Brief Articles

Substituted Pyridazino[3,4-*b*][1,5]benzoxazepin-5(6*H*)ones as Multidrug-Resistance Modulating Agents

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Pyridazino[3,4-*b*][1,5]benzoxazepin-5(6*H*)ones substituted with propylene-linked basic side chains were synthesized and investigated for the ability to reverse multidrug resistance (MDR) at vincristine-pretreated HeLa-MDR1 cells. The substances were found to be effective chemosensitizers with activity comparable to that of the known MDR modulator verapamil. The observed antiproliferative effects were not caused by direct drug cytotoxicity.

Introduction

Multidrug resistance (MDR) is defined as the capability of leukemic or tumor cells to survive continuous exposure to a broad variety of chemotherapeutic drugs. The cells may constitutively display mechanisms to confer MDR or acquire resistance during drug administration. Resistance can result from decreased drug influx, activation of DNA repair mechanisms, defective apoptotic pathways (e.g., decreased ceramide levels) or activation of detoxifying systems (e.g., cytochrome P450). An altered membrane transport resulting in lower intracellular concentrations of cytotoxic drugs is considered as major event of MDR.[1] The effect is mediated by the overexpression of a variety of proteins belonging to a family of ATP-binding cassette transporters such as P-glycoprotein (Pgp)[2] and multidrug resistance proteins[3] that act as ATP-dependent extrusion pumps. Pgp is a 170 KDa membrane protein encoded by the MDR1 gene localized to chromosome 7.[4] Pgp and MDR1 mRNA have been shown to be expressed in acute myeloid leukemia,[5] breast cancer,[6] ovarian cancer,[7] and lung cancer.[8]

A number of compounds, so-called chemosensitizers, are able to reverse the effect of Pgp on MDR.[9] However, some MDR modulators such as verapamil were associated with many side effects.[10] Compounds containing heterocyclic rings and basic side chains, like N-substituted quinoline,[11] thioxanthene,[12,13] phenothiazine,[12,14,15] and dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)one derivatives,[16] are known to modulate MDR. Figure 1 shows relevant examples of known potent MDR-modulating agents developed in the past years.[17] Compounds such as MS-209, LY-335979, and the dibenzo[*b*,*f*][1,4]oxazepin-11-(10*H*)ones are substances sharing common structural features. An N-containing di- or tricyclic ring system is connected by a short (C2 or C3) linker to a basic side chain with at least one tertiary nitrogen.

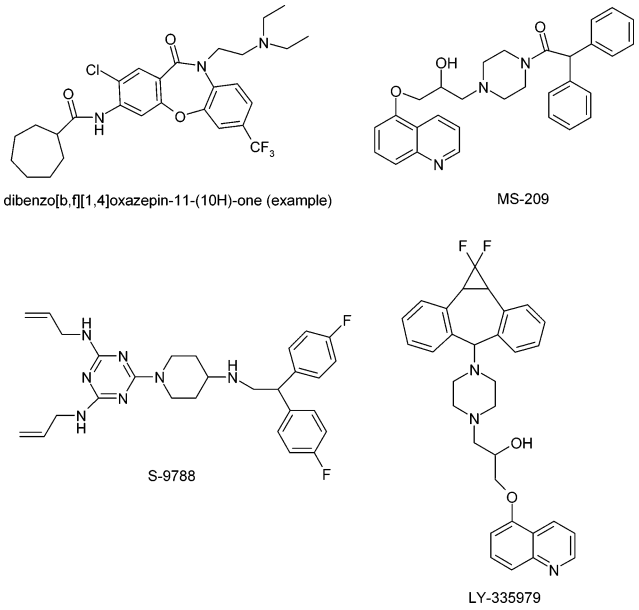

Figure 1. Structures of MDR modulators.

