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Synthesis and biological evaluation of new derivatives of tricyclic heteroaromatic carboxamides as potential topoisomerase I inhibitors

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Summary. A series of new N-functionalized amide derivatives of phenazine-1- and acridone-4-carboxylic acids were synthesized and tested *in vitro* as potential topoisomerase I inhibitors. Their tricyclic heteroaromatic cores with intercalative properties contained carboxamide functions modified with pyridyl and N,N-dimethylamino groups attached via short linkers. These basic substituents are able to be protonated in water and thus could provide additional binding interactions of ligands with DNA and/or topoisomerase complex enhancing the inhibitory activity of compounds. Pyridyl-modified derivatives of both heterocycles were found to inhibit topoisomerase *in vitro* at 100 μM concentration, in contrast to non-modified carboxamides which are inactive against the enzyme.

Keywords: topoisomerase I, inhibitors, acridone, phenazine, carboxamides.

Introduction. Topoisomerases are enzymes catalyzing changes in the topological state of DNA, i.e. the relaxation of supercoiled DNA. Enzymes of this family resolve torsional strains imposed on the double helix during DNA replication. They induce transient breaks in one (topoisomerase I) or two (topoisomerase II) DNA strands to allow the strands to pass through each other via the formed gap thus relaxing the DNA. Then cleaved DNA is religated by the enzyme to restore the normal DNA structure [1, 2].

Topoisomerases are involved in many cellular processes, including replication, transcription, recombination and DNA repair. Thus they are currently considered important biological targets for the design of novel drugs. Inhibitors of these enzymes, in particular topoisomerase I (TopoI), often exhibit antibacterial [3, 4] or anticancer [3, 5, 6] activity. The inhibitory effect of small molecules is usually associated with their binding to DNA (via intercalative or minor groove interactions) or DNA-enzyme complex [3, 6-9]. Topoisomerase inhibitors are almost exclusively based on polycyclic heteroaromatic scaffolds. Among them, numerous acridine [10-14] and phenazine [15-18] derivatives were reported as anticancer and antimicrobial agents targeting topoisomerase I.

Tricyclic carboxamides containing N-alkyl and N-aryl substituents are widely used in the search for antitumor, antibacterial and antiviral drugs [10, 11, 15-17, 19-21]. In general, biological effect of polycyclic heteroaromatic compounds depends on their ability to interact with DNA, RNA or enzymatic complexes participating in biosynthesis and metabolism of nucleic acids, including the topoisomerase complex [9, 10, 12, 13, 21]. Important factors influencing the biological activity are the nature of amide substituent and position of carboxamide group in the core molecule [11, 16, 17]. For example, 2- and

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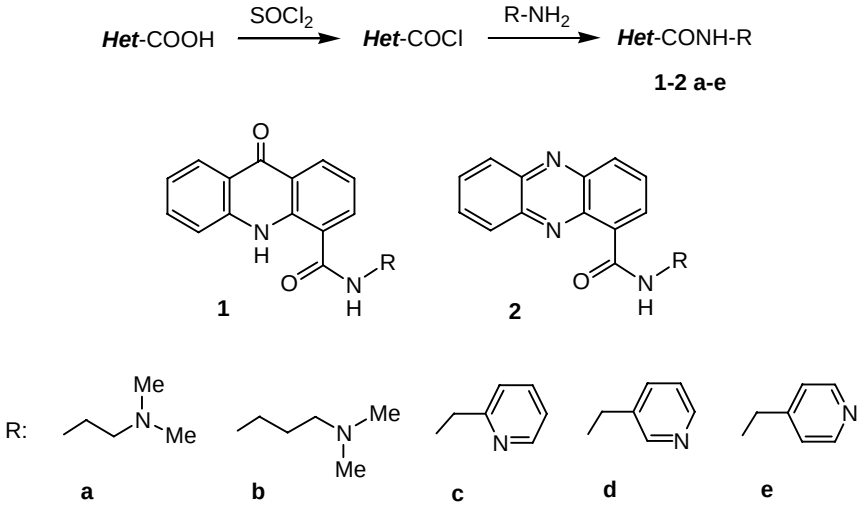
Scheme 1

Synthesis of tricyclic N-functionalized carboxamides. ***Het*** *— heterocycle*



3-carboxamides of acridone were inactive against herpes virus, in contrast to 4-substituted analogs inhibiting topoisomerase [11].

