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Original article

New antiproliferative benzoindolinothiazepines derivatives

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Abstract

New benzoindolinothiazepines containing a piperazine moiety are described as potent antiproliferative agents against PC3 human prostatic cell lines. This activity could be explained by an accumulation of cells in G1 phase.

Keywords: Benzoindolinothiazepines; Cell cycle; PC3

1. Introduction

Cell cycle control in G1 phase has attracted considerable attention in recent cancer research, since key proteins involved in G1 progression or G1/S transition have been found to play a crucial role in proliferation, differentiation, transformation, and apoptosis [1–3]. Particular attention has been focused on cyclin-dependent kinases (CDKs) [4] and farnesyltransferase (FTase) [5]. The transition from one cell cycle phase to another occurs in an orderly fashion and is regulated by regulatory proteins, the CDKs. These proteins, a family of serine/threonine protein kinases, are activated at specific points of the cell cycle [6]. CDK protein levels remain stable during the cell cycle, in contrast to their activating proteins, the cyclins. Cyclin protein levels rise and fall during the cell cycle and in this way they periodically activate CDK [7]. Alterations of CDKs in cancer have been reported and the process of searching for new cancer drugs is a direct inhibition of CDK [8]. The well known CDK inhibitors, olomoucine [9], roscovitine [10] and flavopiridol [11], all arrest proliferation cells at the G1/S and G2/M boundaries and induce apoptosis. Olomoucine also triggers an apoptotic response in cells, which have been arrested in G2 phase by DNA-damaging agents, whereas flavopiridol can induce apoptosis in non-cycling cells. pRb, the most important CDK substrate during G1, is frequently mutated in human retinoblastoma and lung cancer.

Deletion and mis-sense mutations result in truncated, non-functional pRb or in complete absence of pRb. Approximately 90% of human cancers have abnormalities in some components of the pRb pathway and p16/pRb alterations occur commonly in primary and metastatic human prostate cancer [12]. On the other hand, it has been found that some FTase inhibitors (FTI) are able to induce apoptosis of transformed cells. FTIs were designed to target Ras isoforms (H-, N- and K-RasA/K-RasB) mutated in large number of cancers and which require farnesylation for inducing uncontrolled cell proliferation [13]. However, it is now demonstrated that Ras is not the unique target of FTIs [14,15]. Several proteins could be putative targets including Rho B which regulates receptor trafficking and whose activation leads to $p21^{waf1/Cip1}$ inactivation and cell cycle progression to S phase [16] and centromeric proteins CENP-E and CENP-F [17]. Rho B exists in both farnesylated and geranylgeranylated forms with geranylgeranylated predominating Rho B, and FTI treatment induces a loss of farnesylated Rho B and a gain of proapoptotic geranylgeranylated Rho B [18]. FTIs also block the farnesylation of CENP-E and CENP-F, which function in the mitotic spindle checkpoint of the cell cycle. Treatment of the cells with FTIs decreases the association of CENP-E with spindle microtubules and disrupts CENP-F localization [19]. In addition, FTI treatment results in failure of mitotic cells to form bipolar spindles and to align chromosomes along the metaphase plate [17]. These effects are likely to contribute to

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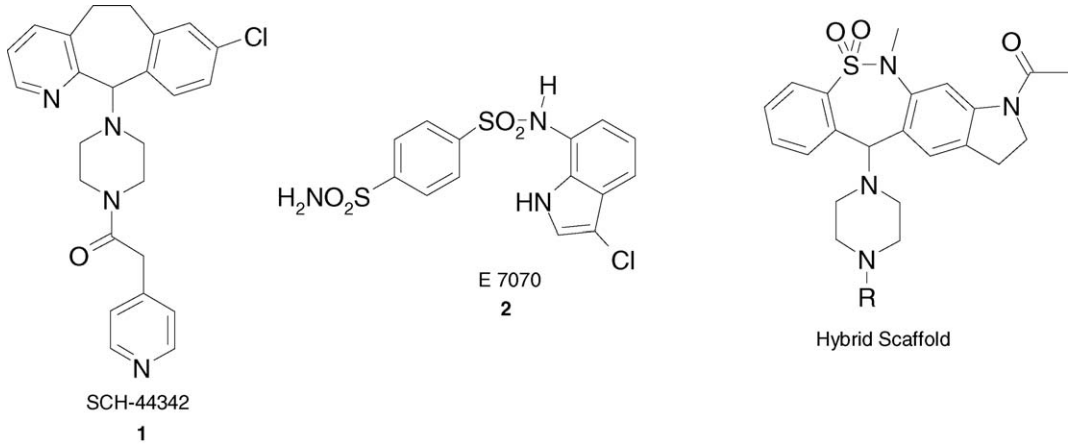