Because related compounds are the subject of our research, we focused our interests on substances structurally close to this kind of MDR reversing agent. The target compounds are characterized by a substituted pyridazino[3,4-*b*][1,5]benzoxazepin-5(6*H*)one core. This tricyclic ring system is closely related to that of the dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)ones. These compounds exhibit carboxamid nitrogens; the exocyclic one is replaced by the pyridazino-N in the pyridazino[3,4-*b*]-[1,5]benzoxazepin-5(6*H*)ones. Hydrophobic substituents such as Cl and CF_3 were of advantage in the dibenzo-[*b*,*f*][1,4]oxazepin-11(10*H*)ones and were kept at the corresponding positions in the target structures. The essential basic substructure represents a substituted piperazine that is linked at the tricyclic system via an

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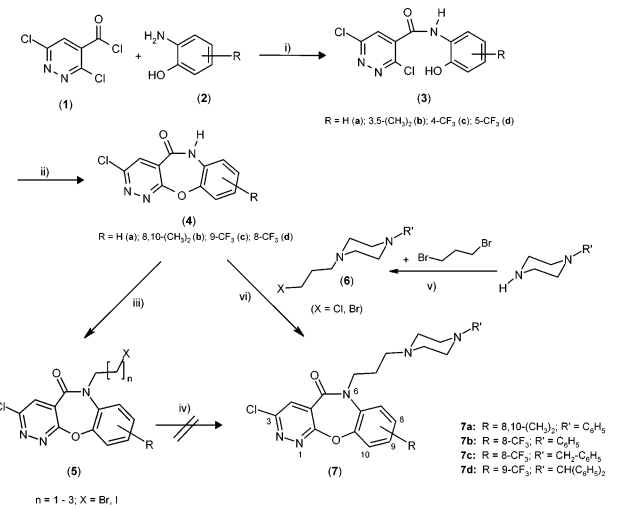
Scheme 1. Synthesis of the Target Compounds of Type **7**[a]



[a] Reagents and conditions: (i) triethylamine, CH_2Cl_2, 0 °C → room temp; (ii) NaH, 1,4-dioxane, 100 °C; (iii) KOH, DMSO, $X-CH_2(CH_2)_n-X'$, room temp; (iv) 1-substituted piperazine, NaI or Na_2CO_3, DMF, 60−80 °C; (v) K_2CO_3, acetone; (vi) dry solvent, base.

alkylene spacer (in accordance to the literature [quinolines] preferably propylene). Furthermore, the piperazine ring is connected to lipophilic substituents (phenyl, benzyl, or diphenylmethylene), a concept that seems promising because of the results obtained with compounds such as MS-209 and LY-335979.

To evaluate the activity of the new target compounds, comparative studies of multidrug-resistant HeLa (HeLa-MDR1) cells and the corresponding wild-type HeLa S3 cells (HeLa-WT) were conducted.

Chemistry

The synthesis of the target compounds of type **7** is summarized in Scheme 1. (Substituted) 2-aminophenol(s) were acylated with 3,6-dichloropyridazine-4-carboxylic acid chloride (**1**) to give the corresponding carboxamides **3**. The carboxamides were then cyclized by treatment with sodium hydride in refluxing 1,4-dioxane based on a method developed by our group.[18] The trifluoromethyl-substituted aminophenols (**2** with R = CF_3)[19] became accessible by reduction of the corresponding 2-nitrophenol derivatives using ammonium formate as a hydrogen source and palladium on charcoal as catalyst. The nitro compounds were prepared as described in the literature by nitration of 3-hydroxybenzotrifluoride[20] or by diazotation of 4-trifluoromethyl-2-nitroanilin and subsequent reaction in aqueous $CuSO_4$ solution.[21]

The key step to the synthesis of the target **7** was the introduction of the propylene-linked basic side chain. First, the appropriate *N*-*ω*-halogenalkyl derivatives were considered as suitable precursors for the target compounds. Such precursors of type **5** can be prepared by reaction of (substituted) 3-chloropyridazino[3,4-*b*]-[1,5]benzoxazepin-5(6*H*)ones **4** with an excess of 1,3-dibromopropane in dry dimethyl sulfoxide in the presence of powdered potassium hydroxide. Treatment of derivatives of type **5** with N-nucleophiles [*N*-methylpiperazine, *N*-benzylpiperazine, or 1-(diphenylmethyl)-piperazine] in dry *N*,*N*-dimethylformamide in the presence of a base at 60−100 °C led to a mixture of products but did not result in the formation of the target **7**. This conclusion is based on the ^{1}H NMR spectra of the isolated reaction products. In all cases the signal of the H4 (pyridazine-H), which appears at ∼8 ppm, was missing. Efforts are underway to elucidate the structures of these isolated compounds, and the results will be published elsewhere. Moreover, 3-chloropyridazino-[3,4-*b*][1,5]benzoxazepin-5(6*H*)one derivatives bearing a 6-(2-bromoethyl) or a 6-(4-iodobutyl) substituent did not represent useful precursors for the target compounds of type **7**.