We have found potent antibacterial agents among N-aryl(hetaryl)-substituted amides of phenazine-1-carboxylic acid, including the derivatives active against drug-resistant *Mycobacterium tuberculosis* strains [22, 23]. Biological screening of a series of N-arylamides of acridone-4-carboxylic acid allowed us to identify compounds active against hepatitis C virus infection inhibiting transcription and RNA replication [24]. N-pyridyl derivatives of acridone carboxamides were found to inhibit NS3 helicase [24, 25].

In this work we have significantly extended the range of N-substituted acridone and phenazine carboxamides as potential inhibitors of topoisomerase I (and possibly other enzymes of nucleic acid biosynthesis).

Results and discussion. A series of carboxamide derivatives of acridone and its close structural analog phenazine were synthesized (Scheme 1). Their amide groups were functionalized with N,N-dimethylamino and pyridyl fragments attached via the alkyl linkers of various lengths (C1-C3). The introduced functions are basic and thus can be protonated in water under physiological conditions to form cationic moieties. Structure design was based on the fact that the tricyclic heteroaromatic systems of phenazine and acridine are known to efficiently interact with DNA by intercalation mechanism [9, 26]; the attachment of basic/cationic substituents could enhance the binding of ligands to topoisomerase complex by additional interactions with either anionic DNA phosphates or acidic groups within the enzyme molecule. At the same time, the aromatic pyridyl residues could also interact with topoisomerase complex via hydrophobic mechanism further enhancing the binding of ligands to their target. Free core heterocycles, i.e. acridone and phenazine, as well as their non-substituted carboxamides, are inactive against TopoI, and additional binding interactions provided by the introduced functional groups were expected to increase the inhibitory potential of tricyclic carboxamides.

The set of structures contained N,N-dimethylaminoethyl- and -propyl groups and all isomeric pyridylmethyl fragments. Several carboxamides of this series were reported previously, e.g. acridone derivatives **1a** and **1d** [24]; phenazine carboxamides **2a-b** were described by Rewcastle *et al.* [28], although no synthetic details and NMR data were presented (melting points were provided for hydrochlorides). Heterocyclic carboxamides containing —$NHCH_2CH_2NMe_2$ pharmacophore residue were extensively studied since N-[2-(dimethylamino)ethyl]carboxamide derivatives of phenazine [28], acridine [20, 29] and 9-aminoacridine [19] were identified as efficient antitumor agents. However, we have covered a broader spectrum of substituents including pyridyl residues to get a library of com-

pounds allowing the analysis of structure-activity relationship among the amides of two tricyclic systems, phenazine-1-carboxylic and acridone-4-carboxylic acids (PCA and ACA, respectively), functionalized with aliphatic and aromatic basic groups.

The synthesis of N-substituted carboxamides of nitrogen-containing heterocycles was based on our previous approach developed for phenazine [23] and acridone [24] derivatives. However, synthesis and purification protocols were optimized to provide better reaction yields. Target products were obtained by the reaction of chloroanhydrides of acridone-4- and phenazine-1-carboxylic acids with corresponding amino components resulting in the formation of amides **1-2a-e** (Scheme 1). Starting ACA and PCA were synthesized according to previously reported protocols [24, 27, 28].

The one-pot process consisting of the formation of acid chloroanhydride followed by its reaction with amine is technologically convenient preparative way to a variety of N-functionalized heterocyclic carboxamides.

