Posters

Antibiotics/Antibacterials

P1

Structure-lipophilicity relationships in series of phenolic moiety ring-substituted pyrazinecarboxanilides

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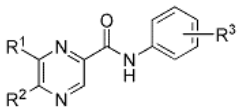
One of the major prerequisites for pharmacological screening and drug development is the prediction of absorption, e.g. the transport of a molecule through cellular membranes. The drugs cross biological barriers most frequently through passive transport, which strongly depends on their lipophilicity. Therefore hydrophobicity is one of the most important physical properties of biologically active compounds.

Various ring-substituted pyrazinecarboxamides have been prepared and evaluated as potential antimycobacterial and antifungal agents. Their herbicidal effects have been reported as well. Twenty-eight anilides of pyrazine-2-carboxylic acid substituted with phenolic moiety in anilide part of the molecule [1-3] were analysed using the RP-HPLC method for the lipophilicity measurement. The procedure was performed under isocratic conditions with methanol as an organic modifier in the mobile phase using end-capped non-polar C18 stationary RP column.



R^1 = H, Cl
R^2 = H, *tert*-Butyl
R^3 = H, 2-OH, 3-OH, 4-OH
2-OH-5-Cl, 2-OH-5-Br, 4-OH-3,5-Br

In the present study the correlation between RP-HPLC retention parameter log *K* (the logarithm of capacity factor *K*) and log *P* data calculated in various ways is discussed as well as the relationships between the lipophilicity and the chemical structure of the studied compounds.

The study was supported by the Ministry of Health of the Czech Republic: IGA 1A/8238-3.

[1] Dolezal M., Hartl J., Miletin M. Antimycobacterial evaluation of some anilides of pyrazine-2-carboxylic acid. Folia Pharm Univ Carol 2000;25:15-20.

[2] Dolezal M., Kutilova K., Kralova K., Kunes J. Substituted pyrazine-2-carboxamides, their synthesis and photosynthesis-inhibiting activity. ECSOC-6 2002;September 1-30:http://www.mdpi.net/ec/papers/ecsoc-6/213/213.htm.

[3] Jampilek J., Dolezal M., Kunes J., Kralova K. Substituted pyrazine-2-carboxamides: preparation and their photosynthesis-inhibiting activity. ECSOC-7 2003;November 1-30:http://www.mdpi.net/ec/papers/ecsoc-7/C001/C001.htm.

P2

Stability studies of novel triazolyl-oxazolidinone antibacterial agents by APCI-LC-MS

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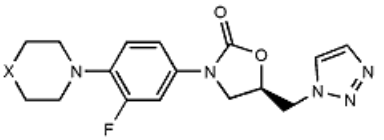
Novel triazolyl-oxazolidinones [1] active against Gram-positive bacteria were synthesized. The stability of compounds in human plasma is important in achieving effective antibacterial therapeutic plasma levels. We conducted the stability studies of triazolyl-oxazolidinones (PH-027, PH-038 and PH-041) in human plasma using APCI-LC-MS method.



PH-027: X=O
PH-038: X=CH3CO-N
PH-041: X= PhCO-N

Plasma samples (50 µl) containing known concentrations of the compounds (stored at 22^{o}C and -20^{o}C for 5 weeks) were drawn at appropriate time-intervals and analyzed by a developed LC-MS method using ion-trap MS, operated in full-MS scan using a positive APCI. Stability profiles were established by plotting the logarithmic values of the percentages of remaining analyte concentrations vs. time. The full MS profiles show the molecular masses of PH-027, PH-038 and PH-041 at m/z 348, 389 and 451, respectively. Calibration plots using (linezolid m/z 338 as internal standard) were linear (r: 0.99) over the selected concentration ranges. The values of RSD% and DEVs% were <8.8% and ±15.5% indicated good precision and accuracy. Stability studies indicated that the compounds were stable in human plasma at 22^{o}C and -20^{o}C. The kinetic parameter ranges were K_{deg} 0.02-0.08 week^{-1}, $t_{1/2}$ 8.5 – 44.1 weeks, t_{90} 1.2- 6.7 weeks. The results showed no significant differences in the kinetic parameters of the compounds at the experimental temperatures. The triazolyl-oxazolidinones were stable in human plasma at room and freezing temperatures with relatively low degradation rates. The morpholino derivative PH-027 was most stable with longer $t_{1/2}$ and t_{90} and lower K_{deg} values.

1. **Phillips, O.A.**; Udo, E.E.; Ali, A.A.M. and Samuel, S. (**2005**). Synthesis and antibacterial activity of new N-linked 5-triazolylmethyl oxazolidinones. *Bioorg Med Chem* 13(12), 4113-4123.

P3

New triazole and triazolothiadiazine derivatives as potential antibacterial and antifungal agents

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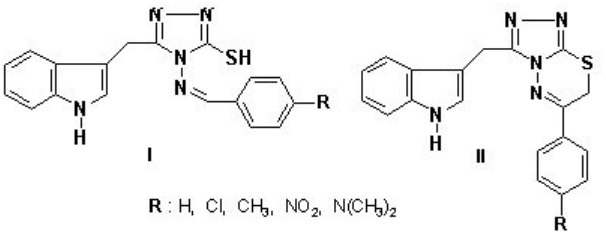
Triazole and triazoles fused with six-membered ring systems are found to possess diverse applications in the field of medicine, agriculture and industry. The commonly known systems are triazoles fused with pyridines, pyridazines, pyrimidines, pyrazines and triazines. The literature survey reveals that there are not many examples of triazoles fused with thiadiazines. Moreover, a large number of triazolothiadiazines has been shown to exhibit bactericidal and fungicidal activity [1-2].



We aimed the synthesis of new triazole and triazolothiadiazines derivatives as novel antimicrobial agents. The reaction of 1H-indol-3-acetic acid with thiocarbohydrazide gave the 4-amino-3-mercapto-5-[(1H-indol-3-yl)methyl]-4H-1,2,4-triazole. The reaction of triazole with arylaldehydes in dioxane gave the 4-arylideneamino-3-mercapto-5-(1H-indol-3-yl)methyl-4H-1,2,4-triazoles (**I**). The 3-[(1H-indol-3-yl)methyl]-6-aryl-7*H*-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines (**II**) were obtained by condensing triazole with phenacylbromides in absolute ethanol . The chemical structures of the compounds were elucidated by IR, ^{1}H-NMR and FAB$^+$-MS spectral data. Their antimicrobial activities against *M. luteus* (NRLL B-4375), *B. cereus* (NRRL B-3711), *P. vulgaris* (NRRL B-123), *S. typhimurium* (NRRL B-4420), *S. aureus* (NRRL B-767), *E. coli* (NRRL B-3704), *C. albicans and C. globrata* (isolates obtained from Osmangazi Uni.Fac.of Medicine) were investigated and significant activity was obtained.

[1] Molina P., Alajarin M., Perez de Vega M.J., Foces-Foces M.C., Hernandez Cano F., Claramunt R.M., Elguero J. Synthesis of 6,7-dihydro-5*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines by a carbon–carbon ring cyclization under mild conditions. J. Chem. Soc., Perkin Trans. I 1987; 1853–1860.

[2] Shivarama Holla B., Akberali P.M., Shivananda M.K. Studies on nitrophenylfuran derivatives: Part XII. Synthesis, characterization, antibacterial and antiviral activities of some nitrophenylfurfurylidene-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines. Farmaco 2001; 56: 919–927.

P4

Synthesis of new triazole derivatives and their antifungal activity and toxicity

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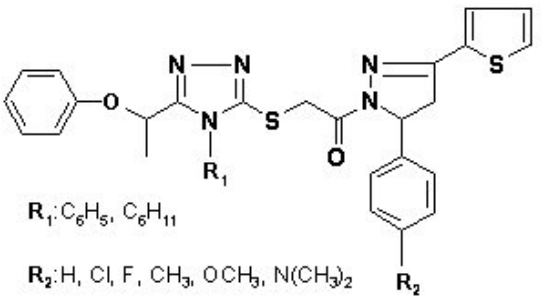
As known, not only biochemical similarity of the human cell and fungi forms a handicap for selective activity, but also the easily gained resistance is the main problem encountered in developing safe and efficient antifungals. The azole antifungals may be regarded as a new class providing truly effective drugs. Triazole derivatives are the major chemical group of antifungal azole derivatives. Nowadays, the most frequently used triazoles are fluconazole and itraconazole. They posses a broad spectrum of antifungal activity and reduced toxicity when compared with the other antifungals [1-2].



We aimed the synthesis of new 1,2,4-triazole derivatives as novel antifungal agents. The reaction of propionic acid hydrazides with various aryl/alkyl isothiocyanates gave thiosemicarbazides which furnished the mercaptotriazoles by alkali cyclization. The 4-phenyl/cyclohexyl-5-(1-phenoxyethyl)-3-[(3,5-diaryl-2-pyrazolin-1-yl)acetyl]thio-4H-1,2,4-triazole derivatives were synthesized by reacting the mercaptotriazoles with 1-(2-chloroacetyl)-3,5-diaryl-2-pyrazoline. The chemical structures of the compounds were elucidated by IR, ^{1}H-NMR, FAB-MS spectral data. Their antifungal activities against *C. albicans* (two strains), *C. glabrata*, *C. tropicali, C. krusei ,C. utilis* were investigated. The results showed that some of the compounds have very strong antifungal activity and low toxicity.

[1] De Pauw, B.E. New antifungal agents and preparations. Int. J. Antimicrob. Agents 2000; 16:147-150.

[2] Sheehan D.J., Hitchcock, C.A., Sibley, C.M. Current and Emerging Azole Antifungal Agents. Clin. Microbiol. Rev. 1999; 12:4

P5

Synthesis and antituberculosis activity of some new 4,5-substituted-4H-1,2,4-triazole-3-thiol derivatives

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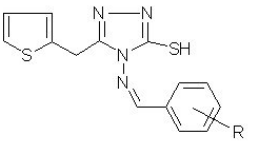
The increasing clinical importance of drug-resistant mycobacterial pathogens has lent additional urgency to microbiological research and new antimycobacterial compound development [1,2]. For this purpose, new triazoles were synthesized and evaluated for antituberculosis activity. The reaction of thienyl-2-acetic acid with thiocarbohydrazide gave the 4-(benzylideneamino)-5-[(thiophen-2-yl)methyl]-4H-[1,2,4]triazole-3-thiol. The chemical structure of the compounds was elucidated by IR, ^{1}H-NMR, FAB$^+$-MS spectral data. Antituberculosis activities of the synthesized compounds were determined by broth microdilution assay ,the Microplate Alamar Blue Assay, in BACTEC12B medium and results were screened *in-vitro,* using BACTEC 460 Radiometric System against *Mycobacterium tuberculosis* H_{37}Rv (ATCC 27294) at 6.25 µg/ml and tested compounds showed important inhibition ranging from 80 to 54%.



R= H, CH_3, OCH_3, CH-$(CH_3)_2$, N$(CH_3)_2$, O-CH_2-O, O-CH_2-Ph, NO_2, CN, OH, Cl, F

[1] Sbardella, G., Mai, A., Artico, M., Loddo, R., Setzu, M.G., La Colla, P., Synthesis and in vitro antimycobacterial activity of novel 3-(1H-pyrrol-1-yl)-2-oxazolidinone analogues of pnu-100480. Bioorg. Med. Chem. Lett. 2004;14: 1537-1541.

[2] D E, Castro K G. The global threat of drug-resistant tuberculosis. New Engl. J. Med. 1998; 338:1689-1690.

P6

Preparation, antimycobacterial, antifungal and photosynthesis-inhibiting evaluation of some anilides of substituted pyrazinecarboxylic acid

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Unsubstituted, halogenated and/or alkylated pyrazine derivatives connected *via* -CONH- bridge with substituted anilines into title compounds were synthesized and tested against *Mycobacterium tuberculosis*. The synthetic approach, analytical, spectroscopic, lipophilicity and biological data of twenty newly synthesized compounds are presented. Structure-activity relationships among the chemical structure, the antimycobacterial, antifungal, photosynthesis-inhibiting and antialgal activity of the evaluated compounds are discussed. Pyrazine-2-carboxylic acid (2-trifluormethyphenyl)amide has shown the highest activity against *M. tuberculosis* strain H_{37}Rv (99% inhibition at 6.25 µg mL^{-1}). The highest antifungal effect against *Trichophyton mentagrophytes*, the most susceptible fungal strain tested, was found for 5-*tert*-butylpyrazine-2-carboxylic acid (3-trifluormethyphenyl)amide (MIC = 62.5 µmol mL^{-1}). The highest reduction of chlorophyll content in *Chlorella vulgaris* was found for 6-chloropyrazine-2-carboxylic acid (3-trifluormethyphenyl)amide (IC_{50} = 12.1 µmol L^{-1}).

