.J. Effect of chlorothiazide and hydrochlorothiazide on blood pressure and thyroid activity of hypertensive rats. *Am. J. Cardiol.* 1961, 8, 890–898. [CrossRef]
10. Maxwell, R.A.; Eckhardt, S.B. *Furosemide in “Drug Discovery”*, The Humana Press Inc.: New York, NY, USA, 1990; pp. 67–77.
11. Stumvoll, M.; Goldstein, B.J.; van Haften, T.W. Type 2 diabetes: Principles of pathogenesis and therapy. *Lancet* 2005, 365, 1333–1346. [CrossRef]
12. Tzoulaki, I.; Molokhia, M.; Curcin, V.; Little, M.P.; Millett, C.J.; Khunti, K.; Wilkins, M.R.; Majeed, A.; et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: Retrospective cohort study using UK general practice research database. *BMJ* 2009, 339, b4731. [CrossRef] [PubMed]
13. Tyrrell, P.N.; Kandasamy, R.A.; Crotty, C.M.; Espie, G.S. Ethoxyzolamide Differentially Inhibits CO$_2$ Uptake and Na$^+$-Independent and Na$^+$-Dependent HCO$_3$$^-$ Uptake in the Cyanobacterium *Synechococcus* sp. UTEX 625. *Plant Physiol.* 1996, 112, 79–88. [CrossRef] [PubMed]
14. De Clercq, E. Dancing with chemical formulæ of antivirals: A personal account. *Biochem. Pharmacol.* 2013, 86, 711–725. [CrossRef] [PubMed]
15. De Clercq, E. Dancing with chemical formulæ of antivirals: A panoramic view. *Biochem. Pharmacol.* 2013, 86, 1397–1410. [CrossRef] [PubMed]
16. Mehellou, Y.; de Clercq, E. Twenty-six years of anti-HIV drug discovery: Where do we go? *J. Med. Chem.* 2010, 53, 521–538. [CrossRef] [PubMed]
17. Vere Hodge, R.A. Meeting report: 28th International conference on antiviral research in Rome, Italy. *Antivir. Res.* 2015, 123, 172–187. [CrossRef] [PubMed]
18. Zhan, P.; Pannecoque, C.; de Clercq, E.; Liu, X. Anti-HIV drug discovery and development: Current innovations and future trends. *J. Med. Chem.* 2015, 59, 2849–2878. [CrossRef] [PubMed]
19. López-Labrador, F.X. Hepatitis C Virus NS3/4A protease inhibitors. *Recent Pat. Antinfect. Drug Discov.* 2008, 3, 157–167. [CrossRef] [PubMed]
20. Gerber, L.; Welzel, T.M.; Zeuzem, S. New therapeutic strategies in HCV: Polymerase inhibitors. *Liver Int.* 2013, 3 (Suppl. 1), 85–92. [CrossRef] [PubMed]
21. Bandmann, H.J.; Breit, R. The mafenide story. *Br. J. Dermatol.* 1973, 89, 219–221. [CrossRef] [PubMed]
22. McCormack, P.L.; Celecoxib: A review of its use for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. *Drugs* 2011, 71, 2457–2489. [CrossRef] [PubMed]
23. Bhardwaj, V.; Gumber, D.; Abbot, A.; Dhimana, S.; Sharma, P. Pyrrole: A resourceful small molecule in key medicinal hetero-aromatics. *RCS Adv.* 2015, 5, 15233–15266. [CrossRef]
24. Gordee, R.S.; Matthews, T.R. Systemic antifungal activity of pyrrolnitrin. *Appl. Microbiol.* 1969, 17, 690–694. [PubMed]
25. Cordrey, L.J. Tolmetin sodium, a new anti-arthritis drug: Double-blind and long-term studies. *J. Am. Geriatr. Soc.* 1976, 24, 440–446. [CrossRef] [PubMed]
26. Rényi, L.; Larsson, L.G.; Berg, S.; Svensson, B.E.; Thorell, G.; Ross, S.B. Biochemical and behavioural effects of isamollane, a beta-adrenoceptor antagonist with affinity for the 5-HT1B receptor of rat brain. *Naunyn Schmiedebergs Arch. Pharmacol.* 1991, 343, 1–6. [CrossRef] [PubMed]
27. Aarsand, A.K.; Petersen, P.H.; Sandberg, S. Estimation and application of biological variation of urinary-aminolevulinic acid and porphobilinogen in healthy individuals and in patients with acute intermittent porphyria. *Clin. Chem.* 2006, 52, 650–656. [CrossRef] [PubMed]
28. Roth, B.D. The discovery and development of atorvastatin, a potent novel hypolipidemic agent. *Prog. Med. Chem.* 2002, 40, 1–22. [PubMed]
29. Hopkins, C.R.; Lindsley, C.W.; Niswender, C.M. mGluR4-positive allosteric modulation as potential treatment for Parkinson’s disease. *Future Med. Chem.* 2009, 1, 501–513. [CrossRef] [PubMed]