The yields of acridone derivatives after crystallization were in the range 43-70 %, except for compound **1b** which was obtained in 28 % yield. The isolated yields of phenazine analogs were generally in the same range, although their purification was more difficult and additional chromatographic step was sometimes necessary.

All synthesized carboxamide derivatives are yellow crystalline solids with limited solubility in alcohols and most other organic solvents.

To evaluate the inhibiting activity of carboxamides, they were tested in the *in vitro* system of relaxation of supercoiled plasmid DNA by topoisomerase I from *E. coli*. During the enzymatic reaction supercoiled DNA is transformed into the relaxed form which is well separated from the initial DNA in agarose gel electrophoresis. The inhibitory effect of a compound is reflected in the decrease of the amount of DNA relaxation products, as compared to the control reaction performed without inhibitors (where fully relaxed DNA is formed), and in the appearance of partially relaxed DNA or even its initial form.

Phenazine and acridone derivatives containing aromatic pyridyl fragments were found to partially inhibit the enzyme at 100 μM concentration, whereas their analogs with aliphatic basic substituents at carboxamide fragment (**1,2 a-b**) were less efficient under these conditions. Non-modified carboxamides, i.e. heterocycles with $CONH_2$ function, were inactive against topoisomerase I.

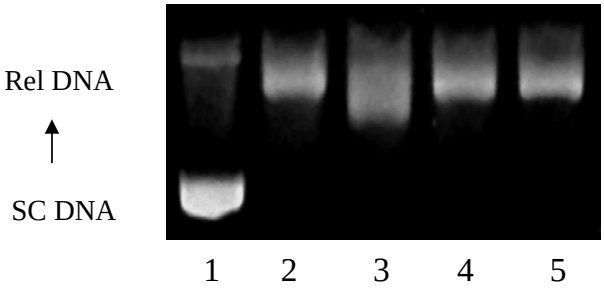


Fig. 1. Agarose gel electrophoresis of in vitro topoisomerase reaction products. Lane 1 — supercoiled plasmid pBR322, lane 2 — control reaction (plasmid + TopoI), lanes 3-5 — reaction of DNA with TopoI in the presence of compound ***2d*** *at concentration 100, 50 and 25 μM, respectively. Gel was stained with ethidium bromide. SC DNA — supercoiled plasmid DNA, Rel DNA — fully relaxed DNA.*

The effect of *o*-pyridylmethyl phenazine derivative **2d** on topoisomerase activity is shown in representative Fig. 1. The supercoiled plasmid (the lowest band in the gel) is relaxed by topoisomerase I to form a relaxed DNA (upper band). The inhibitor decreases the relative amount of the latter and causes the formation of new bands in the gel (which typically appear as a ladder or a smear) below the band of fully relaxed DNA.

Thus, the introduction of basic pyridyl substituents, significantly increased the inhibitory activity of carboxamides, and we expect that the modification of core heterocycles will allow obtaining more efficient enzyme inhibitors.

Full details of the study of biological activity of N-functionalized acridone and phenazine carboxamides as topoisomerase I inhibitors and their antiproliferative properties associated with Topo inhibition will be published in a separate communication.

Conclusion. We have developed convenient one-pot synthetic protocols allowing the preparation of a range of N-functionalized derivatives of tricyclic carboxamides. A library of compounds based on two fused heteroaromatic systems containing aliphatic and aromatic basic groups was obtained and characterized. Prelimi-

nary data on biological activity of synthesized compounds demonstrated that pyridyl-functionalized phenazine and acridone carboxamides are promising structural scaffolds for the design of topoisomerase I inhibitors.