These results prompted us to investigate an alternative approach. It consists of reaction of the tricycles **4** with *N*-(*ω*-halogenpropyl)-substituted piperazine derivatives **6**. The derivatives were prepared by treatment of a 1-substituted piperazine (i.e., 1-phenylpiperazine, 1-benzylpiperazine, and 1-(diphenylmethyl)piperazine) with 1,3-dibromopropane and a base in dry acetone at room temperature in analogy to a method described in the literature.[22] GC/MS determination showed that the alkylpiperazines formed represent mixtures of the bromo and chloro derivatives that may result from halogen exchange reaction during the workup. These mixtures were used for subsequent reaction without separation. For the preparation of the target compounds the *N*-(*ω*-halogenalkyl)-substituted piperazines **6** were reacted with a (substituted) 3-chloropyridazino[3,4-*b*]-[1,5]benzoxazepin-5(6*H*)one **4** in a dry solvent (e.g. *N*,*N*-dimethylformamide) in the presence of base at room temperature or elevated temperature. The crude compounds **7** thus obtained were purified by column chromatography and subsequent recrystallization. The structures of the novel compounds were confirmed by elemental analyses and IR and ^{1}H NMR spectroscopy.

In Vitro Activity

The MDR effect was analyzed by incubating the cells with concentrations of vincristine sulfate (VCR) ranging from 1 pg/mL to 10 ng/mL. A concentration of 1 ng/mL VCR inhibited proliferation of HeLa-WT cells from 100% (in the absence of all compounds) to 75.7 ± 23.9% (p is not significant) and a concentration of 10 ng/mL to 21.3 ± 3.7% ($p = 0.0022$). The HeLa-MDR1 cell line was more resistant to VCR. Proliferation was inhibited from 100% to 89.0 ± 1.7% by 1 ng/mL ($p = 0.0239$) and to 44.7 ± 8.4% by 10 ng/mL VCR ($p = 0.022$). The effectiveness of the compounds in inhibiting the MDR effect was tested on the ability to modulate proliferation of VCR-pretreated HeLa-WT and HeLa-MDR1 cells.

An anti-MDR effect was already observed with 1 μM of either compound. The VCR (10 ng/mL) reduced proliferation of HeLa-MDR1 cells was further decreased from 44.7 ± 8.4% to 16.0 ± 3.6% by **7a** ($p = 0.0497$), to 19.7 ± 3.8% by **7b** ($p = 0.031$), to 19.3 ± 4.6% by **7c** ($p = 0.029$), and to 19.0 ± 5.3% by **7d** ($p = 0.0241$) (Figure 2). This decrease was identical to that of 1 μM verapamil (19.3 ± 4.9%, $p = 0.0641$; Figure 2). Higher compound concentrations almost blocked proliferation of HeLa-MDR1 cells. Proliferation was inhibited by 5 μM **7a** from 44.7 ± 8.3% to 6.7 ± 1.2% ($p = 0.0576$), by **7b** to 2.7 ± 0.7% ($p = 0.0344$), by **7c** to 2.7 ± 0.7% ($p = 0.0344$), and by **7d** to 2.3 ± 0.3% ($p = 0.0353$) (Figure 2). Verapamil at 5 μM reduced the proliferation to 6.0 ± 1.0% ($p = 0.0496$; Figure 2).