Fig. 1. Structure of SCH-44342, E7070 and hybrid scaffold.

the G2/M arrest observed in FTI treated cells and may contribute to the synergistic antitumor interaction between FTIs and taxanes, anticancer drugs that also target the mitotic apparatus [20]. Other FTI effects on farnesylation of nuclear envelope proteins lamin A and B, nuclear tyrosine phosphatases (PTPCAAX 1, 2 and 3) and cochaperone protein HDJ-2, are likely involved in their antitumor activity [21]. On the other hand, in a recent study, it has been claimed that CDK inhibitors dramatically enhance FTI's induced apoptosis of human cancer cell lines. Thus, it was tempting to design new hybrid molecules able to possess these two sets of properties [22].

Considering SCH-44342, a potent inhibitor of FTase [23] and E7070 [24], a suppressor of the expression of cyclin E and inhibitor of CDK2 and pRb phosphorylations (Fig. 1), we designed tetracyclic new compounds combining structural features of **1** and **2**. Here are reported the synthesis, the antiproliferative effect and the G1 phase study of these compounds against PC3 tumor cell lines.

2. Chemistry

1-Acetyl-5-chlorobenzo[*f*]indolino[6,5,*c*] [1,2]thiazepine **(12)** was prepared as described in Fig. 2. The nitration of **3** was achieved by using a mixture of nitric acid and sulfuric acid (yield 80%) yielding **4** which subsequently formed 1-acetyl-6-nitroindoline by reaction with acetic anhydride (yield 95%) [25]. The reduction of nitro entity in amino was realized by hydrogenation with palladium on activated carbon (yield 95%). The sulfonamide compound was obtained by coupling **6** with methyl 2-chlorosulfonylbenzoate in pyridine (yield 72%) and exposure of **7** to methyl iodide gave *N*methylsulfonamide (yield 70%). Treatment of **8** by potassium hydroxide gave the carboxylic acid (yield 90%) and the cyclization of **9** under Friedel–Crafts conditions with aluminum chloride resulted in the formation of the expected tetracycle **10** (yield 41%).

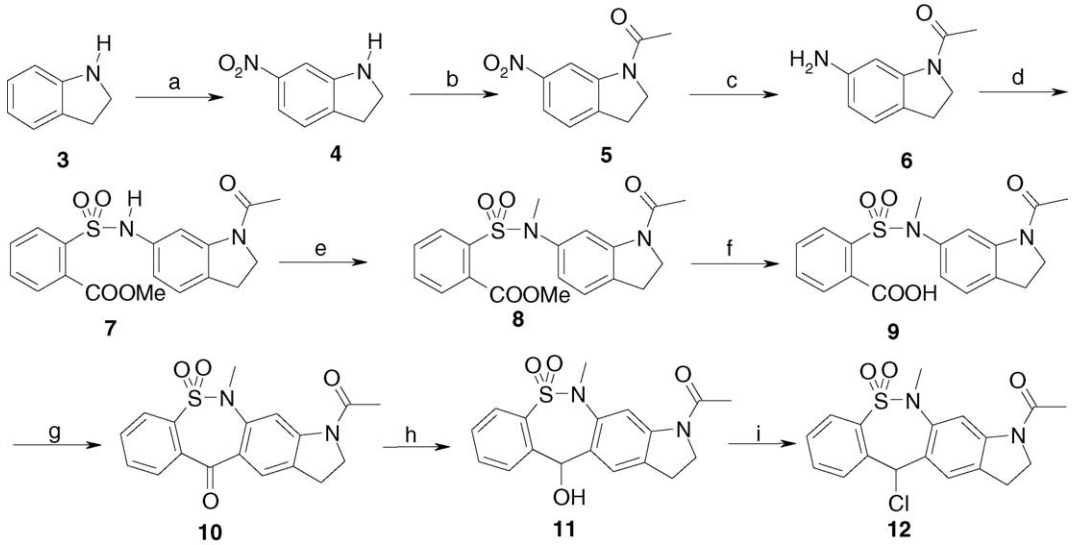

Fig. 2. (a) HNO_3, H_2SO_4, r.t.; (b) Ac_2O, 160 °C; (c) H_2, Pd/C 10%, MeOH, r.t.; (d) methyl 2-chlorosulfonylbenzoate, pyridine, DMF, 65 °C; (e) CH_3I, NaH, DMF, r.t.; (f) KOH, H_2O/EtOH, 100 °C; (g) (1) $SOCl_2$, toluene, 80 °C (2) $AlCl_3$, $CHCl_3$, 60 °C; (h) $NaBH_4$, MeOH/CH_2Cl_2, 50 °C; (i) $SOCl_2$, CH_2Cl_2, r.t.