Experimental part. Chemical reagents and solvents were from UkrOrgSynthez (Ukraine), Fluka (Switzerland) and Acros Organics (Belgium). The solvents were purified and dried by standard methods. Agarose for electrophoresis, ethidium bromide, sodium salt of ethylenediamine tetraacetic acid (EDTA) and sodium dodecylsulfate (SDS) were purchased from Sigma (USA), topoisomerase I from *E. coli* and bovine serum albumin were obtained from New England BioLabs (USA), pBR322 plasmid DNA was from Fermentas (Lithuania). Thin-layer chromatography (TLC) was performed on Silica gel $60F_{254}$ plates (Merck, Germany) in solvent systems $CHCl_3$/MeOH 9:1 (A) and $CHCl_3$/HOAc/acetone 10:0.125:0.125 (B). ^{1}H NMR spectra were recorded on a Mercury-400 spectrometer (400 MHz, Varian, USA) in DMSO-d_6 with tetramethylsilane as an internal standard; chemical shifts are given in ppm. Melting points were determined using a Boethius PNMK 05 apparatus (Nagema, Germany). ACA and PCA were obtained by established synthetic methods ([27] and [28], respectively).

*9-Oxo-9,10-dihydroacridine-4-carboxylic acid (2-dimethylaminoethyl)-amide (**1a**).* ACA (1.0 mmol, 239 mg) was suspended in dry toluene (8 ml). Thionyl chloride (1.4 mmol, 0.1 ml) and dry pyridine (1.4 mmol, 0.12 ml) were added with stirring and the mixture was kept at room temperature for 3 h. N,N-dimethylethylene diamine and triethylamine (2.5 mmol each) were then added to a yellow suspension and stirring was continued until the reaction was complete (TLC control in system A). The mixture was evaporated *in vacuo* and the residue was treated with chloroform (25 ml) and washed with saturated aq. $NaHCO_3$ (3x5 ml). Organic layer was dried over Na_2SO_4 and evaporated to dryness.

The residue was crystallized from acetonitrile. Yield 134 mg (43 %), mp 171-172 ˚C. ^{1}H NMR: δ 12.61 (br.s, 1H, NH), 8.83 (br.s, 1H, CONH), 8.44 (d, 1H, J=8.4 Hz, H-Ar), 8.25-8.20 (m, 2H, H-Ar), 7.75-7.68 (m, 1H, H-Ar), 7.60-7.57 (m, 1H, H-Ar), 7.28-7.22 (m, 2H, H-Ar), 3.47 (m, 2H, NHCH_2), 2.55 (t+DMSO, CH_2N), 2.27 (s, 6H, NMe_2).

Compounds **1b-e** were synthesized by the above general protocol.

*9-Oxo-9,10-dihydroacridine-4-carboxylic acid (3-dimethylaminopropyl)-amide (**1b**).* Yield 28 %, mp 158-163 ˚C (heptane/ethanol). ^{1}H NMR: δ 12.50 (br.s, 1H, NH), 9.07 (br.t, 1H, CONH), 8.45 (d, 1H, J=8.0 Hz, H-Ar), 8.26-8.20 (m, 2H, H-Ar), 7.75 (m, 2H, H-Ar), 7.36-7.30 (m, 2H, H-Ar), 3.41 (m, 2H, NHCH_2), 2.34 (t, 2H, J=6.8 Hz, CH_2N), 2.15 (s, 6H, NMe_2), 1.75 (m, 2H, CH_2).

*9-Oxo-9,10-dihydroacridine-4-carboxylic acid (pyridin-2-ylmethyl)-amide (**1c**).* Yield 54 %, mp 219-223 ˚C (*i*-PrOH/EtOH) (lit. 211-214 ˚C [24]). ^{1}H NMR: δ 12.63 (s, 1H, NH), 9.52 (br.t, 1H, CONH), 8.52 (d, 1H, J=4.0 Hz, H-Ar), 8.47 (d, 1H, J=8.0 Hz, H-Ar), 8.38 (d, 1H, J=7.2 Hz, H-Ar), 8.23 (d, 1H, J=7.6 Hz, H-Ar), 7.76-7.58 (m, 3H, H-Ar), 7.41 (d, 1H, J=8.0 Hz, H-Ar), 7.33-7.22 (m, 3H, H-Ar), 4.68 (d, 2H, J=5.6 Hz, CH_2).