30. Gogliotti, R.D.; Blobaum, A.L.; Morrison, R.M.; Daniels, J.S.; Salovich, J.M.; Cheung, Y.Y.; Rodriguez, A.L.; Loch, M.T.; Conn, P.J.; Lindsley, C.W.; et al. Discovery and characterization of a novel series of N-phenylsulfonyl-1H-pyrrole picolinamides as positive allosteric modulators of the metabotropic glutamate receptor 4 (mGlu4). *Bioorg. Med. Chem. Lett.* 2016, 26, 2984–2987. [CrossRef] [PubMed]

31. Stefancich, G.; Silvestri, R. Research on nitrogen containing heterocyclic compounds. XVI. Synthesis of 1,3,4,14b-tetrahydro-2,10-dimethyl-2H,10H-pyrazino-[2,1-d]pyrrolo[1,2-b][1,2,5]benzothiadiazepine (1:1) maleate (10-methyl-10-azaaptazepine). *J. Heterocycl. Chem.* 1989, 26, 745–746. [CrossRef]

32. Stefancich, G.; Artico, M.; Silvestri, R.; Pagnozzi, E.; Loi, A.G.; Musu, D.; Doa, M.; Scano, P.; Palumbo, G. Research on psychotropic agents. III. Antidepressant activity and neuropsycobehavioural effects of new 5H-pyrrolo[1,2-b][1,2,5]benzothiadiazepine derivatives. *Farmaco* 1990, 45, 7–27. [PubMed]

33. Stefancich, G.; Artico, M.; Silvestri, R.; Prosinil, P.P.; Pantaleoni, G.C.; Giorgi, R.; Palumbo, G. Non-steroidal antiinflammatory agents. VII. Synthesis and antiinflammatory activity of 5-methyl-10,11-dihydro-5H-pyrrolo[1,2-b][1,2,5]-benzothiadiazepine-11-acetic acid and its 10-aryl derivatives. *Farmaco* 1990, 45, 817–831. [PubMed]

34. Artico, M.; Silvestri, R.; Stefancich, G. Heterocycles with a benzothiadiazepine moiety. 1. Synthesis of pyrrolo[1,2-b]-s-triazolo[3,4-d][1,2,5]benzothiadiazepine 5,5-dioxide. *Synth. Commun.* 1992, 22, 1433–1439. [CrossRef]

35. Stefancich, G.; Silvestri, R.; Pagnozzi, E.; Artico, M. Heterocycles with a benzothiadiazepine moiety. 2. Synthesis of 2-methyl-1,3,4,14b-tetrahydro-2H-pyrazino[2,1-d]pyrrolo[1,2-b][1,2,5]benzothiadiazepine 10,10-dioxide (Tiaaptazepine). *J. Heterocycl. Chem.* 1994, 31, 867–869.