Acknowledgements. This study was supported by the Ministry of Health of the Czech Republic (No. 1A8238-3) and by the Slovak Scientific Grant Agency VEGA (No. 1/0089/03). Antimycobacterial data were provided by the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) through a research and development contract with the U.S. National Institute of Allergy and Infectious Diseases.

P7

Quinoxaline-2-carboxylate 1,4-N-dioxide derivatives as anti-Mycobacterium tuberculosis agents

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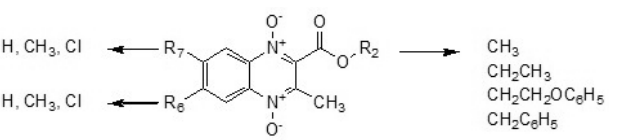
Universidad de Navarra

Tuberculosis (TB) is one of the leading infectious causes of death in the world and has become a growing global health problem. According to the World Health Organization, in 2003, 8.8 million new TB cases arose, and an estimated 1.7 million deaths resulting from TB occurred. One of the major problems of TB is the development of new active compounds against multidrug-resistant tuberculosis strains.

The quinoxaline derivatives show very interesting biological properties (antibacterial, antiviral, anticancer, antifungal, antihelmintic, insecticidal) [1]. In this sense, several quinoxaline 1,4-di-*N*-oxide derivatives have been reported as *in vitro* anti-*Mycobacterium tuberculosis* agents [2]. The quinoxaline-3-methyl-2-carboxylate 1,4-dioxide derivatives, active in previous assays, were selected for the determination of MIC against different strains of single drug resistant *Mycobacterium tuberculosis* and *in vivo* assay.



In general, the compounds were active in the different drug-resistant strains, and there were no toxic effects in the MTD assay. The activity shown by ethyl 7-chloro-3-methyl-quinoxaline-2-carboxylate 1,4-di-*N*-oxide is noteworthy because it produced a significant reduction of the

bacterial load in both lungs and spleen. The bacterial numbers in lung and spleen were reduced by 3.02 and 2.62 $\log_{10}$ CFU, respectively.

Acknowledgments: Antimycobacterial data was provided by the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) through a research and development contract with the U.S. National Institute of Allergy and Infectious Diseases (NIAID).

[1] Carta A, Corona P, Loriga M. Quinoxaline 1,4-dioxide: a versatile Scaffold endowed with manifol activities. *Curr Med Chem* 2005;12:2259-2272.

[2] Jaso A, Zarranz B, Aldana I, Monge A. Synthesis of new Quinoxaline-2-carboxylate 1,1-dioxide derivatives as Anti-*Mycobacterium tuberculosis* agents. *J Med Chem* 2005;48:2019-2025.

P8

Synthesis of new ethyl 3-phenylquinoxaline-2-carboxylate 1,4-di-N-oxide derivatives as Anti-Mycobacterium tuberculosis agents

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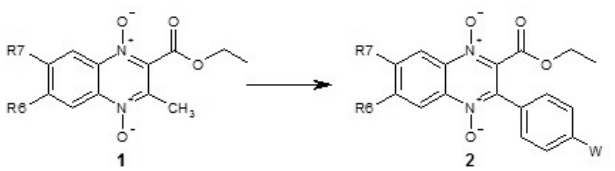
*Universidad de Navarra. **Universidade Federal do Rio de Janeiro

Tuberculosis (TB), an infection of *Mycobacterium tuberculosis,* still remains the leading cause of worldwide death among infectious diseases. The statistics indicate that 3 million people throughout the world die annually from tuberculosis.

As a continuation of our research in 3-methylquinoxaline-2-carboxylate 1,4-di-N-oxide derivatives **1** as antituberculosis agents [1] and in order to improve their activity, fourteen new ethyl 3-phenylquinoxaline-2-carboxylate 1,4-di-N-oxide derivatives **2** were synthesized [2] and evaluated by TAACF for antituberculosis activity.

The synthesis of these compounds was carried out using a base catalyst condensation of benzofurazan oxide with ethyl benzoylacetate. The use of K_2CO_3 in acetone or solvent free KF-Al_2O_3 improved the yields notably.

All of these compounds showed growth inhibition



1 2

greater than 99% and MIC values less than 6.25mg/mL. At present, they are being tested in toxicity assays and some of them have shown positive results.

Acknowledgements: Antimycobacterial data were provided by the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) through a research and development contract with the U.S. National Institute of Allergy and Infectious Diseases (NIAID).

[1] Jaso A, Zarranz B. Aldana I, Monge A. Synthesis of new quinoxaline-2-carboxylate 1,4-dioxide Derivatives as Anti-*Mycobacterium tuberculosis* Agents. *J Med Chem* 2005; 48(6); 2019-2025.

[2] Lima L.M, Zarranz B, Marin A, Solano B, Vicente E, Pérez Silanes S, Aldana I and Monge A. Comparative use of solvent-free KF-Al_2O_3 and K_2CO_3 in acetone in the synthesis of quinoxaline 1,4-dioxide derivatives designed as antimalarial drug candidates. *J Heterocycl Chem* 2005; 42(7): 1381-1385.

P9

Synthesis, Antimycobacterial Activity and SAR of 9-Benzyl-6-(2-furyl)purines and Non-Purine Analogs

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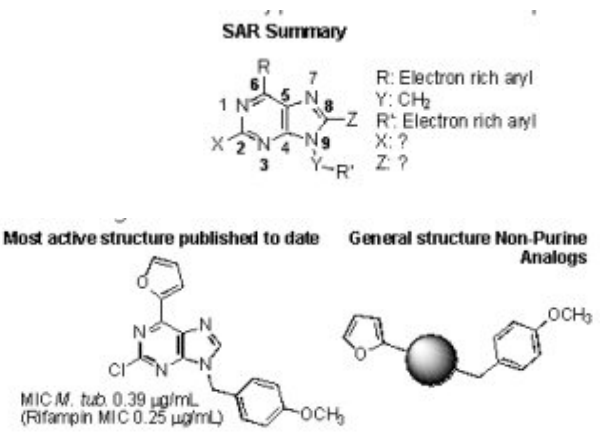
It has been estimated that ca. 30 million people will die from tuberculosis (TB) within the next 10 years. There is an urgent need for new drugs to treat TB, especially drugs against multi-drug resistant tuberculosis as well as drugs able to target the bacilli in a dormant stage, drugs able to penetrate sites that are difficult to treat, and drugs that can be used concurrently with drugs commonly employed in HIV-treatment |1]. We have identified 9-substituted 6-arylpurines as potent antimycobacterials [2-5]. High antimycobacterial activity and low toxicity against mammalian cells makes these compounds interesting potential anti-tuberculosis drugs. The mechanism by which the purines exhibit their activity is currently not known, but our results point toward a specific mycobacterial target for the drug action.We have previously shown that purines carrying an electron rich aryl group in the purine 6-position [5] and a 9-benzyl group [3,4], exhibit profound antimycobacterial activity. We now present synthesis, bioactivity and SAR of 2- and 8-substituted 6-furyl-9-benzylpurines as well as non-purine analogs.



[1] Spigelman M, Gillespie S. Tuberculosis drug development pipeline: progress and hope. Lancet 2006; 367: 945-947.

[2] Bakkestuen AK, Gundersen LL, Langli G, Liu F, Nolsøe JMJ. 9-Benzylpurines with Inhibitory Activity against Mycobacterium tuberculosis. Bioorg Med Chem Lett 2000; 10:1207-1210.

[3] Gundersen LL, Nissen-Meyer J, Spilsberg B. Synthesis and Antimycobacterial Activity of 6-Arylpurines; the Requirements for the N-9 Substituent in Active Antimycobacterial Purines. J Med Chem 2002; 45:1383-1386.

[4] Bakkestuen AK, Gundersen LL, Utenova BT. Synthesis, Biological Activity and SAR of Antimycobacterial 9-Aryl-, 9-Arylsulfonyl- and 9-Benzyl-6-(2-furyl)purines. J Med Chem 2005; 48: 2710-2723.

[5] Brændvang M, Gundersen LL. Selective Anti-tubercular Purines. Synthesis and Chemotherapeutic Properties of 6-Aryl- and 6-Heteroaryl-9-benzylpurines. Bioorg Med Chem 2005; 13: 6360-6373.

P10

Redesign of Aminoglycosides for Treatment of Human Genetic Diseases Caused by Premature Stop Mutations

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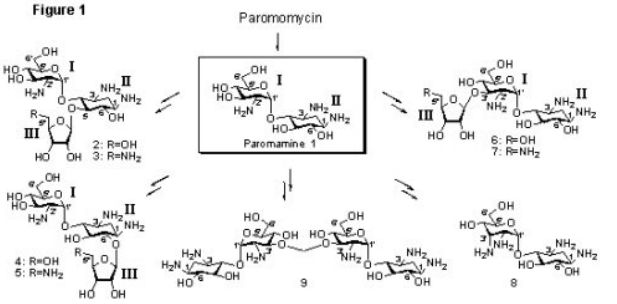
A large number of human genetic diseases result from mutations that cause premature termination of the synthesis of proteins encoded by mutant genes. Currently, hundreds of such nonsense mutations are known, and several where shown to account for certain cases of fatal diseases, including cystic fibrosis (CF), Duchenne muscular dystrophy (DMD), Tay-Sachs, and more. While several *in vitro* and *in vivo* experiments have clearly demonstrated that many of the above mutations can be functionally rescued by treatment with aminoglycoside antibiotics, especially by treatment with geneticin (G-418), gentamicin or paromomycin, still their use as therapeutic agents is highly restricted because of their high toxicity.

The main objective of this research is to develop novel aminoglycosides that will have efficient termination suppression activity, and at the same time will have reduced toxicity against mammalian cells.

For this purpose a series of new derivatives (**2-9**) (Fig. 1) were synthesized and their nonsense suppression was assayed in an *in vitro* and *ex vivo* mammalian systems. One of these structures, the pseudo-trisaccharide **3** showed significantly higher stop codon read-through activity and lower toxicity compared to that of the parent paromomycin and gentamicin. Antibacterial tests against both Gram-negative and Gram-positive bacterial strains indicate that **3** is highly selective in its action in eukaryotic cells than in prokaryotic cells. Taken together, these results suggest that compound **3** could represent an alternative to gentamicin and paromomycin for suppression therapy. Thus, this study provides a new direction for the development of novel aminoglycoside-based small molecules that selectively target mammalian cells; this progress may offer promise for the treatment of many genetic diseases.

Figure 1



P11

Synthesis and Antifungal Activity of Alkylglycero- and Alkylphosphocholines

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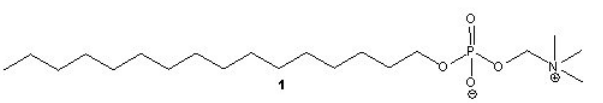
Invasive fungal infections are a serious and escalating health issue. Current therapies are limited in safety and/or efficacy and resistant fungi are an emerging problem. It is widely recognised that new antifungal drugs with a novel mode of action are required.

Fungal phospholipase B (PLB1), which has PLB, lysophospholipase (LPL) and lysophospholipase transacylase (LPTA) activities, is a virulence factor in a number of pathogenic fungi.[1] Using a series of bis-ammonium compounds, we have partly validated this multifunctional enzyme as a new antifungal drug target.[2] Recently we discovered that hexadecylphosphocholine **1** (miltefosine), a compound approved for treatment of eishmaniasis, inhibits PLB1, is orally active in a mouse model of cryptococcosis and has broad-spectrum antifungal activity.[3] Aiming to improve the therapeutic index of miltefosine, we set out to investigate how structure relates to antifungal potency and tested for potential cytotoxicity by an erythrocyte haemolysis assay.

We report here the synthesis of novel analogues of **1** and show how introduction of amide-, ester-, ether- and double bonds into the alkyl chain affects the properties of alkylphosphocholines.



[1] Chen S, Wright L, Golding J, Sorrell T. Biochem. J. 2000; 347: 431-439.

[2] Ng C, Obando D, Widmer F, Wright L, Sorrell T, Jolliffe K. J. Med. Chem. 2006; 49: 811-816.

[3] Widmer F, Wright L, Obando D, Handke R, Ganendren R, Ellis D, Sorrell T. Antimicrob. Agents Chemother. 2006; 50: 414-421.