*9-Oxo-9,10-dihydroacridine-4-carboxylic acid (pyridin-3-ylmethyl)-amide (**1d**).* Yield 48 %, mp 255-259 ˚C (*i*-PrOH/EtOH). 1H NMR: δ 12.61 (s, 1H, NH), 9.52 (br.t, 1H, CONH), 8.60 (s, 1H, H-Ar), 8.45 (m, 2H, H-Ar), 8.31 (d, 1H, J=7.2 Hz, H-Ar), 8.23 (d, 1H, J=7.6 Hz, H-Ar), 7.79 (d, 1H, J=8.0 Hz, H-Ar), 7.67 (m, 1H, H-Ar), 7.60-7.58 (m, 1H, H-Ar), 7.34-7.25 (m, 3H, H-Ar), 4.60 (d, 2H, J=5.6 Hz, CH_2).

*9-Oxo-9,10-dihydroacridine-4-carboxylic acid (pyridin-4-ylmethyl)-amide (**1e**).* Yield 70 %, mp 245-248 ˚C (*i*-PrOH/EtOH). ^{1}H NMR: δ 12.38 (s, 1H, NH), 9.65 (br.s, 1H, CONH), 8.54-8.22 (m, 5H, H-Ar), 7.74 (s, 2H, H-Ar), 7.45-7.25 (m, 4H, H-Ar), 4.62 (s, 2H, CH_2).

*Phenazine-1-carboxylic acid (2-dimethylaminoethyl)-amide (**2a**).* To a suspension of 260 mg (1.16 mmol) of PCA in 3 ml of dry toluene were added thionyl chloride (1.5 mmol) and dry pyridine (1.5 mmol), and the mixture was stirred at room temperature for 3 h. Then N,N-dimethylaminoethylene diamine and triethylamine (1.8 mmol each) were added and the reaction mixture was left overnight. Solvent was removed under reduced pressure, and the residue was treated with chloroform and aq. $NaHCO_3$. Organic phase was washed with water, dried over Na_2SO_4 and concentrated. The precipitate was purified by silica gel flash chromatography

(eluent $CHC1_3$ + 1 % TEA) and crystallized from acetonitrile. Yield 81 mg (24 %), mp 137-139 °C. ^{1}H NMR: δ 10.85 (br.s, 1H, CONH), 8.73 (d, 1H, J=7.2 Hz, H-Ar), 8.39 (d, 1H, J=8.4 Hz, H-Ar), 8.30-8.22 (m, 2H, H-Ar), 8.10-8.0 (m, 3H, H-Ar), 3.60 (q, 2H, J=5.2 Hz, $NHCH_2$), 2.59 (t, 2H, J=6.0 Hz, CH_2N), 2.35 (s, 6H, NMe_2).

This general protocol was used for the synthesis of compounds **2b-e**.

*Phenazine-1-carboxylic acid (3-dimethylaminopropyl)-amide (**2b**).* Yield 46 %, mp 55-58 °C (heptane). ^{1}H NMR: δ 10.31 (br.t, 1H, CONH), 8.63 (d, 1H, J=6.8 Hz, H-Ar), 8.42-8.28 (m, 3H, H-Ar), 8.08-8.03 (m, 3H, H-Ar), 3.54 (m, 2H, $NHCH_2$), 2.41 (t, 2H, J=7.2 Hz, CH_2N), 2.17 (s, 6H, NMe_2), 1.83 (m, 2H, CH_2).