36. Silvestri, R.; Pagnozzi, E.; Stefancich, G.; Artico, M. Heterocycles with a benzothiadiazepine moiety. 4. Synthesis of novel tetracyclic rings by intramolecular cyclization of 10-bromoacetetyl-10,11-dihydropyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide and its derivatives. *Synth. Commun.* 1994, 24, 2685–2695. [CrossRef]

37. Silvestri, R.; Artico, M.; La Regina, G.; di Pasquali, A.; de Martino, G.; la Torre, F.; Cirilli, R.; Cagnotto, A.; Mennini, T. Chiral resolution and binding study of 1,3,4,14b-tetrahydro-2,10-dimethyl-2H,10H-pyrazino [2,1-d]pyrrolo[1,2-b][1,2,5]benzothiadiazepine (10-methyl-10-azaaptazepine) and 2-methyl-1,3,4,14b-tetrahydro-2H-pyrazino[2,1-d]pyrrolo[1,2-b][1,2,5]benzothiadiazepine 10,10-dioxide (Tiaaptazepine). *Farmaco* 2005, 60, 931–937.

38. Silvestri, R.; Artico, M.; Pagnozzi, E.; Stefancich, G. Heterocycles with a benzothiadiazepine moiety. 3. Synthesis of imidazo[5,1-d]pyrrolo[1,2-b][1,2,5]benzothiadiazepine 9,9-dioxide. *J. Heterocycl. Chem.* 1994, 31, 1033–1036. [CrossRef]

39. Artico, M.; Silvestri, R.; Pagnozzi, E.; Stefancich, G.; Massa, S.; Loi, A.G.; Scano, P.; Corrias, S.; Spiga, M.G.; La Colla, P. 5H-Pyrrolo[1,2-b][1,2,5]benzothiadiazepines (PBTDs): A novel class of HIV-1-specific non-nucleoside reverse transcriptase inhibitors. *Bioorg. Med. Chem.* 1996, 4, 837–885. [CrossRef]

40. Ettorre, A.; Silvestri, R.; Artico, M.; Massa, S.; La Colla, P. Crystal structure of 7-chloro[1,2-b][1,2,5]benzothiadiazepine-10(11H)-one-5,5-dioxide, C\textsubscript{14}H\textsubscript{22}N\textsubscript{2}O\textsubscript{3}Cl. Z. Kristallogr. NCS 2001, 216, 57–58.

41. Schäfer, W.; Friebe, W.G.; Leinert, H.; Mertens, A.; Poll, T.; von der Saal, W.; Ziech, H.; Nuber, B.; Ziegler, M.L. Non-nucleoside inhibitors of HIV-1 reverse transcriptase: Molecular modeling and X-ray structure investigations. *J. Med. Chem.* 1993, 36, 726–732. [CrossRef] [PubMed]

42. Artico, M.; Silvestri, R.; Pagnozzi, E.; Stefancich, G.; Massa, S.; La Colla, P. Synthesis and anti-HIV activity of 10,11-dihydropyrrolo[1,2-b][1,2,5]benzothiadiazepine-11-acetic acid 5,5-dioxide derivatives and related compounds. *Farmaco* 1996, 51, 425–430.

43. Silvestri, R.; Artico, M.; Bruno, B.; Massa, S.; Novellino, E.; Greco, G.; Marongiu, M.E.; Pani, A.; de Montis, A.; La Colla, P. Synthesis and biological evaluation of 5H-indolo[3,2-b][1,5]benzothiazepine derivatives, designed as conformationally constrained analogues of the human immunodeficiency virus type 1 reverse transcriptase inhibitor L-737,126. *Antivir. Chem. Chemother.* 1998, 9, 139–148. [CrossRef]