P12

Anti-Pneumocystis carinni activity of primaquine imidazolidin-4-ones

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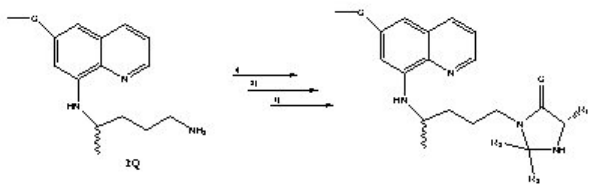
Pneumocystis pneumonia (PCP) is one of the most frequent causes of mortality among HIV-infected patients. Primaquine (PQ) is an antimalarial 8-aminoquinoline effective against PCP when given in combination with clindamycin. This has drawn the attention of Medicinal Chemists towards the anti-PCP activity of 8-aminoquinolines, not only confined to those exhibiting antimalarial activity [1]. It is thought that anti-PCP 8-aminoquinolines exert their anti-PCP activity by acting on the electronic transport and redox system of the *P. carinii* pathogen [1]. Recently, our research group has been developing imidazolidin-4-one derivatives of PQ (Scheme 1), targeting novel compounds with improved therapeutic action, namely, higher resistance to metabolic inactivation, lower toxicity and equal or higher antimalarial activity than that of the parent drug [2,3]. These imidazolidin-4-ones were seen to block the transmission of rodent malaria, caused by *Plasmodium berghei* on BalbC mice, to the mosquito vector *Anopheles stephensi* [3].



Scheme 1. Synthetic route to primaquine imidazolidin-4-ones

1) *N*-Boc-protected amino acid dicyclohexilcarbodiimide, 1-hydroxybenzotriazole; 2) i. neat trifluoroacetic acid; ii. Na2CO3; 3) propanone or a cyclic symmetrical ketone (cyclopentanone, cyclohexanone and cycloheptanone); CH3OH (reflux); triethylamine; 4 Å molecular sieves.

The anti-PCP activity of our PQ derivatives is now under study and preliminary *in vitro* assays [4] show that some of the compounds exhibit slight to moderate activity after a 72 h incubation period against *P. carinii.* In one case, the IC_{50} was comparable to that of parent PQ. Both these studies and forthcoming results from ongoing biological assays will be presented and discussed.

[1] Queener F, Bartlett S, Nasr M, Smith W. 8-aminoquinolines effective against *Pneumocystis carinii in vitro* and *in vivo.* Antimicrob Agents Chemother 1993; 37: 2166-2172.

[2] Gomes P, Araújo MJ, Rodrigues M, Vale N, Azevedo Z, Iley J, Chambel P, Morais J and Moreira, R. synthesis of imidazolidin-4-one and 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-dione derivatives of primaquine: scope and limitations. Tetrahedron 2004; 60: 5551-5562.

[3] Araújo MJ, Bom J, Capela R, Casimiro C, Chambel P, Gomes P, Iley J, Lopes F, Morais J, Moreira R, Oliveira E, Rosário V, Vale N. Imidazolidin-4-ones derivatives of primaquine as novel transmission-blocking antimalarials. J Med Chem 2005; 48: 888-892.

[4] Cushion MT, Chen F, Kloepfer N. A cytotoxicity assay for evaluation of candidate anti-Pneumocystis agents. Antimicrob Agents Chemother 41; 379-384, 1997.

P13

Synthesis of agelasine and agelasimine analogs and evaluation of antibacterial and cytotoxic activities

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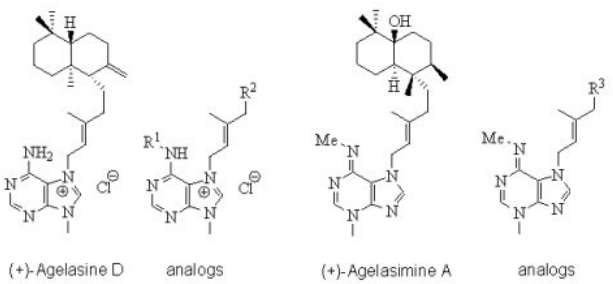
Agelasines and agelasimines are adenine-related diterpenoids isolated from marine sponges. Both classes of compounds display a wide range of interesting biological activities, such as antimicrobial and cytotoxic effects, contractive response of smooth muscles, inhibition of NaK-ATPase, and others.

Our group has recently synthesized Agelasine D [1,2] and E [3] , together with a vide range of agelasine and agelasimine analogs [3,4]. The analogs have been screened for antimicrobial and cytotoxic effects. Synthesis and SAR-results so far will be presented.



[1] Vik A, Hedner E, Charnock C, Samuelsen Ø, Larsson R, Gundersen L-L, Bohlin L. (+)-Agelasine D: Improved Synthesis and Evalutaion of Antibacterial and Cytotoxic Acitivies. J Nat Prod 2006;69;381-386.

[2] Utenova B, Gundersen L-L. Synthesis of (+)-Agelasine D from (+)-Manool. Tetrahedron Lett 2004;45;4233-4235.

[3] Bakkestuen A K, Gundersen L-L, Petersen D, Utenova B T, Vik A. Synthesis and Antimycobacterial Activity of Agelasine E and Analogs. Org Biol Chem 2005;3; 1025-1033.

[4] Vik A, Charnock C, Gundersen L-L, Samuelsen Ø, Tangen L W. Manuscript under preparation.

P14

Synthesis and Bioactivities of Agelasine E and F Analogs

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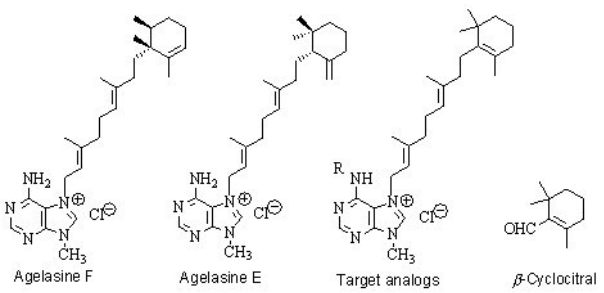
Agelasines are 7,9-dialkylpurinium salts isolated from marine sponges (*Agelas* sp.). All compounds carry a diterpenoid side chain in the adenine 7-position. The agelasines are associated with bioactivities such as antimicrobial and cytotoxic effects, as well as contractive response of smooth muscles and inhibition of NaK-ATPase. Furthermore, *in vitro* activity against *Mycobacterium tuberculosis* is reported for agelasine F [1].

Our group recently published the first synthesis of (-)-agelasine E [2] and (+)-agelasine D [3,4]. We now report synthesis of agelasine E and F analogs starting from β cyclocitral, together with cyclotoxic and antibacterial data for these compounds.



[1] Mangalindan GC, Talaue MT, Cruz LJ, Franzblau SG, Adams LB, Richardson AD, Ireland CM, Conception GP. Agelasine F from a Philippine *Agelas* sp. Sponge Exhibits *in vitro* Antituberculosis Activity. Planta Med 2000;66:364-365.

[2] Bakkestuen AK, Gundersen LL, Petersen D, Utenova BT, Vik A. Synthesis and antimycobacterial activity of agelasine E and analogs. Org Biomol Chem 2005;3:1025-1033.

[3] Utenova BT, Gundersen LL. Synthesis of (+)-Agelasine D from (+)-Manool. Tetrahedron Lett 2004;45:4233-4235.

[4] Vik A, Hedner E, Charnock C, Samuelsen Ø, Larsson R, Gundersen LL, Bohlin L. (+)-Agelasine D: Improved Synthesis and Evaluation of Antibacterial and Cytotoxic Acrivities. J Nat Prod 2006;69:381-386.

P15

Synthesis and biological action of 4-substituted-3-[(1H-tetrazol-5-yl)methyl]-1,2,4-triazoline-5-thione

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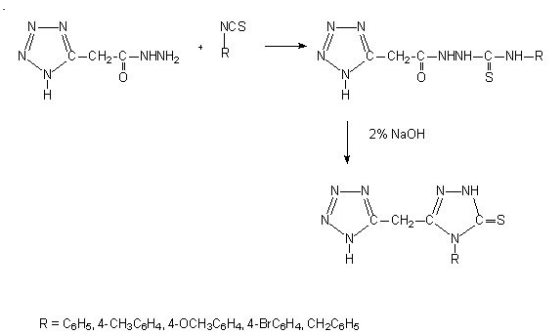
Depending on the nature of substituents 1,2,4-triazole derivatives show different biological activities, such as antidepressant, antitumor, antibacterial, and they also be used as herbicidal or fungicides. On the other hand the tetrazole ring is a structural element of many drugs that have antibacterial activity such as Cefoperazon, Cefamandol and Cefazolin. One of the methods of preparing of derivatives of 1,2,4-triazole is the cyclization reaction of acyl derivatives of thiosemicarbazide in alkaline media. In this paper ethyl 1H-tetrazole-5-acetate was used for preparation of hydrazide of 1H-tetrazole-5-acetic acid. This compound was converted to the respective thiosemicarbazide derivatives and after cyclization reaction in alkaline media a number of new derivatives of 4-substituted-3-[(1H-tetrazol-5-yl)methyl]-1,2,4-triazoline-5-thione were obtained.

Some of new compounds were screened for their antibacterial activity.

The reaction were performed according to the Scheme:



R = C_6H_5, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-BrC_6H_4, $CH_2C_6H_5$

P16

Design and synthesis of new low-molecular-weight inhibitors of MurC

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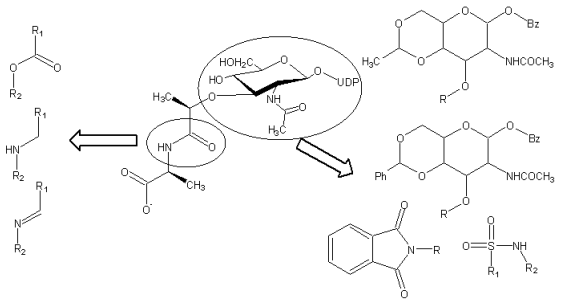
The most important building block of bacterial cell-wall is peptidoglycan, a unique polymer present only in bacteria. Early phases of its biosynthesis take place in the cytoplasm are appropriate targets for the discovery of new effective compounds. Amino acid ligases catalyse the synthesis of UDP-*N*-acetylmuramoyl-pentapeptide. MurC (UDP-*N*-acetylmuramate: L-alanine ligase) is an enzyme that catalyses the addition of L-alanine on UDP-*N*-acetylmuramic acid, according to the following reaction [1]:

UDP-MurNAc + L-Ala + ATP ↔ UDP-MurNAc-L-Ala + ADP + Pi

In our laboratory we prepared several low-molecular-weight inhibitors in which we modified the UDP-*N*-acetyl-D-glucosamine part of a molecule and replaced it with several aromatic or heteroaromatic moieties. Instead of peptides, depsipeptides, aminomethyl and imine derivatives were prepared. This modification results in overall change in conformation of the side chain and the metabolic stability of the resulting compounds.



The resulting compounds were *in vitro* tested for their inhibitory activity and showed moderate activity against MurC, making them one of first low-molecular-weight inhibitors of this enzyme.

[1] El Zoeiby, A ; Sanschagrin, F ; Levesque, R. C: Mol. Microbiol. 2003, 47, 1–12.

P17

Interaction Mechanisms of INH and Benzimidazole Derivatives with Mycobacterium tuberculosis

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Tuberculosis remains the leading cause of death from a single infectious disease. According to WHO about 2 million people die each year from this curable infirmity. The outbreak of tuberculosis in both developed and developing countries is one of the most alarming aspects of the problem. Many efforts have been made towards the understanding of the mechanisms of action of active compounds against *Mycobacterium tuberculosis* but the knowledge about these complex mechanisms is still rather limited.

To shed some light into the issue of tuberculostatic activity, we have analyzed two families of active compounds: isoniazide (INH) and benzimidazole derivatives. Using a QSPR's approach (eqn. 1) we established a correlation between the biological activity, MIC, and several solute descriptors, X_i, of physicochemical, geometrical, steric and electronic nature.

$$\log(1/MIC) = a_0 + \sum_i a_i X_i$$

Our results show that the relevant interaction mechanisms that explain the biological activity are different for the two families and that lipophilicity seems to play a significant role in the benzimidazole but not in the INH derivatives.

Based on previously established QSAR's, we synthesized compounds from both families and determined their *in vitro* activity against *Myc. tb.* With these, and some experimental log P values, we tested the robustness and predictability of the new QSAR's presented in this work.