NMR studies confirmed the structure of these new tetracyclic system. The ketone **10** was reduced by sodium borohydride (yield 65%), then the hydroxylated compound **11** was treated by thionyl chloride to form **12** (yield 74%).

The piperazine derivatives have been prepared by two different methods (Fig. 3). **Method A**: The *N*benzylpiperazine was coupled with commercially acyl chloride using triethylamine to afford *N*-acylpiperazine derivative in good yield. The deprotection was realized by hydrogenation with palladium on activated carbon. **Method B**: The *N*-benzylpiperazine was coupled with commercially acid available using NMM, EDCI, HOBt to afford *N*-acylpiperazine derivative in good yield. The deprotection was achieved by hydrogenation with palladium on activated carbon.

The synthesis of compounds **16a–f** was carried out. The final substitution of C–Cl was achieved by reaction of five equivalents of appropriate amine **14** and **15** with **12** in acetonitrile at 110 °C for 1 h (Fig. 4).

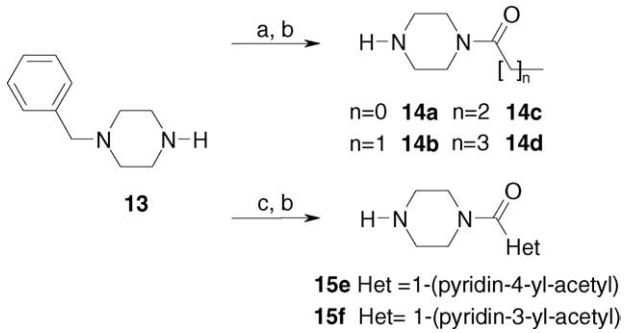

Fig. 3. Method A (a) acyl chloride, Et_3N, CH_2Cl_2, r.t.; (b) H_2, Pd/C 10%, MeOH, r.t.; Method B (c) pyridacetique hydrochloric acid, NMM, HOBt, EDCI, DMF, r.t. (d) H_2, Pd/C 10%, MeOH, r.t.

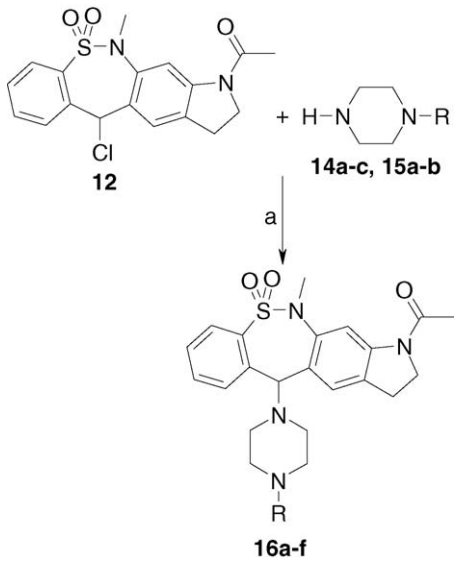

Fig. 4. (a) CH_3CN, 110 °C.

3. Pharmacological studies

3.1. Cell culture and cytotoxicity

Human prostate cancer PC3 cells were maintained in RPMI 1640 culture medium supplemented with 10% FCS. For growth assays, the cells were seeded onto 96-well plates at a density of approximately 3×10^4 cells per well. After 3 days, the cell medium was changed to serum-free medium and the cells were starved for 24 h for culture synchronization. The stimulation of the growth of quiescent cells was then performed by 10 ng/ml EGF plus TSe (50 pg/ml selenium) and the tested compounds were added to culture medium. After an additional 72 h, the cell growth was estimated by the colorimetric MTT test (Table 1).

3.2. Cell cycle and apoptosis

The PC3 cells were grown at a density of about 5×10^5 cells on 25 cm^2 dishes, synchronized during 24 h in serum-free medium and stimulated by EGT–TSe in the presence of different tested agents for 3 days. An analysis by FACS was then performed using the method described in the cell cycle test kit from Becton Dickinson. The propidium iodide-stained cell populations in sub-G1 (corresponding to sub-diploid nuclei), G1, S and G2/M phases were quantified using the Cellquest logiciel program (Table 2).