44. Artico, M.; Stefancich, G.; Silvestri, R.; Massa, S.; Pagnozzi, E.; Loi, A.G.; Musu, D.; Doa, M.; Scano, P.; la Colla, P. Pyrrolobenzothiazepines: A new class of non-nucleoside HIV-1 reverse transcriptase inhibitors. *Med. Chem. Res.* 1994, 4, 283–290.
45. Silvestri, R.; Pagnozzi, E.; Artico, M.; Stefancich, G.; Massa, S.; la Colla, P. Synthesis of 9H-pyrrolo[2,1-b][1,3,6]benzo triazadiocin-10(11H)-one 4,4-dioxide, potential anti-HIV agent. *J. Heterocycl. Chem.* 1995, 32, 683–685. [CrossRef]

46. Thurston, D.E.; Bose, D.S. Synthesis of DNA-interactive pyrrolo-[2,1-c][1,4]benzodiazepines. *Chem. Rev.* 1994, 94, 433–465. [CrossRef]

47. Silvestri, R.; Marfè, G.; Artico, M.; La Regina, G.; De Martino, G.; Lavecchia, A.; Novellino, E.; Morgante, E.; di Stefano, C.; Catalano, G.; et al. Pyrrolo[1,2-b][1,2,5]benzo triazadiazipines (PBTDs): A new class of agents endowed with high apoptotic activity in chronic myelogenous leukemia K562 cells and in cells from patients at onset and imatinib-resistant. *J. Med. Chem.* 2006, 49, 5840–5844. [CrossRef][PubMed]

48. Marfè, G.; di Stefano, C.; Silvestri, S.; Abruzzese, E.; Catalano, G.; di Renzo, L.; Filomeni, G.; Giostra, E.; la Regina, G.; Morgante, E.; et al. Pyrrolo[1,2-b][1,2,5]benzo triazadiazipines (PBTDs) induce apoptosis in chronic myelogenous leukemic K562 cells. *BMC Cancer* 2007, 7, 207–218. [CrossRef][PubMed]

49. Di Stefano, C.; Marfè, G.; Trawinska, M.M.; Sinibaldi-Salimei, P.; Silvestri, R.; Amadori, S.; Abruzzese, E. Pyrrolo[1,2-b][1,2,5]benzo triazadiazipines (PBTDs) exert their anti-proliferative activity by interfering with Akt-mTOR signaling and bax:bcl-2 ratio modulation in cells from chronic myeloid leukemic patients. *Cancer Sci.* 2010, 101, 991–1000. [CrossRef][PubMed]

50. Silvestri, R.; Marfè, G.; di Stefano, C.; Sinibaldi Salimei, P.; Silvestri, R.; Amadori, S.; Abruzzese, E. Synthesis of pyrryl aryl sulfones targeted at the HIV-1 reverse transcriptase. *Arch. Pharm. (Weinheim)* 1995, 328, 223–229. [CrossRef][PubMed]

51. Langlois, N.; Andriamialisoa, R.Z. Synthesis of sulfonamide analogs of the pyrrolo[1,4]benzodiazepine antibiotic abbeymycin. *Heterocycles* 1989, 3, 1529–1536. [CrossRef]

52. McMahon, J.B.; Gulakowski, R.J.; Weislow, O.S.; Schultz, R.J.; Narayanam, V.L.; Clanton, D.J.; Pedemonte, R.; Wassmundt, F.W.; Buckheit, R.W., Jr.; Decker, W.D.; et al. Diarylsulfones, a new chemical class of nonnucleoside antiviral inhibitors of human immunodeficiency virus type 1 reverse transcriptase. *Antimicrob. Agents Chemother.* 1993, 37, 754–760. [CrossRef][PubMed]

53. Artico, M.; Silvestri, R.; Pagnozzi, E.; Bruno, B.; Novellino, E.; Greco, G.; Massa, S.; Ettorre, A.; Loi, A.G.; Scintu, F.; et al. Structure-based design, synthesis and biological evaluation of novel pyrrolyl aryl sulfones (PASs), HIV-1 non-nucleoside reverse transcriptase inhibitors active at nanomolar concentrations. *J. Med. Chem.* 2000, 43, 1886–1891. [CrossRef][PubMed]

54. Pawels, R. Discovery of TIBO, a new family of HIV-1 specific reverse transcriptase inhibitors. In *For Antiviral Drugs*; Adams, J., Merluzzi, V.J., Eds.; Birkhäuser: Boston, MA, USA, 1993; Chapter 4; pp. 71–104.