P18

New potential antimycobacterials and antifungals: structure-activity relationships in 3-arylaminopyrazine-2.5-dicarbonitriles

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A series of new pyrazinamide analogues derived from pyrazine-2,5-dicarbonitrile have been prepared and assayed as new potential antimycobacterials and/or antifungals. The preparation was followed by structure analyses, liphophilicity determination and biological activity assays. Report that 5-chloropyrazinamide has different mode of action [1] than pyrazinamide itself [2] promises good chance to reach new structures with high antimycobacterial activity and new action mechanism. New antituberculars are urgently needed because of global incidence increasement caused by multi-drug resistant *Mycobacterium tuberculosis* strains.

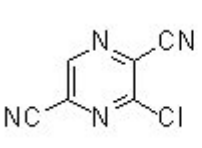

Fig. 1: Model compound

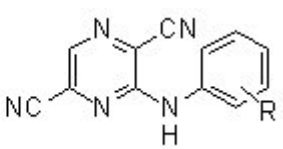

Fig. 2: New derivatives

Compounds derived from 3-chloropyrazine-2,5-dicarbonitrile [Fig.1 and Fig.2] promise good starting point to further studies (best activity reached yet is 3-(3-chlorophenylamino)pyrazine-2,5-dicarbonitrile, with MIC = 8 μmol.l^{-1} against classical TBC strains and with lower activity against atypical strains. Compared to pyrazinamide with MIC = 4 μmol.l^{-1} against classical strains and no activity against atypical ones).

Acknowledgements: This study was suported by the Ministry of Health of the Czech Republic (No. 1A8238-3), by the Ministry of Education of the Czech Republic (MSM 002162082 and FRVS 1412/2006). Antimycobacterial data were provided by the Tuberculosis Antimicrobial Acquisition and Coordinating facility (TAACF) though a research and development contract with the U.S. National Institute of Allergy and Infectious Diseases.

[1] Cynamon MH, Speirs RJ, Welch JT.In vitro antimycobacterial activity of 5-chloropyrazinamide. *Antimicrob Agents Chemother.* 1998;42(2):462-3.

[2] Zhang Y, Wade MM, Scorpio A, Zhang H, Sun Z. Mode of action of pyrazinamide: disruption of Mycobacterium tuberculosis membrane transport and energetics by pyrazinoic acid. J. Antimicrob Chemother. 2003;52(5):790-5. Epub 2003 Oct 16.

P19

Structural characterization of the interactions between UDP-galactopyranose mutase and substrate analogues

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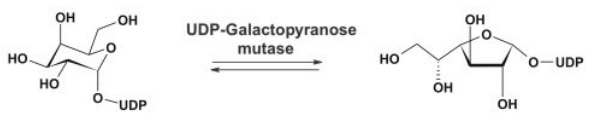
*Laboratoire de chimie biologique structurale and **Laboratoire de chimie bioorganique, FUNDP, 61 rue de Bruxelles 5000 Namur, Belgique

The flavoenzyme UDP-galactopyranose mutase (UGM) catalyses the interconversion of UDP-galactopyranose (UDP-Galp) and UDP-galactofuranose (UDP-Galf). The UDP-Galf is a key cell wall component of many bacterial pathogens, such as *Mycobacterium tuberculosis*. While the crystallographic structure of UGM is known, the mechanism, although speculated on, is not completely understood [1-2]. The flavin cofactor, in its reduced form FADH$^-$, is thought to realize a nucleophilic attack on the anomeric position of the galactose residue with release of UDP. This reaction would initiate the pyranose ring breakage and closure.



As the clarification of the catalytic mechanism for UGM would facilitate the development of anti-mycobacterial agents, some substrate analogues have been synthesized and evaluated [3]. In an attempt to rationalize the obtained inhibitory activities and to better understand how the enzyme works, we performed structural characterization of the ligands/UGM interactions. Surexpression and purification protocols have been applied in order to conduct crystallographic experiments. In parallel, we used molecular modelling techniques to simulate the docking of these analogues into the UGM active site.

[1] Sanders DA, Staines AG, McMahon SA, McNeil MR, Whitfield C, Naismith JH. UDP-galactopyranose mutase has a novel structure and mechanism. Nat Struct Biol. 2001 8(10):858-63.

[2] Soltero-Higgin M, Carlson EE, Gruber TD, Kiessling LL. A unique catalytic mechanism for UDP-galactopyranose mutase. Nat Struct Mol Biol. 2004 11(6):539-43.

[3] Caravano A, Menguin-Lecreux D, Brondello JM, Vincent SP, Sinay P. Synthesis and inhibition properties of conformational probes for the mutase-catalyzed UDP-galactopyranose/-furanose interconversion. Chem Eur J. 2003 9(23):5888-98.

P20

Synthesis and Biochemical Characterization of a New Generation of Aminoglycoside Antibiotics Based Upon the Neamine Core

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Aminoglycosides are clinically used drugs that exert their antimicrobial activities by selectively binding to the decoding A site of the bacterial ribosome and inhibiting protein synthesis. The primary mechanism for resistance to aminoglycosides is the bacterial acquisition of enzymes that selectively detoxify them either by phosphorylation, acetylation or adenylation. Among these enzymes families are aminoglycoside 3'-phosphotransferases [APH(3')s] that catalyze the transfer of a g-phosphoryl group of ATP to the 3'-hydroxyl of the majority of aminoglycosides, rendering them inactive because the resulting phosphorylated antibiotics no longer bind to the bacterial ribosome with high affinity.Since the neamine **1** (Fig. 1) represents a minimal aminoglycoside structure that possesses antibacterial activity, we selected it as a core structure to which various appendages were attached. In attempt to solve the problem of resistance caused by APH(3') enzyme we masked the C3'-OH of **1** by introducing C3'-C4' methylidene protection and prepared the new derivative **2**. As an alternative solution to the same problem, we synthesized the new types of symmetrical dimers, in which the two neamine moieties are regioselectively connected by methylene spacers **6** and **7**. Finally, the derivative **2** was employed as a common acceptor to which various donors were added to afford the first generation of pseudo-trisaccharide derivatives **3**-**5** (Fig. 1).

All new structures (**2**-**7**) were tested for their antibacterial performance against a series of bacterial strains

and minimal inhibitory concentration (MIC) values were determined. In parallel, their substrate/inhibitor activities for the APH(3') enzyme were evaluated. These tests show that all new derivatives possess higher antibacterial activities than the parent neamine **1** while in parallel they lack substrate activity for the APH(3'). Most importantly, the dimers **6** and **7** were proved to be very powerful against resistant strains of *Pseudomonas aeruginosa* isolated from Cystic Fibrosis patients, exhibiting MIC values up to two orders of magnitude better than the parent drug, neomycin B.

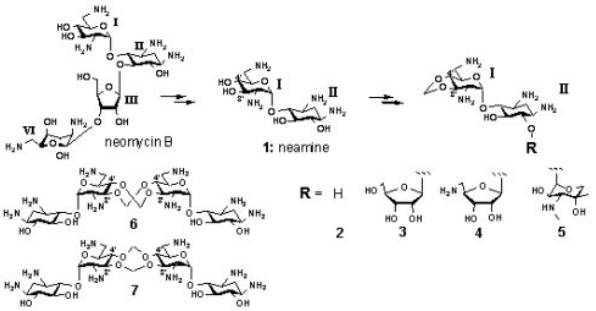

Fig. 1: Neamine 1 and its new derivatives 2-7

P21

Synthesis of novel 2-substituted 5,7-di-tert-butylbenzoxazoles and their open forms with antitubercular activity

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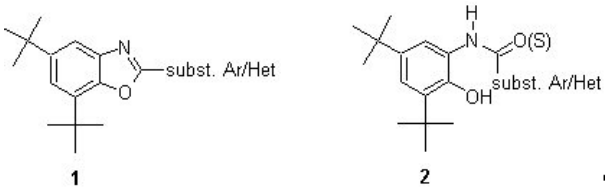
Tuberculosis is still a challenging worldwide health problem, especially the emergence of multidrug resistant strains of *Mycobacterium tuberculosis.* A great number of people are carriers of the latent form that creates dangerous source of illness for the future. Therefore, there is an urgent need to develop new structural classes of antituberculosis drugs.

Benzoxazoles belong to biologically very active skeletons. Various benzoxazole derivatives were extensively studied for their antibacterial and antifungal activity, anticancer activity, also as new non-nucleoside topoisomerase I poisons and HIV-1 reverse transcriptase inhibitors [1]. They can be considered as structural bioisosters of naturally occurring nucleotides such as adenine and guanine, which allow them to interact easily with the biopolymers of a living system. They have shown also low toxicity in warm-blooded animals [2].

We have prepared a series of novel heterocyclic/aromatic 2-substituted 5,7-di-*tert*-butylbenzoxazoles **1** and open forms of the most active 5,7-di-tert-butylbenzoxazoles **2**. Several of them showed antituberculotic activity comparable or higher than the standard isoniazide. *In vitro* cytotoxicity testing of he most active benzoxazoles were evaluated by MTT assay and compared with isoniazid as a reference drug.

Synthesis and biological activity will be presented.



[1] Vinsova J. Biologically active benzoxazoles. Cesk. Slov. Farm. 2003, 52, 282-290

[2] Dunwell DH, Evans J.: J. Med. Chem 1977, 20, 797-801

This work was financially supported by the Research project MSM 002162082 and, Grant IGA MZ 1A/8238-3.

P22

Synthesis, antituberculosis activity and stability of new hydrazonoformamide derivates of isoniazid

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Isonicotinic acid hydrazide (INH) is a frontline tuberculosis-specific-drug that is used usually in combination with other drugs. Modification of its molecule is still up to date. Isoniazid is also used for prevention of TB in people who have been exposed to the active disease but have no symptoms[1].

Several Schiff bases, hydrazones and hydrazides of isoniazid have shown good activity against tubercular, fungal and bacterial infections[2, 3].

In the quest for biologically more potent antituberculosis compounds we have designed and synthesized hydrazonoformamide derivates of isoniazid and other simple antiTB drugs as prodrug forms as it is shown in **Figure 1.**

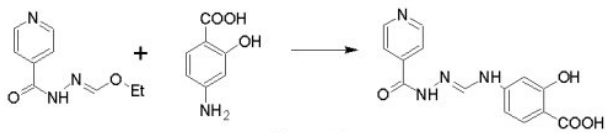

Figure 1

Their synthesis, lipophilicity, stability and antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$, *M. avium* and *M. bovis* will be demonstrated.

[1] http://www.who.int/mediacentre/events/2005/tbday/en/index.html (March 2006).

[2] De Logu, A.; Onnis, V.; Saddi, B.; Congiu, C.; Schivo, M. L.; Cocco, M. T.: J. Antimicrob. Chem. 2002, 49, 275-278.

[3] Sinha, N.; Jain, S.; Tilekar, A.; Upadhayays, R. S.; Kishore, N.; Jana, G. H.; Arora, S.K.: Bioorg. Med. Chem. Lett. 2005, 15, 1573-1576.

This work was financially supported by Research project MSM 0021620822, Grant IGA MZ 1A/8238-3 and GAUK 285/2006.

P23

Hydrazones of 4-fluorobenzoic acid hydrazide: Synthesis , characterization and antibacterial and antifungal activities

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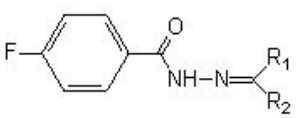
The heterocyclic hydrazones constitute an important class of biological active drug molecules which have atracted attention of medicinal chemists due to their wide ranging pharmacological properties including antibacterial and antifungal anticonvulsant, antiinflammatory, antitubercular activities [1-4].

In our previous studies, the antibacterial and antituberculosis activities of 4-substitutedbenzoic acid (substitutedmethylene)hydrazides were found to be active against *Staphylococcus aures* ATCC 29213 and *Mycobacterium tuberculosis* H37Rv [1]. Prompted by these observations, we decided to synthesise various hidrazide-hydrazone derivatives carrying the heterocyclic ring. The novel synthesized hydrazones were prepared by reacting equimolar amounts of properly 4-fluoro benzoic acid hydrazide and substituted aldehydes and ketons in ethanol. These compounds characterized by ^{1}H-NMR and elemental analysis and were screened for antifungal and antibacterial activities.



R_1=H,CH_3,CH_2CH_3
R_2=Alkyl, substitutedphenyl,pyrolyl,thiophenyl,pyridyl

[1] Rollas S, Gulerman N, Erdeniz H. Synthesis and antimicrobial activity of some new hydrazones of 4-fluorobenzoic acid hydrazide and 3-acetyl-2,5-disubstituted-1,3,4-oxadiazolines. Farmaco 2002; 57:171-174.

[2] Dimmock JR, Vashishtha SC, Stables JP. Anticonvulsant properties of various acetyl-hydrazones, oxamoylhydrazones and semicarbazones derived from aromatic and unsaturated carbonyl compounds. Eur J Med Chem 2000;35: 241-248.