4. Results and discussion

The aim of this work was to gather on the same scaffold by pharmacophoric elements of reference compounds of SCH-44342 and E7070 in view of designing new heterocyclic compounds able to exhibit interesting cytostatic properties. Two objectives were fixed to qualify these new molecules: (i) they had to present relevant IC_{50} in terms of proliferation inhibition and (ii) their mechanism of action would imply an arrest of cell cycle. The first point is reached

Table 1
Activity of compounds **16a–16f** (1 μM) on PC3 cell proliferation (% inhibition)

Compounds	R	PC3
16a	CH_3	29.6%
16b	CH_3CO	IC_{50} = 0.19 μM
16c	CH_3CH_2CO	IC_{50} = 6.49 μM
16d	$CH_3CH_2CH_2CO$	IC_{50} = 9.85 μM
16e	1-(pyridin-4-yl-acetyl)	43.10%
16f	1-(pyridin-3-yl-acetyl)	37.94%

Table 2
Effects of **16b** on treated PC3 cell cycle

Compounds	Cell populations in cycle phases (%)			
	Sub-G1	G1	S	G2/M
Control	5.41	65.30	9.86	19.69
16b	5.27	74.68	4.68	15.93

since one of the benzoindolinothiazepines **(16b)** inhibits PC3 proliferation with an IC_{50} of 0.19 μM. It is known that PC3 cells responsible of invasive aspects of prostate cancer, are highly resistant to classical therapies and these primary results are very promising. Moreover, a set of structure–activity relationship could be delineated: an alkyl group on piperazinyl ring seems necessary for a reasonable proliferation inhibition and aromatic substituents are not favorable. In addition, it is clear that an amide group on distal piperazinyl N-atom increases the antiproliferative properties. The second point deals with the ability of these compounds to induce accumulation of PC3 cells in G1 phase. Such is the case for **16b** and this result is in accordance with our hypothesis. This hybrid molecule behaves like E7070 and it may be that it also acts on targets of certain FTI since it has been reported that SCH-663365 (SARAMAR), an analog of SCH-44342, is an inhibitor of CENP-E and CENP-F prenylation in A549 lung carcinoma cells lines altering association between CENP-E and microtubules and affecting microtubulecentromere interaction and also is an inhibitor of FTase in H-ras transformed cells to accumulation in G1 phase [20]. The concept of hybrid molecules developed here is also in accordance with the principe of combination of FTI with standard and mitotic agents such as FTI/docetaxel in the treatment of breast cancer and of FTI/paclitaxel in the treatment of prostate cancer [26,27].

5. Experimental protocols

Melting points (m.p.) were determined on a Büchi SMP-540 apparatus. ^{1}H NMR spectra were recorded on an AC 300 P (300 MHz) spectrometer using d_6-DMSO or $CDCl_3$ as solvents. Chemical shifts are expressed downfield from the internal standard, tetramethylsilane. Coupling constants (*J*) are expressed in Hz. Key: t = triplet, s = singlet, d = doublet, dd = double doublet, m = multiplet. Mass spectra were recorded on a Funnigan Mat SSQ710 mass spectrometer. Elemental analyses (C, H, N) were determined by the CNRS Center of Analysis, Vernaison, France, and agreed with proposed structures within 0.4% of the theoretical values.

5.1. N-*acetyl-6-nitroindoline* ***(5)*** *and* N-*acetyl-6-aminoindoline* ***(6)***

Compounds **5** and **6** were prepared according to a procedure already described [25].

5.2. Methyl N-*(1-acetylindolin-6-yl)-2-sulfamoyl benzoate* ***(7)***

Methyl 2-chlorosulfonylbenzoate (7.62 g, 0.033 mol) in DMF was added dropwise to a solution of 1-acetyl-6 aminoindoline **(6)** (6.88 g, 0.039 mol) in DMF and pyridine (3.15 g, 0.039 mol) at room temperature (r.t.). The reaction mixture was stirred at 65 °C for 60 min and then evaporated under reduced pressure. The residue was taken up in water, stirred at r.t. for 1 h and the precipitate formed was filtered. The product was purified by recrystallization from methanol. Yield 72%. **7**: As white crystals, m.p. 165–166 °C (methanol). IR (KBr): ν_{max} = 3230 (NH) and 1350, 1160 (SO_2N) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ = 2.16 (3H, s, CH_3CO), 3.11 (2H, t, J = 8.36 Hz, CH_2), 4.02 (2H, t, J = 8.36 Hz, CH_2), 4.04 (3H, s, $COOCH_3$), 7.05 (2H, m, ArH), 7.55 (2H, m, ArH), 7.86 (3H, m, ArH), 8.10 (1H, m, NH); MS: *m*/*z* (%) = 374 (100).