55. Högberg, M.; Sahlberg, C.; Engelhardt, P.; Nøræen, R.; Kangasmetsä, J.; Johansson, N.G.; Oberg, B.; Vrang, L.; Zhang, H.; Sahlberg, B.L.; et al. High resolution structures of HIV-1 RT from four RT-inhibitor complexes. *Nat. Struct. Biol.* 1995, 2, 293–302. [CrossRef][PubMed]

56. Baba, M.; Okamoto, M.; Kimura, Y.; Ikeuchi, T.; Sakaguchi, T.; Okamoto, T. Potent and selective inhibition of human immunodeficiency virus type 1 transcription by piperazinyloxoquinoline derivatives. *Antimicrob. Agents Chemother.* 1997, 41, 1250–1255. [PubMed]

57. Högberg, M.; Sahlberg, C.; Engelhardt, P.; Nørøen, R.; Kangasmetsä, J.; Johansson, N.G.; Oberg, B.; Vrang, L.; Zhang, H.; Sahlberg, B.L.; et al. Urea-PETT compounds as a new class of HIV-1 reverse transcriptase inhibitors. 3. Synthesis and further structure-activity relationship studies of PETT analogues. *J. Med. Chem.* 1999, 40, 4150–4160. [CrossRef]

58. De Clercq, E. Antiviral therapy for human immunodeficiency virus infections. *Clin. Microbiol. Rev.* 1995, 8, 200–239. [PubMed]

59. Baba, M.; Okamoto, M.; Makino, M.; Kimura, Y.; Ikeuchi, T.; Sakaguchi, T.; Okamoto, T. Potent and selective inhibition of human immunodeficiency virus type 1 transcription by piperazinyloxoquinoline derivatives. *Antimicrob. Agents Chemother.* 1997, 41, 1250–1255. [PubMed]

60. Lavecchia, A. Benzodiazepine Derivatives and Uses Thereof in Medical Field. Patent WO 2007/015280, 8 February 2007.

61. Ren, J.; Esnouf, R.; Garman, E.; Somers, D.; Ross, C.; Kirby, I.; Keeling, J.; Darby, G.; Jones, Y.; Stuart, D.; et al. Pyrrolo[1,2-b][1,2,5]benzo triazadiazipines (PBTDs) induce apoptosis in chronic myelogenous leukemic K562 cells. *BMC Cancer* 2007, 7, 207–218. [CrossRef][PubMed]

62. Di Stefano, C.; Catalano, G.; et al. Pyrrolo[1,2-b][1,2,5]benzo triazadiazipines (PBTDs): A new class of agents endowed with high apoptotic activity in chronic myelogenous leukemia K562 cells and in cells from patients at onset and imatinib-resistant. *J. Med. Chem.* 2006, 49, 5840–5844. [CrossRef][PubMed]

63. McMahon, J.B.; Gulakowski, R.J.; Weislow, O.S.; Schultz, R.J.; Narayanam, V.L.; Clanton, D.J.; Pedemonte, R.; Wassmundt, F.W.; Buckheit, R.W., Jr.; Decker, W.D.; et al. Diarylsulfones, a new chemical class of nonnucleoside antiviral inhibitors of human immunodeficiency virus type 1 reverse transcriptase. *Antimicrob. Agents Chemother.* 1993, 37, 754–760. [CrossRef][PubMed]