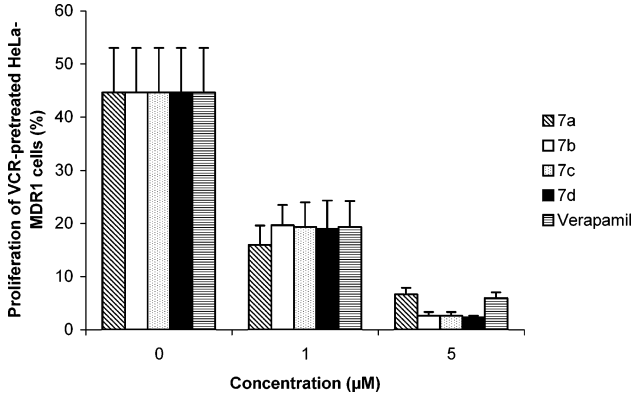


Figure 2. Effect of compounds **7a**−**d** and verapamil on the proliferation of VCR-pretreated HeLa-MDR1 cells.

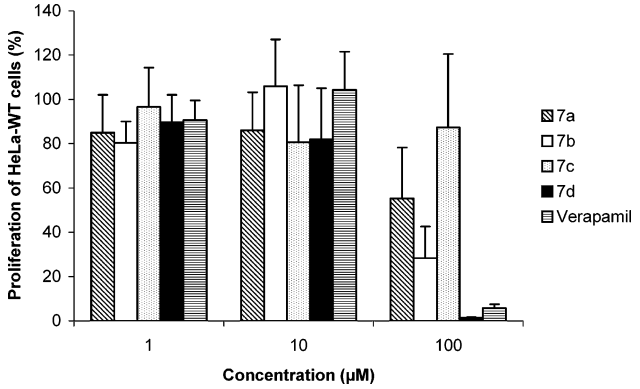


Figure 3. Effect of compounds **7a**−**d** and verapamil on the proliferation of HeLa-WT cells.

The proliferation of VCR-pretreated HeLa-MDR1 incubated with compound concentrations higher than 5 μM was similarly low as that of HeLaWT, indicating that the drug resistance effect is completely removed at higher concentrations (data not shown).

To exclude that the effect of the compounds on proliferation of HeLa-WT and HeLa-MDR1 cells could be due to toxicity, both cell lines were incubated with the compounds in the absence of VCR. Low concentrations (1−10 μM) of the compounds and verapamil showed no significant antiproliferative activity on HeLa-WT cells (Figure 3). At 100 μM, strong differences between the compounds could be observed. The proliferation was only slightly reduced from 100.0 ± 0.0% in the absence of either compound to 87.3 ± 33.2% by **7c** ($p = 0.7395$). **7a** decreased the proliferation to 55.3 ± 22.9% ($p = 0.1907$) and **7b** to 28.3 ± 14.3% ($p = 0.0376$). **7d** and verapamil blocked the proliferation (decrease to 1.3 ± 0.3% ($p = 0.0001$) and 5.7 ± 1.9% ($p = 0.0004$), respectively). Similar results were obtained with HeLa-MDR1 cells (data not shown).

Conclusion

The compounds synthesized in this initial study are potent MDR-modulating drugs. The drug resistance of vincristine-pretreated HeLa-MDR1 cells was lowered to the same extent as by the known chemosensitizer verapamil. The absence of toxicity of **7c** and the low toxicity of **7a** even at high concentrations (verapamil blocks proliferation at this concentration) suggest that these compounds are promising candidates for further developments.

Experimental Section

General Procedure for the Synthesis of 6-Piperazinylalkyl Substituted 3-Chloropyridazino[3,4-*b*][1,5]benzoxazepin-5(6*H*)ones of Type 7. To a solution of 1 equiv of the substituted 3-chloropyridazino[3,4-*b*][1,5]benzoxazepin-5(6*H*)one of type **4** (1.5−2.0 mmol) in 25 mL of an appropriate solvent (dimethyl sulfoxide, acetone, or *N*,*N*-dimethylformamide) was added 2 equiv of base (potassium hydroxide or sodium carbonate). After the mixture was stirred for 1 h, 1.1 equiv of the appropriate alkylating agent (4-substituted 1-(3-halogenpropyl)-piperazine) were added and stirring was continued until the starting material was completely alkylated (TLC monitoring, dichloromethane/ethyl acetate 9/1, or ethyl acetate).