5.3. Methyl N-*(1-acetylindolin-6-yl)*-N-*methyl-2-sulfamoyl benzoate* ***(8)***

Methyl *N*-(1-acetylindolin-6-yl)-2-sulfamoyl benzoate (**7**) (7.40 g, 0.019 mol) in DMF was added dropwise to a solution of NaH (1.52 g, 0.038 mol) in DMF. The solution was stirred at r.t. while a red color slowly developed. After 3 h, CH_3I diluted in DMF was added dropwise over 10 min and the mixture was stirred for 16 h at r.t. The solution was evaporated under reduced pressure. The residue was taken up in water, stirred at r.t. for 1 h and the precipitate formed was filtered. The product was purified by recrystallization from methanol. Yield 70%. **8**: As white crystals, m.p. 163–164 °C (methanol); IR (KBr): ν_{max} = 1350, 1170 (SO_2N) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si): δ = 2.20 (3H, s, CH_3CO), 3.19 (2H, t, J = 8.47 Hz, CH_2), 3.28 (3H, s, NCH_3), 3.90 (3H, s, $COOCH_3$), 4.11 (2H, t, J = 8.47 Hz, CH_2), 7.05 (1H, m, ArH), 7.15 (1H, d, J = 7.92 Hz, ArH), 7.55 (4H, m, ArH), 7.94 (1H, m, ArH); MS: *m*/*z* (%) = 388 (100).

5.4. N-*(1-acetylindolin-6-yl)*-N-*methyl-2-sulfamoyl benzoic acid* ***(9)***

To Methyl *N*-(1-acetylindolin-6-yl)-*N*-methyl-2-sulfamoyl benzoate (**8**) (5.00 g, 0.013 mol) in ethanol/water (1:1) was added potassium hydroxide (2.16 g, 0.038 mol). The resulting mixture was stirred at 100 °C for 2 h. After cooling, the reaction medium was added to water and acidified with HCl 12 N for pH 1. The precipitate formed was filtered off and recrystallized from MeOH. Yield 90%. **9**: As white crystals, m.p. 228–229 °C (methanol); IR (KBr): ν_{max} = 3420 (OH) and 1350, 1160 (SO_2N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO, Me_4Si): δ = 2.12 (3H, s, CH_3CO), 3.13 (2H, t, J = 8.49 Hz, CH_2), 3.15 (3H, s, NCH_3), 4.11 (2H, t, J = 8.49 Hz, CH_2), 6.77 (1H, m, ArH), 7.18 (1H, m, ArH), 7.38 (1H, m, ArH), 7.57 (2H, m, ArH), 7.69 (1H, m, ArH), 7.92 (1H, m, ArH), 13.50 (1H, m, COOH); MS: *m*/*z* (%) = 374 (100).

5.5. 1-Acetyl-5,11-dihydro-11-methylbenzo[f]indolino[6,5,c][1,2]thiazepin-5-one 10,10-dioxyde ***(10)***

To *N*-(1-acetylindolin-6-yl)-*N*-methyl-2-sulfamoyl benzoic acid (**9**) (2.00 g, 0.005 mol) in toluene was added thionyl chloride (1.11 ml, 0.016 mol). The reaction was refluxed for 1 h. After cooling, the reaction medium was evaporated under

reduced pressure. The resulting mixture was taken up in chloroform. Aluminum chloride was added (2.12 g, 0.016 mol) and refluxed for 1 h. After cooling, the reaction was evaporated under reduced pressure. The resulting mixture was taken up in water and extracted with dichloromethane. The organic layer was washed with NaOH 1 N, water and dried with magnesium sulfate. The precipitate was recrystallized from EtOH. Yield 41%. **10**: m.p. 228–229 °C (ethanol); IR (KBr): ν_{max} = 1650 (CO) and 1320, 1170 (SO_2N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, Me_4Si): δ = 2.31 (3H, s, CH_3CO), 3.28 (2H, t, J = 8.45 Hz, CH_2), 3.31 (3H, s, NCH_3), 4.17 (2H, t, J = 8.45 Hz, CH_2), 7.72 (2H, m, ArH), 7.97 (2H, m, ArH), 8.15 (1H, s, ArH), 8.21 (1H, s, ArH); MS: *m/z* (%) = 356.