64. Langlois, N.; Andriamialisoa, R.Z. Synthesis of sulfonamide analogs of the pyrrolo[1,4]benzodiazepine antibiotic abbeymycin. *Heterocycles* 1989, 3, 1529–1536. [CrossRef]
63. Silvestri, R.; Artico, M.; la Regina, G.; de Martino, G.; Loddo, R.; la Colla, P. Anti-HIV-1 activity of pyrrolyl aryl sulfone (PAS) derivatives. Synthesis and SAR studies of novel esters and amides at the position 2 of the pyrrole nucleus. *Farmaco* 2004, 59, 201–210. [CrossRef] [PubMed]

64. Silvestri, R.; Artico, M.; De Martino, G.; Novellino, E.; Greco, G.; Lavecchia, A.; Massa, S.; Loi, A.G.; Doratiotto, S.; la Colla, P. Computer-assisted design, synthesis and biological evaluation of novel pyrrolyl heteroaryl sulfones targeted at HIV-1 reverse transcriptase as non-nucleoside inhibitors. *Bioorg. Med. Chem. 2000*, 8, 2305–2309. [CrossRef]

65. Cantrell, A.S.; Engelhardt, P.; Högberg, M.; Jaskunas, S.R.; Johansson, N.G.; Jordan, C.L.; Kangasmetsä, J.; Kinnick, M.D.; Lind, P.; Morin, J.M., Jr; et al. Phenethylthiazolylthiourea (PETT) compounds as a new class of HIV-1 reverse transcriptase inhibitors. 2. Synthesis and further structure-activity relationship studies of PETT analogs. *J. Med. Chem. 1996*, 39, 4261–4274. [CrossRef] [PubMed]

66. Breslin, H.J.; Kukla, M.J.; Kromis, T.; Cullis, H.; de Knaep, F.; Pauwels, R.; Andries, K.; de Clercq, E.; Janssen, M.A.; Janssen, P.A. Synthesis and anti-HIV activity of 1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (TBO) derivatives. Truncated 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-on es (TIBO) analogues. *Bioorg. Med. Chem. 1999*, 7, 2427–2436. [CrossRef]

67. Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kukla, M.J.; Breslin, H.J.; Raeymaekers, A.; van Gelder, J.; Woestenborghs, R.; Heykants, J.; et al. Potent and selective inhibition of HIV-1 replication in vitro by a novel series of TIBO derivatives. *Nature 1990*, 343, 470–474. [CrossRef] [PubMed]

68. Das, K.; Ding, J.; Hsiou, Y.; Clark, A.D., Jr.; Moereels, H.; Koymans, L.; Andries, K.; Pauwels, R.; Janssen, P.A.; Boyer, P.L., et al. Crystal structures of 8-Cl and 8-Cl TIBO complexed with wild-type HIV-1 RT and 8-Cl TIBO complexed with the Tyr181Cys HIV-1 RT drug-resistant mutant. *J. Mol. Biol. 1996*, 26, 1085–1100. [CrossRef]

69. Silvestri, R.; de Martino, G.; Artico, M.; la Regina, G.; Ragno, R.; Loddo, R.; la Colla, P.; Marongiu, M.E.; la Colla, M.; Pani, A. Anti-HIV-1 NNRT agents: Acylamino pyrryl aryl sulfones (APASs) as truncated analogues of tricyclic PBTDs. *Med. Chem. Res. 2002*, 11, 195–218.

70. Chan, J.H.; Hong, J.S.; Hunter, R.N., 3rd; Orr, G.F.; Cowan, J.R.; Sherman, D.B.; Sparks, S.M.; Reitter, B.E.; Andrews, C.W., 3rd; Hazen, R.J., et al. 2-Amino-6-arylsulfonylbenzonitriles as non-nucleoside reverse transcriptase inhibitors of HIV-1. *J. Med. Chem. 2001*, 44, 1866–1882. [CrossRef] [PubMed]

71. Titmuss, S.J.; Keller, P.A.; Griffith, R. Docking experiments in the flexible non-nucleoside inhibitor binding pocket of HIV-1 reverse transcriptase. *Bioorg. Med. Chem. 1999*, 7, 1163–1170. [CrossRef]

72. Silvestri, R.; Pifferi, A.; de Martino, G.; Saturnino, C.; Artico, M. Reductive Smiles rearrangement of 1-[5-chloro-2-nitrophenyl)sulfonyl]-1-[(5-chloro-2-nitrophenyl)sulfonyl] benzimidazole. *Heterocycles* 2000, 53, 2163–2174.