[3] Kalsi R, Pande K, Bhalla TN, Barthwal JP, Gupta GP, Parmar SS. Antiinflammatory activity of quinazolinoformazans. J Pharm Sci 1990; 79: 317-320.

[4] Kucukguzel SG, Mazi A, Sahin F, Ozturk S, Stables J. Synthesis and biological activities of diflunisal hydrazide-hydrazones. Eur J Med Chem 2003; 38:1005-1013

P24

Telomers of 1,3-butadiene with c-nucleofiles in the synthesis of cygerolum analogues

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Cygerolum - 2-cyclohexyl-5,9-dimethyl-decadien-4,8-oic acid – demonstrate antibacterial, dehydrative and repairable effects and is constituent of ointments for skin restoration. Cygerolum is isolated from flipper of shark. Recently we have published the syntheses of cygerolum and its analogues based on isoprene[1]. Herein we present simple syntheses of analogues of cygerolum based on butadiene by Scheme.

Telomerization of butadiene with malonic or acetoacetic esters gives appropriate octadienyl esters by method[2]. Their alkylation and following decarboxylation and saponification result in cygerolum analogues.

[1] E.A. Petrushkina “Pd-catalyzed allylation of C-nucleofile by isoprene telomers in the synthesis of cygerolum and its analogues”. Book of Abstracts of XXI[st] IUPAC International Conference on Organometallic Chemistry. Vancouver. Canada. 2004. 211. p.145.

[2] G. Hata, K. Takahashi, A. Miyake J Org Chem 1971. 36. 2116.

P25

Design and Synthesis of 1-2-4-Triazole Derivatives as antifungal agents

Z. Rezaei, S. Khabnadideh, F. Amiri

Department of Medicinal Chemistry, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

Invasive fungal infections are major problems in immune-compromised patients. The recent expansion of antifungal drug research has occurred because there is a critical need for new antifungal agents to treat these life–threatening invasive infections.

In pervious report we described the preparation of some imidazole derivatives with biological interest. In this study a series of 1,2,3-benzotriazole derivatives were synthesized using alkylation on the N_1-position of 1,2,3-benzotriazole with trityl substitution and also alkyl chains in the presence of potassium carbonate, sodium hydroxide and tetraethylammonium iodide.

The structures of all the new compounds were determined by ^{1}H-NMR and Mass spectroscopy. The cytochrome P450 sterol 14 α-demethylase enzyme (CYP51) is the target of azoles antifungal. These compounds also docked into the active site of MT-CYP51 (PDB code, 1EA1) using Autodock program and compared with clotrimazole and fluconazole. Some of these compounds showed good affinity for the enzyme like fluconazole and clotrimazole.

[1] S. khabnadideh; Z. Rezaei; A. Khalafi-Nezhad; R. Bahrinajafi; R. Mohamadi; A. A. Farrokhroz. Synthesis of N-Alkylated Derivatives of Imidazole as Antibacterial Agents. Bioorganic & Medicinal Chemistry Letters 13 (2003) 2863-2865.

[2] L. Xiao; V. Madison; A.S. Chau; D. Loebenberg; P.M. McNicholas. Three-Dimensional Models of Wild-Type Mutated Forms of Cytochrom P 450 14a-Demethylases from Aspergillus Fumigatus and Candida albicans Provide Insight into Posaconazole binding. Antimicrob Agents Chemother. 2004 Feb; 48(2):568-74.

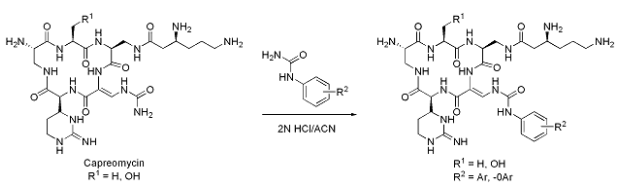
P26

Capreomycin derivatives and their activity against Gram positive bacteria including methicillin resistant S. aureus

S. Wenglowsky, J. Lyssikatos, S. Brown, P. Lee, J. Winkler, R. Rieger, S. Allen

Array BioPharma, 3200 Walnut Street, Boulder, CO, USA

Bacterial resistance to the armamentarium of antibiotic drugs is a growing problem worldwide, predominantly in the hospital setting, but with an increasing prevalence in the community.[1] Decades of selection pressure, overuse of antibiotics, and poor patient compliance are the main drivers of the evolution of bacterial resistance. Methicillin resistant *Staphylococcus aureus* (MRSA) is a serious nosocomial pathogen with limited treatment options.[2] We have developed synthetic derivatives of capreomycin, an anti-mycobacterial agent, that have potent *in vitro* activity against MRSA and other Gram positive bacteria. Furthermore, these derivatives were potent *in vivo*, as demonstrated in the murine bacteremia and thigh-infection models.



[1] Levy, S. B., Marshall, B. Antibacterial Resistance Worldwide: Causes, Challenges and Responses, *Nature Medicine Reviews*, (2004) 10(12), S122-S129.

[2] Barrett, J. F. MRSA – What is it, and How Do We Deal With the Problem?, *Expert Opin. Ther. Targets*, (2005) 9(2), 253-265.

P27

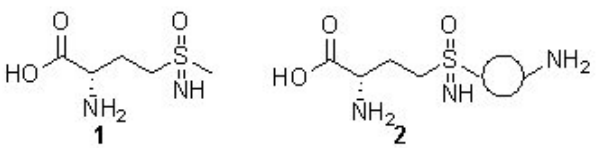
Design, synthesis and activity of methionine sulfoxyimine derivatives as glutamine synthetase inhibitors

Ł. Berlicki, A. Grabowiecka, P. Kafarski

Wrocław University of Technology

Glutamine synthetase is one of the most important enzymes of nitrogen metabolism [1]. It catalyzes formation of glutamine from glutamate and ammonium ion in presence of ATP as energy source. Their inhibitors have potential application in medicine as antituberculosis drugs [2]. Mycobacterium tuberculosis excretes large amounts of glutamine synthetase into intercellular space in order to build polyglutamate/glutamine cell wall structure. It was proved that application of methionine sulfoxyimine (1) – strong glutamine synthetase inhibitor blocks cell wall biosynthesis and subsequent death of the pathogen.

We have recently shown that incorporation of amino group into the structure of glutamine synthetase inhibitor could yield in highly active structure [3]. In the presented study similar approach was applied for construction of methionine sulfoxyimine derivatives (2). Molecular modelling proved that additional amino group should interact favourably with ammonium binding site and enhance inhibitor potency. Compounds 2 were obtained in enantiomerically pure form starting from homocystine derivatives. Their activity was measured against bacterial glutamine synthetase.



[1] Eisenberg D Gill HS Pfluegl GM Rotstein SH Structure-function relationships of glutamine synthetases. Biochim Biophys Acta 2000, 1477: 122 – 145

[2] Harth G Horwitz MA Inhibition of Mycobacterium tuberculosis glutamine synthetase as a novel antibiotic strategy against tuberculosis: demonstration of efficacy in vivo. Infect Immun 2003 71:456 - 464.

[3] Berlicki Ł Obojska A Forlani G Kafarski P Design, Synthesis, and Activity of Analogues of Phosphinothricin as Inhibitors of Glutamine Synthetase. J Med Chem 2005 48:6340 - 6349.

P28

Synthesis And Antituberculosis Activity Of 1,3,4-Thiadiazole Derivative Schiff Bases

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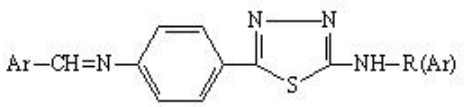
Tuberculosis is the most prevalent infectious disease worldwide with apparoximately three million patients dying every year. In the view of the drug-resistant problem and the lengthy tuberculosis therapy, it is important to develop new antituberculosis agents. In our previous study, one of the thiadiazole derivatives, 2-(4-chlorophenylamino)-5-(4-aminophenyl)-1,3,4-thiadiazole, showed 57% inhibition against *Mycobacterium tuberculosis* [1]. With the aim to obtain more active and selective antitubercular compounds, we synthesized a series of schiff bases, and combined with 1,3,4-thiadiazole in the same molecule due to the importance of thiadiazole and schiff bases in biological systems as antituberculosis activity [2-4]. The structures of the synthesized compounds were elucidated using UV, IR, ^{1}H-NMR, mass spectroscopy and elemental analysis. The Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) of the Southern Research Institute screened the compounds for antituberculosis activity.



[1] Karakus S, Rollas S. Synthesis and antituberculosis activity of new N-phenyl-N'-[4-(5-alkyl/aryl amino-1,3,4-thiadiazole-2-yl)phenyl] thioureas. Farmaco 2002; *57*:577- 581.

[2] Patole J, Shingnapurkar D, Padhyea S, Ratledgeb C. Schiff base conjugates of *p*-amino-salicylic acid as antimycobacterial agents.Bioorg Med Chem Lett 2006; 16: 1514–1517.

[3] Shucla HK, Desai NC, Astik RR, Thaker KA. Studies on some thiosemicarbazones and 1,3,4-thiadiazoles as potential antitubercular and antibacterial agents. J Indian Chem Soc 1984; 61: 168-171.

[4] Oruç EE, Rollas S, Kandemirli F, Shvets N, Dimoglo AS. The 1,3,4-Thiadiazole derivati-ves synthesis, structure elucidation and structure-antituberculosis activity relationships ýnvestigation. J Med Chem 2004; 47 (27): 6760-6767.

P29

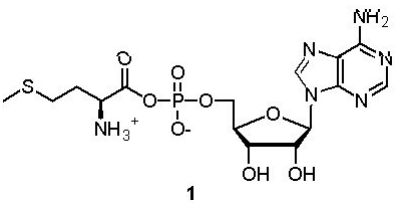
Design and Synthesis of Quinolinones as Methionyl-tRNA Synthetase Inhibitors

Farhanullah,[a] Su Yeon Kim,[a] Eun-Jung Yoon,[b] Eun-Chil Choi,[b] Sunghoon Kim,[c] Taehee Kang,[d] Farhana Samrin,[e] Sadhna Puri,[e] Jeewoo Lee*[a]

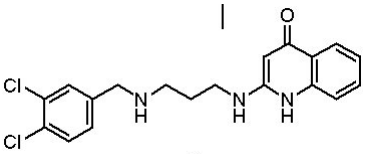
[a] Laboratory of Medicinal Chemistry and [b]Microbiology, and [c]Center for ARS Network, College of Pharmacy, Seoul National University, Seoul, Korea. [d] Imagene Co. Ltd., Seoul, Korea. [e] Department of Chemistry,Dayanand Girls Post Graduate College, Kanpur, India

Aminoacyl-tRNA synthetases (aaRSs) are a group of enzymes that precisely transfer amino acids from cellular pool to their corresponding tRNA cognates to form aminoacyl-tRNAs which serve as substrates for protein synthesis. The transfer of a particular amino acid to tRNA under influence of aaRS occurs through formation of an active intermediate aminoacyladenylate (aa-AMP) by the reaction of the amino acid and ATP. The catalytic activity of aaRSs is organism specific and it is different in pathogens and human beings. This difference in catalytic activity of aaRSs provides an opportunity to inhibit pathogens aaRSs selectively without perturbing host aaRSs. Thus aminoacyl-tRNA synthetases make an alternative drug target to develop antibacterial agents for the treatment of antibiotic resistant bacterial strains such MRSA and VRE.

In our continuing pursuit to develop new potent aminoacyl-tRNA synthetase inhibitors, pharmacophoric analysis of a recently reported [1] *S. aureus* MRS inhibitor **2** was performed and compared with structure of methionyl adenylate **1** by overlay investigation. The RMS superposition of the pharmacophoric groups verified excellent correlation between **1** and **2**. Further, it is evident from the superimposition of the two structures that linear chain of compound **2** provides appropriate separation between quinolone and 3,4-dichlorobenzene ring but does not fully superimpose with ribose ring of **1.** We therefore hypothesized that the linker with a hydrophilic functionality such as hydroxy, methoxy, or hydroxymethyl might provide a better surrogate for ribose ring. This notion led us to design and synthesize linear chain derivatives of compound **2**. The presentation comprises of the rationale, syntheses and biological activities of designed quinolinones.