5.6. 1-Acetyl-5,11-dihydro-11-methylbenzo[f]indolino [6,5,c] [1,2]thiazepin-5-ol 10,10-dioxyde ***(11)***

To 1-acetyl-5,11-dihydro-11-methylbenzo[*f*]indolino [6,5,*c*] [1,2] thiazepin-5-one 10,10-dioxyde (**10**) (0.80 g, 0.002 mol) in dichloromethane was added sodium borohydride (0.13 g, 0.003 mol). The reaction was refluxed for 2 h. After cooling, water was added dropwise to the reaction and the resulting mixture was filtered. Yield 65%. **11**: m.p. 189–190 °C; IR (KBr): ν_{max} = 1650 (CO) and 1320, 1160 (SO_2N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, Me_4Si): δ = 2.13 (3H, s, CH_3CO), 3.13 (2H, t, J = 8.45 Hz, CH_2), 3.37 (3H, s, NCH_3), 4.10 (2H, t, J = 8.45 Hz, CH_2), 6.20 (1H, s, ArH), 6.51 (1H, m, OH), 7.41 (1H, s, ArH), 7.48 (1H, m, ArH), 7.61 (1H, m, ArH), 7.80 (2H, m, ArH), 8.15 (1H, s, ArH); MS: *m/z* (%) = 358.

5.7. 1-Acetyl-5-chloro-5,11-dihydro-11-methylbenzo[f]-indolino[6,5,c] [1,2]thiazepine 10,10-dioxyde ***(12)***

1-Acetyl-5,11-dihydro-11-methylbenzo[*f*]indolino[6,5,*c*] [1,2]thiazepin-5-ol 10,10-dioxyde (**11**) (0.41 g, 0.001 mol) in dichloromethane was added thionyl chloride (0.12 ml, 0.002 mol). The reaction was stirred overnight. The resulting mixture was filtered. Yield 74%. **12**: m.p. 112–113 °C; IR (KBr): ν_{max} = 1670 (CO) and 1350, 1160 (SO_2N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, Me_4Si): δ = 2.16 (3H, s, CH_3CO), 3.10 (2H, t, J = 8.45 Hz, CH_2), 3.34 (3H, s, NCH_3), 4.10 (2H, t, J = 8.45 Hz, CH_2), 6.20 (1H, s, ArH), 7.41 (1H, s, ArH), 7.48 (1H, m, ArH), 7.62 (1H, m, ArH), 7.80 (2H, m, ArH), 8.10 (1H, s, ArH); MS: *m/z* (%) = 376.

*5.8. Method A: General procedure for the preparation of 1-acylpiperazines (****14b–14d****)*

To *N*-benzylpiperazine (**13**) (2.00 g, 0.011 mol) in dichloromethane was added triethylamine (0.95 ml, 0.011 mol) and dropwise acylchloride (0.017 mol). The reaction was strirred overnight and was evaporated under reduced pressure. The resulting mixture was taken up in water and extracted with ethyl ether. The organic layer was dried with magnesium sulfate.

*5.9. Method B: General procedure for the preparation of 1-acylpiperazines (****15e–15f****)*

To *N*-benzylpiperazine (**13**) (0.50 g, 0.002 mol) in dimethylformamide was added *N*-methylmorpholine (1.87 g, 0.017 mol), 1-hydroxybenzotriazole (0.38 g, 0.002 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbo diimide (0.81 g, 0.004 mol) and pyridylacetic acid hydrochloride (0.56 g, 0.003 mol). The reaction was stirred for 2 days and was evaporated under reduced pressure. The resulting mixture was taken up in dichloromethane and washed with potassium hydrogencarbonate solution and water. The organic layer was dried with magnesium sulfate. The white oil was used for further purification in the next step.

*5.10. General procedure for the preparation of 1-acetyl5-(1-acylpiperazine)-5,11-dihydro-11-methylbenzo[f]indolino[6,5,c] [1,2]thiazepine 10,10-dioxyde (****16a–16f****)*

To 1-Acetyl-5-chloro-5,11-dihydro-11-methylbenzo[*f*] indolino[6,5,*c*] [1,2]thiazepine 10,10-dioxyde (**12**) (0.0002 mol) in acetonitrile was added l-acylpiperazine (0.001 mol). The reaction was stirred for 1 h and was evaporated under reduced pressure. The resulting mixture was taken up in water and extracted with dichlromethane. The organic layer was washed with NaOH 1 N and dried with magnesium sulfate. The precipitate was recrystallized from EtOH.