*Phenazine-1-carboxylic acid (pyridin-2-ylmethyl)-amide (**2c**).* Yield 54 %, mp 157-160 °C (acetonitrile). ^{1}H NMR: δ 11.33 (t, 1H, J=5.2 Hz, CONH), 8.71 (m, 2H, H-Ar), 8.40 (t, 2H, J=8.8 Hz, H-Ar), 8.28 (d, 1H, J=8.0 Hz, H-Ar), 8.09-8.04 (m, 3H, H-Ar), 7.88-7.83 (m, 1H, H-Ar), 7.62 (d, 1H, J=7.6 Hz, H-Ar), 7.38-7.34 (m, 1H, H-Ar); 4.87 (d, 2H, J=5.2 Hz, CH_2).

*Phenazine-1-carboxylic acid (pyridin-3-ylmethyl)-amide (**2d**).* Yield 51 %, mp 158-160 °C (acetonitrile). ^{1}H NMR: δ 10.60 (t, 1H, J=6.0 Hz, CONH), 8.80 (s, 1H, H-Ar), 8.58 (d, 1H, J=7.0 Hz, H-Ar), 8.51 (d, 1H, J=4.8 Hz, H-Ar), 8.44-8.35 (m, 2H, H-Ar), 8.29 (m, 1H, H-Ar), 8.08-8.02 (m, 3H, H-Ar), 7.96 (d, 1H, J=8.0 Hz, H-Ar), 7.45-7.42 (m, 1H, H-Ar), 4.79 (d, 2H, J=6.0 Hz, CH_2).

*Phenazine-1-carboxylic acid (pyridin-4-ylmethyl)-amide (**2e**).* Yield 33 %, mp 182-186 °C (acetonitrile). ^{1}H NMR: δ 10.63 (br.s, 1H, CONH); 8.63-8.56 (m, 3H, H-Ar); 8.46-8.40 (m, 2H, H-Ar); 8.32-8.29 (m, 1H, H-Ar), 8.15-8.03 (m, 3H, H-Ar), 7.55 (m, 2H, H-Ar), 4.79 (d, 2H, J=4.8 Hz, CH_2).

DNA relaxation assay was based on the protocol described in [30]. The 20 μl assay mixture contained Tris-acetate (20 mM, pH 7.9), potassium acetate (50 mM), magnesium acetate (10 mM), dithiothreitol (1 mM), bovine serum albumin (100 μg/ml), pBR322 plasmid DNA (0.5 μg) and tested compound at certain concentration (25-100 μM). The reaction was started by the addition of TopoI (1 unit) and the mixture was incubated at 37 °C for 30 min. The reaction was stopped by adding 6x loading buffer (60 % glycerol, 1 % SDS, 0.03 % bromophenol blue, 100 mM EDTA, pH 7.6), and the mixture was kept at 65 °C for 10 min. It was chilled in ice and analyzed by electrophoresis in 1 % agarose gel. The gel was stained with ethidium bromide and photographed with FujiFilm FinePix S5600 digital camera under UV transillumination. Two independent experiments were carried out for each compound.

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Синтез і біологічна оцінка нових похідних трициклічних гетероароматичних карбоксамідів як потенційних інгібіторів топоізомерази I

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Резюме. Синтезовано й досліджено *in vitro* серію нових N-функціоналізованих амідних похідних феназин-1- та акридон-4-карбонової кислот як потенційних інгібіторів топоізомерази I. Їхні трициклічні гетероароматичні ядра з інтеркаляційними властивостями містять карбоксамідні функції, модифіковані піридильними та N,N-диметиламіногрупами, приєднаними через короткі лінкери. Ці основні замісники здатні протонуватись у воді й, таким чином, можуть забезпечити додаткові взаємодії при зв'язуванні лігандів з ДНК і/або топоізомеразним комплексом із метою підвищення інгібувальної активності сполук. Встановлено, що піридил-модифіковані похідні обох гетероциклів інгібують топоізомеразу *in vitro* в концентрації 100 мкМ, на відміну від немодифікованих карбоксамідів, неактивних щодо фермента.

Ключові слова: топоізомераза I, інгібітори, акридон, феназин, карбоксаміди.

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