Then the mixture was poured into cold water (50 mL) and the mixture was extracted with dichloromethane. The combined organic phases were washed with water and saturated NaCl solution, dried over anhydrous Na_2SO_4, and evaporated. Pure products could be obtained after column chromatography and recrystallization.

3-Chloro-8,10-dimethyl-6-[3-(4-phenylpiperazin-1-yl)-propyl]pyridazino[3,4-*b*][1,5]benzoxazepin-5(6*H*)one (7a). Compound **7a** was prepared by reaction of 3-chloro-8,10-dimethylpyridazino[3,4-*b*][1,5]benzoxazepin-5(6*H*)one (**4** with R = 8,10-$(CH_3)_2$) with 1-(3-bromopropyl)-4-phenylpiperazine in DMSO in the presence of KOH (5 h). The crude product was purified by column chromatography (eluent, ethyl acetate) followed by recrystallization from diisopropyl ether to give 13% yield of colorless crystals: mp 185−186 °C; IR (KBr) 1654 cm^{-1}; MS *m*/*z* 478/480 (M^+); ^1H NMR ($CDCl_3$) δ 7.94 (s, 1 H, H-4), 7.29−7.21 (m, 3 H), 6.96−6.81 (m, 4 H) (H-7, H-9, phenyl-H), 4.20 ("s", br, 2 H, N−CH_2), 3.13 (t, $J = 5.1$ Hz, 4 H, 2 × piperazine-CH_2), 2.57−2.41 (m, 9 H, 2 × piperazine-CH_2, N−CH_2, CH_3), 2.29 (s, 3 H, CH_3), 2.00−1.86 (m, 2 H, CH_2). Anal. ($C_{26}H_{28}ClN_5O_2$) C, H, N.

3-Chloro-8-trifluoromethyl-6-[3-(4-phenylpiperazin-1-yl)propyl]pyridazino[3,4-*b*][1,5]benzoxazepin-5(6*H*)-one (7b). Compound **7b** was prepared by reaction of 3-chloro-8-trifluoromethylpyridazino[3,4-*b*][1,5]benzoxazepin-5(6*H*)-one (**4** with R = 8-CF_3) with 1-(3-bromopropyl)-4-phenylpiperazine in acetone in the presence of KOH (48 h). The crude product was purified by column chromatography (eluent, ethyl acetate) followed by recrystallization from diisopropyl ether/ethyl acetate to give 15% yield of colorless crystals: mp 160−162 °C; IR (KBr) 1658 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00 (s, 1 H, H-4), 7.70−7.53 (m, 3 H), 7.29−7.21 (m, 2 H), 6.91−6.81 (m, 3 H) (H-7, H-9, H-10, phenyl-H), 4.27 (t, $J = 6.8$ Hz, 2 H, N−CH_2), 3.10 (t, $J = 4.9$ Hz, 4 H, 2 × piperazine-CH_2), 2.55−2.43 (m, 6 H, 2 × piperazine-CH_2, N−CH_2), 2.04−1.91 (m, 2 H, CH_2). Anal. ($C_{25}H_{23}ClF_3N_5O_2$) C, H, N.

6-[3-(4-Benzylpiperazin-1-yl)propyl]-3-chloro-8-trifluoromethylpyridazino[3,4-*b*][1,5]benzoxazepin-5(6*H*)one (7c). Compound **7c** was prepared by reaction of 3-chloro-8-trifluoromethylpyridazino[3,4-*b*][1,5]benzoxazepin-5(6*H*)one (**4** with R = 8-CF_3) with 4-benzyl-1-(3-bromopropyl)piperazine in DMF in the presence of Na_2CO_3 and catalytic amounts of KI (25 h at 60 °C, 3 h at 90 °C). The crude product was purified by column chromatography (eluent 1, ethyl acetate; eluent 2, dichloromethane/ethanol = 19/1) followed by recrystallization from diisopropyl ether to give 26% yield of colorless crystals: mp 170−171 °C; IR (KBr) 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.99 (s, 1 H, H-4), 7.68−7.63 (m, 2 H, H-7, H-10), 7.54 (dd, $J = 8.3$ Hz, $J = 1.7$ Hz, 1 H, H-9), 7.31−7.22 (m, 5 H, phenyl-H), 4.22 (t, $J = 7.0$ Hz, 2 H, N−CH_2), 3.45 (s, 2 H, CH_2), 2.41−2.35 (m, 10 H, 4 × piperazine-CH_2, N−CH_2), 1.98−1.84 (m, 2 H, CH_2). Anal. ($C_{26}H_{25}ClF_3N_5O_2$) C, H, N.