5.10.1. 1-Acetyl-5-(1-methylpiperazine)-5,11-dihydro-11-methylbenzo[f]indolino[6,5,c] [1,2]thiazepine 10,10-dioxyde ***(16a)***

Yield 55%. M.p. 154–155 °C; ^1H NMR (300 MHz), 2.00 (3H, s), 2.20 (7H, m), 3.25 (5H, m), 3.55 (3H, s), 3.69 (1H, m), 4.08 (3H, m), 7.08 (1H, s), 7.30 (1H, dd), 7.44 (2H, m), 7.99 (1H, dd), 8.32 (1H, s); IR (KBr): 2980, 1670, 1580, 1340 cm^{-1}; Anal. ($C_{23}H_{28}N_4O_3S$).

5.10.2. 1-Acetyl-5-(1-acetylpiperazine)-5,11-dihydro-11-methylbenzo[f]indolino[6,5,c] [1,2]thiazepine 10,10-dioxyde ***(16b)***

Yield 70%. M.p. 163–164 °C; ^1H NMR (300 MHz), 2.00 (3H, s), 2.20 (7H, m), 3.25 (5H, m), 3.55 (3H, s), 3.69 (1H, m), 4.08 (3H, m), 7.08 (1H, s), 7.30 (1H, dd), 7.44 (2H, m), 7.99 (1H, dd), 8.32 (1H, s); IR (KBr): 2940, 1680, 1580, 1330 cm^{-1}; Anal. ($C_{24}H_{28}N_4O_4S$).

5.10.3. 1-Acetyl-5-(1-propionylpiperazine)-5,11-dihydro11-methylbenzo[f]indolino[6,5,c] [1,2]thiazepine 10,10-dioxyde ***(16c)***

Yield 71%. M.p. 182–183 °C; ^1H NMR (300 MHz), 1.12 (3H, m), 2.26 (9H, s), 3.25 (5H, m), 3.52 (3H, s), 3.70 (1H, m), 4.09 (3H, m), 7.07 (1H, s), 7.29 (1H, m), 7.46 (2H, m), 7.99 (1H, dd), 8.32 (1H, s); IR (KBr): 2950, 1680, 1580, 1330 cm^{-1}; Anal. ($C_{25}H_{30}N_4O_4S$).

*5.10.4. 1-Acetyl-5-(1-butyrylpiperazine)-5,11-dihydro-11-methylbenzo[f]indolino[6,5,c] [1,2]thiazepine 10,10-dioxyde **(16d)***

Yield 68%. M.p. 178–179 °C; ^{1}H NMR (300 MHz), 0.96 (3H, m), 1.63 (2H, m), 2.23 (9H, m), 3.25 (5H, m), 3.54 (3H, s), 3.73 (1H, m), 4.09 (3H, m), 7.07 (1H, s), 7.28 (1H, m), 7.46 (2H, m), 7.99 (1H, m), 8.32 (1H, s); IR (KBr): 2940, 1680, 1580, 1330 cm^{-1}; Anal. ($C_{26}H_{32}N_4O_4S$).

*5.10.5. 1-Acetyl-5-(1-(pyridin-4-yl-acetyl)piperazine)5,11-dihydro-11-methylbenzo[f]indolino[6,5,c] [1,2]thiazepine 10,10-dioxyde **(16e)***

Yield 55%. M.p. 182–183 °C; ^{1}H NMR (300 MHz), 2.20 (7H, m), 3.12 (3H, m), 3.40 (6H, m), 3.70 (3H, s), 4.13 (2H, m), 4.33 (1H, s), 7.20 (2H, m), 7.28 (2H, m), 7.56 (3H, m), 7.82 (1H, dd), 8.06 (1H, s), 8.47 (2H, d); IR (KBr): 2980, 1670, 1580, 1340 cm^{-1}; Anal. ($C_{29}H_{31}N_5O_4S$).

*5.10.6. 1-Acetyl-5-(1-(pyridin-3-yl-acetyl)piperazine)5,11-dihydro-11-methylbenzo[f]indolino[6,5,c] [1,2]thiazepine 10,10-dioxyde **(16f)***

Yield 57%. M.p. 176–177 °C; ^{1}H NMR (300 MHz), 2.20 (7H, m), 3.11 (3H, m), 3.37 (6H, m), 3.70 (3H, s), 4.13 (2H, m), 4.33 (1H, s), 7.20 (2H, m), 7.28 (2H, m), 7.56 (3H, m), 7.82 (1H, dd), 8.06 (1H, s), 8.47 (2H, d); IR (KBr): 2980, 1670, 1580, 1340 cm^{-1}; Anal. ($C_{29}H_{31}N_5O_4S$).