1



2

P30

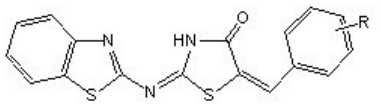
Synthesis and antimicrobial activity of benzylidene derivatives of 2-(benzo[d]thiazol-2-ylimino)thiazolidin-4-one

F. Zani*, A. Geronikaki**, M. Incerti*, P. Vicini*

*Pharmaceutical Department, Faculty of Pharmacy, Parma University, Parma, Italy. **Aristotelian University of Thessaloniki, School of Pharmacy, Thessaloniki University , Thessaloniki, Greece

The emergence of microbial resistance represents a severe problem that has intensified the search for new

drugs with improved antimicrobial activity. In our studies on design and development of antimicrobial agents [1,2], several 2-thiazolylamino-5-arylidene-thiazol-4-ones carrying hydroxy, methoxy, nitro and chloro groups on the arylidene moiety have been reported to possess excellent antibacterial properties against a wide spectrum of Gram positive bacteria [3]. This finding prompted us to synthesize a new series of analogues, by replacing the thiazole heterocycle with a benzo[*d*]thiazole system, a well know bioactive heterocyclic system widely explored by us in previous researches [1,2].



R= OH, OCH_3, NO_2, Cl

The new benzylidene derivatives of 2-(benzo[*d*]thiazol-2-ylimino)thiazolidin-4-one were investigated for their *in vitro* antimicrobial potency against a number of Gram positive and Gram negative bacteria, yeasts and moulds. Most of the tested compounds display good inhibition of the growth of Gram positive bacilli and staphylococci, including methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* strains, but in general, 2-benzothiazole-5-benzylidene-4-thiazolidinones exhibit a lower antibacterial activity when compared with that of the thiazole analogues. On the contrary the parent 2-(benzo[*d*]thiazol-2-ylimino)thiazolidin-4-one shows significant antifungal properties against both yeasts and moulds, properties not shown by the analogous 2-(thiazol-2-ylimino)thiazolidin-4-one. These results suggest that the presence of the benzene ring plays an important role in the modulation of the biological activity of the thiazolidinones under study and deserve further investigation**.**

P31

Design and Synthesis of 1,2,3-benzotriazole Derivatives as antifungal agents

Z. Rezaei, S. Khabnadideh, F. Amiri

Department of Medicinal Chemistry, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

Invasive fungal infections are major problems in immune-compromised patients. The recent expansion of antifungal drug research has occurred because there is a critical need for new antifungal agents to treat these life–threatening invasive infections.

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P32

Synthesis and antimicrobial activity of some new 3-[[1(2H)-phthalazinon-2-yl]methyl/ethyl]-4-aryl-1,2,4-triazole-5-thiones

S. Adak*, D. Doğruer*, T. Önkol*, L. Uzun*, S. Özkan**, M. Şahin*

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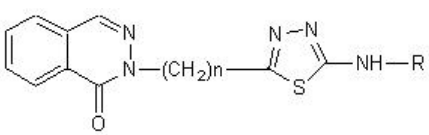
1,2,4-Triazoles have been reported to have antimicrobial activity. On the other hand, antimicrobial property has been reported to be associated with phthalazinone ring. In the design of new compounds, the development of hybride molecules through the combination of different pharmacophores in one frame may lead to compounds with increased antimicrobial activity. So, we synthesized new twelve 1,2,4-triazole derivatives which bind at two position of phthalazinone ring with methyl or ethylene bridges. Structures of the synthesized compounds have been confirmed by IR, ^{1}H-NMR and elemental analysis.

The synthesized compounds will be tested against two Gram (+) bacteria (*S. aureus, B. subtilis*), two Gram (-) bacteria (P. *aeruginosa, E.coli)* and two yeast-like fungus such as *C. albicans* and *C. parapsilosis* by using disc diffusion method. Ciprofloxacin and Ketoconazole will be used as control agents.



n	R
1	Phenyl
1	Benzyl
1	Phenethyl
1	4-Chlorophenyl
1	4-Metoxyphenyl
1	4-Methylphenyl
2	Phenyl
2	Benzyl
2	Phenethyl
2	4-Chlorophenyl
2	4-Metoxyphenyl
2	4-Methylphenyl

P33

Microwave-assisted synthesis of morpholine glycomimetics as surrogates for N-acetylmuramic acid

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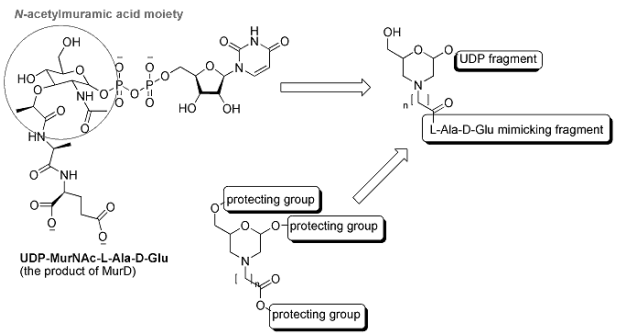
The Chair of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia

Saccharides play essential roles in many biological processes and are recognized as important leads for drug development [1]. Numerous carbohydrate mimetics (glycomimetics) have been investigated in order to obtain drug-like compounds [2]. Morpholine derivatives that mimic monosaccharide moiety have been synthesized and evaluated as a part of aminoglycoside antibiotics [3]. We were interested in developing optimal surrogates for *N*-acetylmuramic acid. The last one is recognised as one of the key structures in the design of transition-state mimicking MurD ligase inhibitors (a novel class of bacterial peptidoglycan biosynthesis inhibitors) [4].

We have designed morpholine glycomimetics as surrogates for *N*-acetylmuramic acid (figure 1).



We performed docking studies of model compounds into MurD active site in order to compare binding modes of native *N*-acetylmuramic acid and morpholine glycomimetics. Furthermore, we optimised synthetic route to morpholine derivatives from glucose derivatives using microwave-assisted synthesis and synthesized orthogonally protected morpholine glycomimetic (figure 1) that will be used in synthesis of MurD inhibitors.

[1] Boons GJ. DDT 1996;1:331-342.

[2] Compain P, Martin OR. Bioorg Med Chem 2001;9:3077-3092.

[3] a) Du M, Hindsgaul O. Synlett 1997; 395. b) Clark SM, Osborn HMI. Tetrahedron: Asymmetry 2004;15:3643-3652. c) Hanessian S, Tremblay M, Kornienko A, Moitessier N. Tetrahedron 2001;57:3255-3265.

[4] Gegnas LD, Waddell ST, Chabin RM, Reddy S, Wong KK. Bioorg Med Chem Lett 1998;8:1643-1648.

P34

The activity of Bisbenzimidazoles derivatives to Staphylococcus epidermidis

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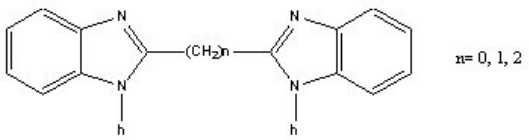
*Mersin University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Yenişehir Campus, 33169, Mersin, TURKEY. **Mustafa Kemal University, Faculty of Medicine, Department of Microbiology, 31100, Hatay, Turkey. ***Mersin University, Faculty of Pharmacy, Department of Pharmacology, Yenişehir Campus, 33169, Mersin, TURKEY

Staphylococcus epidermidis, the most common member of coagulase negative staphylococci (CNS), is an opportunistic pathogen, habitual inhabitant of the human epithelia and the most prevalent and persistent species on most skin and mucous membranes[1]. The major virulence factor of this organism is its ability to adhere to devices and form biofilms, which is responsible for a greater resistance to antibiotics. Several different specific molecular entities involved in attachment of *S. epidermidis* to polymer surfaces have been described. The overall aim of the study was to synthesize bisbenzimidazole derivatives (I) and evaluate their *in vitro* antimicrobial activity against *S. epidermidis* (ATCC 12228). To test the antibacterial specifity of our compounds to *S. epidermidis*, we used three Gram positive (*Enterococcus faecalis* (ATCC 29212),, *Staphylococcus aureus* (ATCC 29213) and *Staphylococcus epidermidis*) and two Gram negative (*Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853)) bacteria, employing broth microdilution and ampicillin were used as control. Our compounds showed good activity against *S. epidermidis* with minimum inhibitory concentration (MIC) values of approximately 12.5-25 mg/ml, which was one order of magnitude less than that of ampicillin (1.56 mg/ml). However, they inhibited the growth of the all screened bacteria in a wide concentration range, except *S. epidermidis,* with MIC values between 200-800 mg/ml. Considering all results obtained from antibacterial tests, it can be concluded that entire compounds tested more active towards *S. epidermidis* than other bacteria used. The experiments regarding the structure-activity relationship are still underway.



(I)

[1] Mohanty S S, Kay P R. Infection in total joint replacements. Why we screen MRSA when MRSE is the problem? J Bone Joint Surg Br 2004;86(2):266–8.

[2] Tojo M, Yamashita N, Goldmann DA, Pier GB. Isolation and characterization of a capsular polysaccharide adhesin from Staphylococcus epidermidis. J Infect Dis 1988; 157: 713-722.

P35

Activity of dinitroimidazole derivatives against Helicobacter pylori

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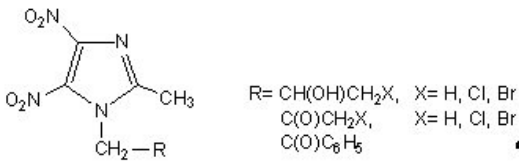
*Chair and Department of Organic Chemistry, Pharmaceutical Faculty, Poznan University of Medical Sciences, Poznań, Poland. **Chair and Department of Microbiology and Immunology, Silesian University of Medical Sciences, Zabrze, Poland

Nitroimidazole derivatives are chemotherapeutically important as agents in treatment different infections. The nitroimidazoles, in particular metronidazole the most commonly used, are accepted as the drugs of choice for the chemotherapy of anaerobic bacteria and protozoa diseases and also for the radiosensitization of hypoxic tumors. Metronidazole has become an important therapeutic option for patients suffering from peptic ulcers and the associated risk of gastric cancer resulting from infection by Helicobacter pylori.A synthesis of N-substituted derivatives of 2-methyl-4,5-dinitroimidazoles has been the subject of several recent reports, because they are interesting intermediates in the syntheses of important drug candidates as for example the antifungal and antioxidant agents. Now we are presenting results of test of some N-substituted derivatives of 2-methyl-4,5-dinitroimidazoles against CCUG 17874 Helicobacter pylori, a strain resistant to metronidazole. Many of examined compounds found to be high active.



The activity of some 4,5-dinitroimidazoles against bacteria organism was increased compared to metronidazole. Compounds containing hydroxypropyl chain at N-1 position of imidazole ring were the best active. The most potent activity showed 1-(3-bromo-2-hydroxypropyl)-2-methyl-4,5-dinitroimidazole. Among dinitroimidazoles with carbonyl group, two compounds with atoms of chlorine and bromine in three-carbon aliphatic chain were equiactive as metronidazole. Our studies have been shown that these compounds can be use as anti-Helicobacter drugs.

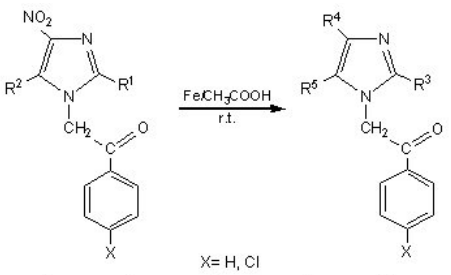
P36

Synthesis of aminonitroimidazole derivatives

D. Olender, L. Zaprutko

Chair and Department of Organic Chemistry, Pharmaceutical Faculty, Poznan University of Medical Sciences, Poznań, Poland

Nitroazole derivatives consisting of various 5-, 4- and 2-nitroimidazoles are used as therapeutic agents against a variety of protozoan and bacterial infections of human. Some of them are tested as antiviral, antimycotic and as radiosensitizing agents of anoxic cells.Now we are presenting results of reduction reactions of some N-substituted derivatives of dinitroimidazoles.N-Phenacyl derivatives of dinitroimidazoles were obtained in the reactions of phenacyl bromide or (p-Cl)-phenacyl bromide with 2,4-, 4,5- and 2-methyl-4,5-dinitroimidazole. Acting on these compounds with iron dust in acid, at room temperature selective reduction of one from among two groups of imidazole was carried out and as a result 2-amino-, 4-amino- and 5-amino derivatives were obtained. The result of reduction depended on the position of the nitro groups and the presence of methyl group at C-2 position of heterocyclic ring. As the main reduction product of N-phenacyl derivatives of 2,4-dinitroimidazole, we obtained appropriate 2-amino-4-nitroimidazoles. The reduction of derivatives of 4,5-dinitroimidazole, led to obtaining compounds, which were classified as 4-amino-5-nitroimidazole. These derivatives were separated only just after extraction. If the methyl group was presented at C-2 position of imidazole ring, the reduction of nitro group proceeded in direction forming appropriate 5-amino-4-nitro and 4-amino-5-nitro isomers.The aminonitroimidazoles were tested on their biological activity by the PASS C&T method. Some of them were predicted as notable radiosensitizers, antiprotozoal and antibacterial or antiepileptic agents.