3-Chloro-9-trifluoromethyl-6-[3-(4-diphenylmethylpiperazin-1-yl)propyl]pyridazino[3,4-*b*][1,5]benzoxazepin-5(6*H*)one (7d). Compound **7d** was prepared by reaction of 3-chloro-9-trifluoromethylpyridazino[3,4-*b*][1,5]benzoxazepin-5(6*H*)one (**4** with R = 9-CF_3) with 1-(3-bromopropyl)-4-(diphenylmethyl)piperazine in DMF in the presence of Na_2CO_3 and catalytic amounts of KI (18 h at 60 °C). The crude product was purified by column chromatography (eluent 1, ethyl

acetate/ethanol = 10/1; eluent 2, ethyl acetate) followed by recrystallization from diisopropyl ether to give 11% yield of colorless crystals: mp 156−159 °C; IR (KBr) 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.97 (s, 1 H, H-4), 7.79 ("s", 1 H), 7.57−7.52 (m, 2 H), 7.41−7.12 (m, 10 H) (H-7, H-8, H-10, phenyl-H), 4.22−4.14 (m, 4 H, 2 × piperazine-CH_2), 2.42−2.29 (m, 9 H, 2 × piperazine-CH_2, 2 × N−CH_2, CH), 2.04−1.84 (m, 2 H, CH_2). Anal. ($C_{32}H_{29}ClF_3N_5O_2$) C, H, N.

In Vitro Activity. The human HeLa S3 cell line (HeLa-WT) and the multidrug resistant MDR-overexpressing HeLa cell line (HeLa-MDR1) were kindly provided by J. Hofman (Institute of Medical Chemistry and Biochemistry, Medical University Hospital of Innsbruck).

Both cell lines were grown in RPMI 1640 (Biochrom, Berlin, Germany) supplemented with 2 mM glutamine (Biochrom), 100 U/mL penicillin (Biochemie GmbH, Vienna, Austria), 100 μg/mL streptomycin (Grünenthal GmbH, Stolberg, Austria), and 10% fetal calf serum (Life Technologies, Paisley, Scotland) at 37 °C in 5%CO_2/95% air. Logarithmically growing cells were trypsinized, washed with phosphate buffered saline, resuspended in culture medium at 2×10^5 cells/mL, and plated in triplicate in flat bottom microtiter plates (Falcon, Becton Dickinson, Franklin Lakes, NY). Various concentrations of vincristine sulfate (VCR, 0−10 ng/mL, Vincristin, Pharmacia Austria, Vienna, Austria) were added 30 min thereafter. **7a**−**d** and verapamil (Institute of Pharmacy, University Innsbruck) were prepared as stock solutions in DMSO (Sigma-Aldrich, Vienna, Austria) and were adjusted to the final concentrations (1−100 μM) with culture medium. The concentration of DMSO did not exceed 0.1% (v/v). One hour after the addition of VCR, the solutions of the compounds were added and continuously exposed for 72 h. For the last 12−16 h of culture, cells were pulsed with 2 μCi of ^{3}[H]thymidine (40−60 Ci/mmol, Amersham, Arlington Heights, IL) and harvested using a semiautomated device and ^{3}[H]thymidine uptake was measured in a liquid scintillation counter (Beckman LS 1801, Galway, Ireland). The paired Student's *t*-test was used to calculate statistical differences. Results are shown as mean proliferation ± SE. Proliferation in the absence of all compounds was set at 100%.

Supporting Information Available: General remarks, synthesis, and analytical data for **1**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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