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References

[1] J. Downward, Nature 411 (2001) 759–762.
[2] D. Hanahan, A. Weinberg, Cell 100 (2000) 57–70.
[3] G.I. Evan, K.H. Vousden, Nature 411 (2001) 342–348.
[4] T.M. Sielecki, J.F. Boylan, P.A. Benfield, G.L.J. Trainor, Med. Chem. 43 (2000) 1–18.
[5] C.J. Der, A.D. Cox, Cancer Cells 3 (1991) 331–340.
[6] D.O. Morgan, Nature 374 (1995) 131–134.
[7] T. Evans, E.T. Rosenthal, J. Youngblom, D. Distel, T. Hunt, Cell 33 (1983) 389–396.
[8] T. Wolfel, M. Hauer, J. Schneider, M. Serrano, C. Wolfel, E. Klehmann-Hieb, et al., Science 269 (1995) 1281–1284.
[9] R.T. Abraham, M. Acquarone, A. Andersen, A. Asensi, R. Belle, F. Berger, et al., Biol. Cell. 83 (1995) 105–120.
[10] L. Meijer, A. Borgne, O. Mulner, J.P. Chong, J.J. Blow, N. Inagaki, et al., Eur. J. Biochem. 243 (1997) 527–536.
[11] D.S. Schrump, W. Matthews, G.A. Chen, A. Mixon, N.K. Altorki, Clin. Cancer Res. 4 (1998) 2885–2890.
[12] D.F. Jarrard, J. Modder, P. Fadden, V. Fu, L. Sebree, D. Heisey, S.R. Schwarze, A. Friedl, Cancer Lett. 185 (2002) 191–199.
[13] K. Kato, A.D. Cox, M.M. Hisaka, S.M. Graham, J.E. Buss, C.J. Der, Proc. Natl. Acad. Sci. USA 89 (1992) 6403–6407.
[14] L. Sepp-Lorenzino, Z. Ma, E. Rands, N.E. Kohl, J.B. Gibbs, A. Oliff, et al., Cancer Res. 55 (1995) 5302–5309.
[15] T. Nagasu, K. Yoshimatsu, C. Rowell, M.D. Lewis, A.M. Garcia, Cancer Res. 55 (1995) 5310–5314.
[16] M.F. Olson, H.F. Paterson, C.J. Marshall, Nature 394 (1998) 295–299.
[17] N.C. Crespo, J. Ohkanda, T.J. Yen, A.D. Hamilton, S.M. Sebti, J. Biol. Chem. 276 (2001) 16161–16167.
[18] W. Du, G.C. Prendergast, Cancer Res. 59 (1999) 5492–5496.
[19] D. Hussein, S.S. Taylor, J. Cell Sci. 115 (2002) 3403–3414.
[20] H.R. Ashar, L. James, K. Gray, D. Carr, S. Black, L. Armstrong, et al., J. Biol. Chem. 275 (2000) 30451–30457.
[21] A.A. Adjei, J.N. Davis, C. Erlichman, P.A. Svingen, S.H. Kaufmann, Clin. Cancer Res. 6 (2000) 2318–2325.
[22] H. Edamatsu, C.L. Gau, T. Nemoto, L. Guo, F. Tamanoi, Oncogene 19 (2000) 3059–3068.
[23] C.L. Strickland, P.C. Weber, W.T. Windsor, Z. Wu, H.V. Le, M.M. Albanese, et al., J. Med. Chem. 42 (1999) 2125–2135.
[24] T. Owa, H. Yoshino, T. Okauchi, K. Yoshimatsu, Y. Ozawa, N.H. Sugi, et al., J. Med. Chem. 42 (1999) 3789–3799.
[25] A.P. Terent'ev, E.V. Vinogradova, V.P. Chetverikov, V.S. Lenenko, Chem. Heterocycl. Compound 5 (1969) 196–198.
[26] A.D. Cox, C.J. Der, Curr. Opin. Pharmacol. 2 (2002) 388–393.
[27] P. Haluska, G.K. Dy, A.A. Adjei, Eur. J. Cancer 38 (2002) 1685–1700.