The structure of described products has been confirmed with chemical spectral analysis using IR, MS, ^{1}H NMR and ^{13}C NMR methods.

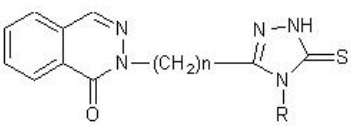
P37

Synthesis and antimicrobial activity of some new 2-[[1(2H)-phthalazinon-2-yl]methyl/ethyl]-5-arylamino-1,3,4-thiadiazoles

L. Uzun*, T. Önkol*, D. Doğruer*, S. Adak*, S. Özkan**, M. Şahin*

*Gazi University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Ankara, Turkey. **Gazi University, Faculty of Pharmacy, Department of Microbiology, Ankara, Turkey.

1,3,4-Thiadiazole have been reported to have antimicrobial activity. On the other hand, antimicrobial property has been reported to be associated with phthalazinone ring. In the design of new compounds, the development of hybride molecules through the combination of different pharmacophores in one frame may lead to compounds with increased antimicrobial activity. So, we synthesized new twelve 1,3,4-thiadiazole derivatives which bind at two position of phthalazinone ring with methyl or ethylene bridges. Structures of the synthesized compounds have been confirmed by IR, ^{1}H-NMR and elemental analysis.



n	R
1	Phenyl
1	Benzyl
1	Phenethyl
1	4-Chlorophenyl
1	4-Metoxyphenyl
1	4-Methylphenyl
2	Phenyl
2	Benzyl
2	Phenethyl
2	4-Chlorophenyl
2	4-Metoxyphenyl
2	4-Methylphenyl

The synthesized compounds will be tested against two Gram (+) bacteria (*S. aureus, B. subtilis*), two Gram (-) bacteria (P. *aeruginosa, E.coli)* and two yeast-like fungus such as *C. albicans* and *C. parapsilosis* by using disc diffusion method. Ciprofloxacin and Ketoconazole will be used as control agents.

P38

HDAC inhibitors as novel anti-Candida agents

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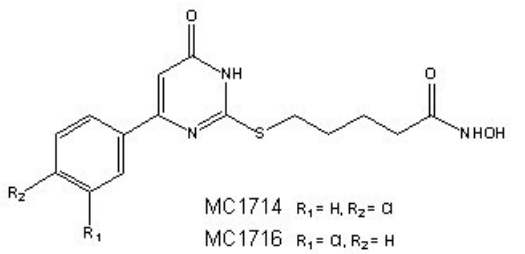
The recent literature about the interesting effects of histone deacetylase inhibitors (HDACi) on the epigenetic modulation of gene expression in fungi, and in particular on drug resistance and on the white-opaque colony morphology switching in *C. albicans* [1], prompted us to test some derivatives of a novel class of HDACi recently reported by us (Uracil-Based Hydroxyamides, UBHAs) [2] as potential *Candida* inhibitors. Two newly designed compounds (MC1714 and MC1716) showed the capability to significantly interfere at epigenetic level with the two major mechanisms of *C. albicans* pathogenicity: the yeast-hypha transition and the high-frequency phenotypic switching that significantly influence the pathogen adherence to human epithelial cells (cultured pneumocytes).



These effects revealed to be mainly due to the HDAC inhibition-mediated downregulation of *Efg1p* and *Cap1p*, two morphogenetic regulators crucial for *Candida* morphologic adaptation programs and virulence.

[1] Klar AJS, Srikantha T, Soll DR. A histone deacetylation inhibitor and mutant promote colony-type switching of the human pathogen *Candida albicans*. Genetics 2001;158:919-924.

[2] Mai A, Massa S, Rotili D, Pezzi R, Bottoni P, Scatena R, Meraner J, Brosch G. Exploring the connection unit in the HDAC inhibitor pharmacophore model: novel uracil-based hydroxamates. Bioorg Med Chem Lett 2005;15:4656-4661.

Antibodies

P39

Affinity Stability of Monoclonal Anti-digoxin Antibody against thermal variation

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Digoxin is one of the large groupe of cardiac glycosides that exerts positive inotropic and electrophysiologic effects on the heart. Cardiac glycosides are pharmaceutically important drugsused for treatment of congestive

heart failure. In this study the affinities of anti-digoxin antibody in different temperatures were evaluated using ELISA method. At room temperature purified antibody was coated onto the wells of microtiter plates, blocked, washed and treated with different concentrations of digoxin prepared from a stock methanolic solution of digoxin such that different concentrations from 10 pico gram per well up to 10000 pico gram per well were covered Results of the affinity calculation on the basis of scatchard analysis was found to be 2.6× 10^8 liter per mole . In further studies the antibody was heated up to 50 and 70 degrees of centigrade. Then the coating process and affinity measurements were carried out as stated above. In mentioned temperatures the affinities were found to be 2 × 10^8 and 1.2 × 10^8 liter per mole, respectively.

Results showed thermal stability of this monoclonal antibody, indicating as a useful tool for serum digoxin detection.

Antipsychotics

P40

Novel Tetracyclic Tetrahydrofuran derivatives as potent Broad-Spectrum Psychotropic Agents

Jose M. Cid*, José M. Alonso*, J. Ignacio Andrés*, Laura Iturrino*, Anton Megens**, Shirley Pullan** and Andrés A. Trabanco*

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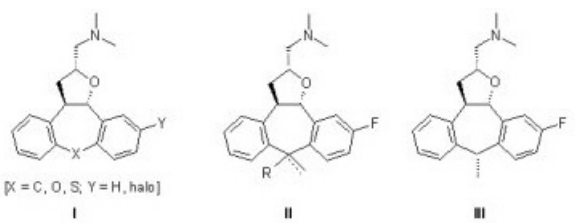
Abstract. We have recently described a series of tetracyclic tetrahydrofuran derivatives represented by structures **I** [1-3]. These tetracycles proved to have a rich pharmacological profile as it was shown through their interaction with multiple dopaminergic, serotonergic, ?-adrenergic and histamine receptors and for the norepinephrine transporter. This binding profile translated into some interesting activities in several *in vivo* assays predictive for antipsychotic, anxiolytic and antidepressant potential [4]

Herein we will report on the synthesis and pharmacological characterization of new carbon-bridge substituted analogues represented by formula **II**, which have led to the identification of **III** as a potent broad-spectrum psychotropic agent [5].



[1] Trabanco A. A.; Alonso, J. M.; Andrés, J. I.; Cid, J. M.; Fernández, J.; Iturrino, L.; Megens, A. *Chem. Pharm. Bull.* **2004**, *52*, 262.

[2] Cid, J. M.; Alonso, J. M.; Andrés. J. I.; Fernández, J.; Gil, P.; Iturrino, L.; Matesanz, E.; Meert, T. F.; Megens, A.; Sipido, V. K.; Trabanco, A. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2765.

[3] Fernández, J.; Alonso, J. M.; Andrés, J. I.; Cid, J. M.; Díaz, A.; Iturrino, L.; Gil, P.; Megens, A.; Sipido, V. K.; Trabanco, A. A. *J. Med. Chem.*, **2005**, *48*, 1709.

[4] Alonso, J. M.; Andrés. J. I.; Cid, J. M.; Díaz, A.; Fernández, J.; Gil, P.; Iturrino, L.; Megens, A.; Sipido, V. K.; Trabanco, A. A. in "Internacional Proceedings, Austrian-German-Hungarian-Italian-Polish-Spanish Joint Meeting on Medicinal Chemistry – JMMC", Ettmayer, P.; Ecker, G. Eds., Monduzzi Editore, **2005**, 63.

[5] Cid Núñez, J. M.; Megens, A.A.H.P.; Trabanco Suárez, A.A.; WO 2005/121113 A1

P41

1-N-Substitetedthiocarbamoyl-3-(4-fluorophenyl)-5-(4-chlorophenyl)-2-pyrazolines and their selective MAO inhibitory properties and antidepressant activities

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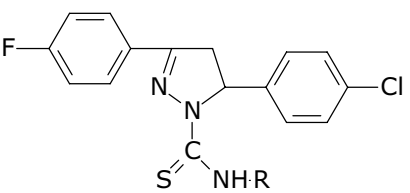
Depression is a severe mental disorder characterized by exaggerated and pervasive feelings of sadness, loss of interest and decreased energy. Earlier studies [1-5] demonstrated that, 1,3,5-triphenyl-2-pyrazolines, 1-thiocarbamoyl-3,5-diphenyl-2-pyrazolines and some bicyclic pyrazolines have selective monoamine oxidase (MAO) inhibitory properties, antidepressant activities and anxiolytic activities. In this study, as an extension of our previously researches, we synthesized some 1-N-substitutedthiocarbamoyl-3-(4-fluorophenyl)-5-(4-chlorophenyl)-2-pyrazolines and evaluated their selective MAO inhibitory properties and antidepressant activities.



R: H, methyl, ethyl, allyl, phenyl

These compounds were synthesized according to the methods reported earlier with slight modifications [1-4]. Chemical structures of the compounds were proved by their UV, IR, ^{1}H-NMR, MASS spectral data and microanalysis. All the compounds showed selective MAO-A inhibitory properties of rat liver homogenates, and the

inhibition of the compounds were time dependent. The antidepressant and anxiogenic activities of the compounds were Porsolt's Behavioural Despair and Evaluated Plus-maze test respectively. 1-N-Allylthiocarbamoyl-3-(4-fluorophenyl)-5-(4-chlorophenyl)-2-pyrazoline reduced 44.65% immobility times at 100 mg/kg dose level.

[1] Bilgin, A.A., Yeşilada, A., Palaska, E., Sunal, R., Synthesis and Antidepressant Activity of Some New 8-Thiocarbamoyl-7,8-diazabicyclo [4.3.0]non-6-ene Derivatives. Arzneim.-Forsch./Drug Res., 42, 1271-1273, 1992.

[2] Bilgin, A.A., Palaska, E., Sunal, R., Studies on the Synthesis and Antidepressant Activity of Some 1-Thiocarbamoyl-3,5-diphenyl-2-pyrazolines. Arzneim.-Forsch./Drug Res., 43, 1041-1044, 1993.

[3] Palaska, E., Erol, D., Demirdamar, R., Synthesis and Antidepressant Activities of Some 1,3,5-Triphenyl-2-pyrazolines. Eur. J. Med. Chem., 31, 43-47, 1996.

[4] Palaska, E., Aytemir, M., Uzbay, I.T., Erol, D., Synthesis and Antidepressant Activities of Some 3,5-Diphenyl-2-pyrazolines. Eur. J. Med. Chem., 36, 539-543, 2001.

[5] Chimenti, F., Maccioni, E., Secci, D., Bolasco, A., Chimenti, P., Granese, A., Befani, O., Turini, P., Alcaro, S., Ortuso, F., Cirilli, R., LaTorre, F., Cardia, M.C., Distinto, S., Synthesis, Molecular Modeling Studies, and Selective Inhibitory Activity against Monoamine Oxidase of 1-Thiocarbamoyl-3,5-diaryl-4,5-dihydro-(1H)-pyrazole Derivatives, J. Med Chem. 48, 7113-7122, 2005.

P42

Syntheses and binding studies of new 4-(N-benzylamino) piperidine and piperazine derivatives as potential antidepressant drugs

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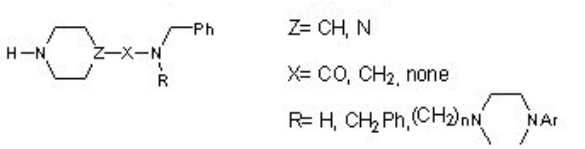
Depression is one of the most prevalent chronic mental illness affecting people of all gender, ages and backgrounds. Different approaches have been undertaken in its treatment producing a broad range of medicaments. However there is still a significant space for improved therapeutics with respect to both efficacy and side effects. The monoamine hypothesis provides a rationale for the development of promising new agents that target specific serotonin receptor subtypes plus one o more of the following transporters: serotonin, norepinephrine and dopamine.

In our laboratory, a research program toward new, efficient and fast acting antidepressant drugs is being developed. With this goal, 4-(*N*-benzylamino)piperidine derivatives have been prepared and tested for affinity in an array of receptors. Some of them displayed a dual binding profile with moderate to high affinity for human serotonin transporter (hSERT) and human norepinephrine transporter (hNET). As a continued effort to improve this pharmacological profile, several lines of research have being pursued to incorporate affinity for specific serotonin receptor subtypes, particularly the 5-$HT_{1A.}$



Here we present new 4-(*N*-benzylamino)piperidine and piperazine derivatives, depicted below, synthesised and pharmacologically studied.