73. Skarzewski, J.; Skrowaczewska, Z. The smiles rearrangement: Mechanism of unusual acyl and 2,4-dinitrophenyl migrations in aryl acylamino ethers. *Tetrahedron 1976*, 32, 1221–1224. [CrossRef]

74. Williams, T.A.; Ciccarone, T.M.; Saari, W.S.; Wai, J.S.; Greenlee, W.J.; Balani, S.K.; Goldman, M.E.; Theoharides, A.D. Indoles as Inhibitors of HIV Reverse Transcriptase. Patent Application EP 0 530 907 A1, 28 August 1992.

75. Williams, T.A.; Ciccarone, T.M.; Greenlee, W.J.; Balani, S.K.; Goldman, M.E.; Hoffinan, A.D. Indoles as Inhibitors of HIV Reverse Transcriptase. Patent Application EP 0 530 907 A1, 28 August 1992.

76. Williams, T.A.; Ciccarone, T.M.; Greenlee, W.J.; Balani, S.K.; Goldman, M.E.; Hoffinan, A.D. Indoles as Inhibitors of HIV Reverse Transcriptase. Patent Application EP 0 530 907 A1, 28 August 1992.

77. Williams, T.A.; Ciccarone, T.M.; Greenlee, W.J.; Balani, S.K.; Goldman, M.E.; Hoffinan, A.D. Indoles as Inhibitors of HIV Reverse Transcriptase. Patent Application EP 0 530 907 A1, 28 August 1992.

78. Williams, T.A.; Ciccarone, T.M.; Greenlee, W.J.; Balani, S.K.; Goldman, M.E.; Hoffinan, A.D. Indoles as Inhibitors of HIV Reverse Transcriptase. Patent Application EP 0 530 907 A1, 28 August 1992.

79. Williams, T.A.; Ciccarone, T.M.; Greenlee, W.J.; Balani, S.K.; Goldman, M.E.; Hoffinan, A.D. Indoles as Inhibitors of HIV Reverse Transcriptase. Patent Application EP 0 530 907 A1, 28 August 1992.

80. Williams, T.A.; Ciccarone, T.M.; Greenlee, W.J.; Balani, S.K.; Goldman, M.E.; Hoffinan, A.D. Indoles as Inhibitors of HIV Reverse Transcriptase. Patent Application EP 0 530 907 A1, 28 August 1992.
80. Piscitelli, F.; Coluccia, A.; Brancale, A.; la Regina, G.; Sansone, A.; Giordano, C.; Balzarini, J.; Maga, G.; Zanoli, S.; Samuele, A.; et al. Indolylarylsulfon bearing natural and unnatural amino acids. Discovery of potent inhibitors of HIV-1 non-nucleoside wild type and resistant mutant strains reverse transcriptase and coxsackie B4 virus. *J. Med. Chem.* 2009, 52, 1922–1934. [CrossRef] [PubMed]

81. La Regina, G.; Coluccia, A.; Piscitelli, F.; Bergamini, A.; Sinistro, A.; Cavazza, A.; Maga, G.; Samuele, A.; Zanoli, S.; Novellino, E.; et al. Indolyl aryl sulfones as HIV-1 non-nucleoside reverse transcriptase inhibitors: Role of two halogen atoms at the indole ring in developing new analogues with improved antiviral activity. *J. Med. Chem.* 2007, 50, 5034–5038. [CrossRef] [PubMed]