Preliminary pharmacological results of these compounds have shown a very promising binding profile, associating a moderate affinity for the 5-HT_{1A} receptor (Ki values up to 133nM) to affinities for hSERT (Ki values up to 78nM) and hNET (Ki values up to 229nM). This affinity profile for three receptors might be interesting in the finding of a new antidepressant and further pharmacological characterisation is in progress for the evaluation of this chemical family as antidepressants.

This work has been funded in part by Ministerio de Industria, Turismo y Comercio of Spain and Consejería de Industria, Comercio y Turismo of the Basque Government

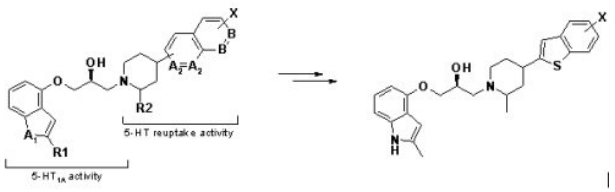
P43

Advances Toward New Antidepressants Beyond SSRIs: Development of Dual-Acting 5-HT1A Antagonist / 5-HT Reuptake Inhibitors

K. Takeuchi, T. Kohn, N. Honigschmidt, V. Rocco, P. Spinazze, D. Koch, D. Nelson, B. Wainscott, D. Koger, D. Lodge, L. Martin, J. Shaw, P. Threlkeld, D. Wong

Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA

Selective serotonin reuptake inhibitors (SSRIs) increase the extracellular serotonin (5-HT) in terminal regions of the serotonergic systems through the prevention of reuptake of the transmitter into nerve terminals. This effect is the basic mechanism for the treatment of depression. In the clinical setting, however, it takes more than two weeks before a significant improvement in the depressed patient is observed. The delayed clinical efficacy of SSRIs has been postulated by the observation that the maximal increase in 5-HT after acute systemic uptake blockade is limited by the feedback inhibitory mechanism of the 5-HT_{1A} autoreceptors [1]. The aim of this work was to design, synthesize and evaluate new compounds that would inhibit 5-HT reuptake and also block somatodendritic 5-HT_{1A} autoreceptors. This dual pharmacological profile should lead, in principle, to a rapid and pronounced enhancement in serotonergic neurotransmission and consequently to a more efficacious treatment of depression [2].



In a search for new and efficient antidepressants, (1-(4-arylpiperidyn-1-yl)-3-((indol-4-yl)oxy)propan-2-ol derivatives were designed, synthesized, and evaluated for 5-HT reuptake inhibition and 5-HT_{1A} receptor antagonism. The design was based on coupling structural moieties related to inhibition of serotonin reuptake, such as gamma-aryloxypropylamines, to arylpiperidines, which mimic the arylpiperazine moiety of $5HT_{1A}$ ligands when coupled with the propyl side chain. The present study demonstrates how the substituents and their stereochemistry on the aryl and piperidine rings would affect the dual action and how the combination of each element was optimized to produce potent and orally active 5-HT_{1A} antagonist / 5-HT Reuptake inhibitors.

[1] Chaput H, de Montigny C, Blier P. Naunyn-Schmiedeberg's Arch Pharmacol 1986; 333:342-348.

[2] Artigas F, Perez V, Alvarez E. Arch Gen Psychiatry 1994; 51:248-251

P44

Piperazine derivatives as selective serotonin re-uptake inhibitors

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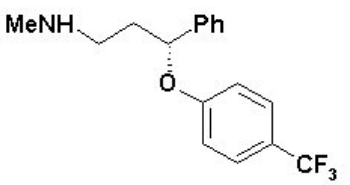
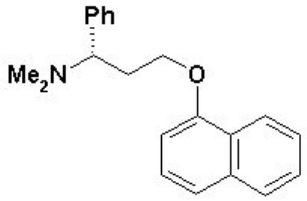
Discovery Chemistry, Pfizer Global Research and Development, Sandwich, Kent, UK

Release of the neurotransmitter serotonin (5-HT) into the synaptic cleft results in receptor activation and is followed by reuptake of the neurotransmitter 5-HT by the serotonin reuptake cognate transporter protein. Inhibition of this transporter constitutes an attractive approach to the treatment of a number of indications. For example, the selective serotonin reuptake inhibitor (SSRI) Fluoxitine is used to treat depression and the SSRI Dapoxetine is under development as a potential treatment for premature ejaculation.

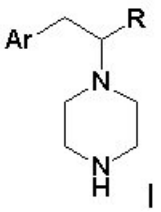


Fluoxetine

Arylethylpiperazines (1) have been identified through pharmacophoric overlap, directed file screening and focused analogue synthesis as a new class of potent, selective serotonin re-uptake inhibitors (SSRi's).



Dapoxetine



(1)

SAR in this series for both SSRi activity and selectivity over related monoamine transporters will be discussed, as will optimisation of pharmacokinetic properties. Synthetic routes to compounds of this class will also be disclosed.

[1] Burger's Medicinal Chemistry and Drug Discovery Copyright © 2003 by John Wiley & Sons, Inc. DOI: 10.1002/0471266949.bmc101

P45

N-(1,2-diphenylethyl)piperazines: A new class of dual serotonin/noradrenaline reuptake inhibitors

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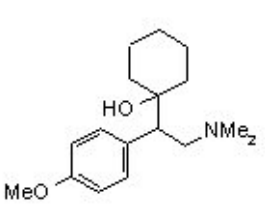
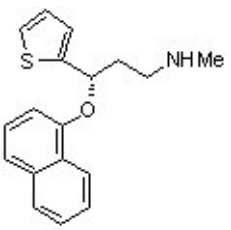
Release of the neurotransmitters serotonin (5-HT), noradrenaline (NA) and dopamine (DA) into the synaptic cleft results in receptor activation, and is followed by reuptake of the neurotransmitters by their respective cognate transporter proteins. Inhibition of these transporters constitutes an attractive approach to the treatment of a number of diseases. For example, dual 5-HT/NA reuptake inhibitors venlafaxine (**1**) and duloxetine (**2**) are used to treat depression[1] and duloxetine has also shown efficacy in stress urinary incontinence (SUI).[2]

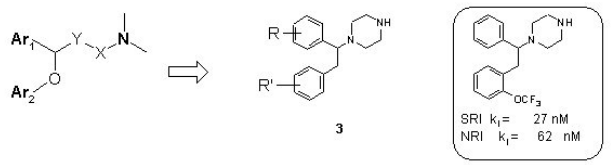


1 venlafaxine



2 duloxetine

N-(1,2-Diphenylethyl)piperazines (**3**) have been identified through pharmacophore overlap, directed file screening and analogue synthesis as a new class of selective dual 5HT/NA reuptake inhibitors (SNRi). [3]



The presentation will include: (i) detailed SAR which led to the identification of preferred compounds; (ii) efficient synthetic routes to **3**; and (iii) the preclinical profiles of preferred compounds to include pharmacokinetic, safety and efficacy data in animal models of SUI.

[1] Duloxetine and venlafaxine-XR in the treatment of major depression disorder. Vis, Peter M. J.; van Baardewijk, Marc; Einarson, Thomas R. *Annals of Pharmacotherapy* **2005**, *39(11),* 1798.

[2] Duloxetine : In stress urinary incontinence. McCormack, Paul L.; Keating, Gillian M. *Drugs* **2004**, *64(22)*, 2567.

[3] Preparation of piperazine derivatives which exhibit activity as serotonin and noradrenaline re-uptake inhibitors. G. Bish, A. D. Brown, P. V. Fish, M. J. Fray, A. Stobie, F. Wakenhut, G. A. Whitlock. **2005**, WO 068447

P46

DOP (delta opioid peptide) receptor related antidepressant activity of carbonyl derivatives of 1-aryl-2-aminoimidazolines-2.

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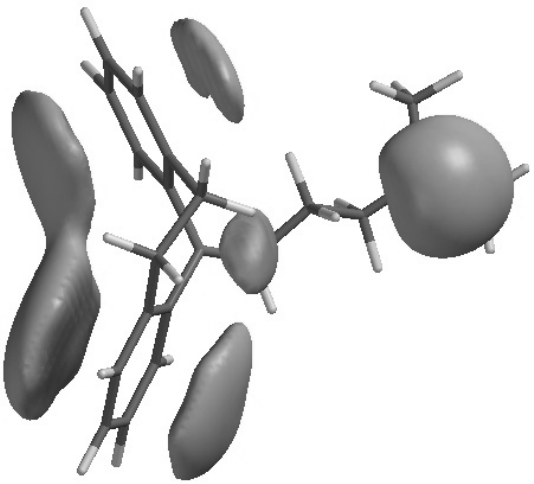
*Department of Synthesis and Chemical Technology of Pharmaceutical Substances, Faculty of Pharmacy, Medical University, 20-081 Lublin, Poland. **Department of Pharmacology and Pharmacodynamics, Faculty of Pharmacy, Medical University, 20-081 Lublin, Poland. ***Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455, USA

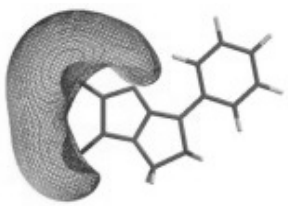
Search for new anxiolytics and antidepressants are still pending because depression is the third main cause of health problems in the world after heart diseases and cancer.

Carbonyl derivatives of 1-aryl-2-aminoimidazoline-2 both of the chain and cyclic structure were found to possess significant or very significant affinity to MOP and 5-HT_2 receptors. In animal test antinociceptive but also significant depressive action on mice was observed [1-3].

Continuing the research on their antidepressant action involvement of the DOP opioid receptor and joint activity toward DOP and 5-HT receptors in that spectrum of action was confirmed. The compounds investigated exhibited antidepressant-like activity in the Porsolt's and reserpine-induced hypothermia tests. In the threshold doses some of them enhanced the antidepressant effect of the threshold dose of Imipramine. The compounds tested administered together with Imipramine did not impaired the locomotor activity in the doses used.

The antidepressant-like effect of some of the compounds was reversed significantly by the selective DOP opioid receptor antagonist – Naltrindole, which can suggests participation of the DOP receptor in the antidepressant action of tested compounds. Moreover their antinociceptive action was also reversed after Naltrindole administration.





[1] Matosiuk D, et al.: Synthesis and pharmacological activity of new carbonyl derivatives of 1-aryl-2-iminoimidazolidine. Part 1. Synthesis and pharmacological activity of chain derivatives of 1-aryl-2-iminoimidazolidine containing urea moiety. Eur J Med Chem 2001; 36: 783-797.

[2] Matosiuk D, et al.: Synthesis and pharmacological activity of new carbonyl derivatives of 1-aryl-2-iminoimidazolidine. Part 2. Synthesis and pharmacological activity of 1,6-diaryl-5,7(1H)dioxo-2,3-dihydroimidazo[1,2-a][1,3,5]triazines. Eur J Med Chem 2002; 37: 761-772.

[3] Matosiuk D, et al.: Synthesis and pharmacological activity of new carbonyl derivatives of 1-aryl-2-iminoimidazolidine. Part 3. Synthesis and pharmacological activity of 1-aryl-5,6(1H)dioxo-2,3-dihydroimidazo[1,2-a]imidazoles. Eur J Med Chem 2002; 37: 845-853.

P47

Novel sulfonamides as potential antipsychotics having high affinity for both dopamine d2 and d3 receptors

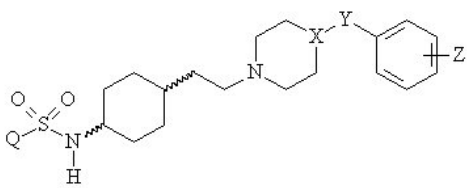
E. Agai-Csongor, J. Galambos, K. Nogradi, I. Vago, G. Keseru, B. Kiss, I. Laszlovszky, K. Saghy, I. Gyertyan, L. Gemesi, M. Zajer-Balazs, G. Domany

Gedeon Richter Ltd. , Budapest, 10. , P. O. B. 27. , H-1475 Hungary

Our quest for new antipsychotics has been based on three interrelated hypotheses: *i)* dopamine D_2 antagonism is required for antipsychotic activity, *ii)* dopamine D_3 antagonism may carry favourable effects such as cognitive enhancement and lack of catalepsy and *iii)* in order to achieve simultaneous *in vivo* manifestation of D_2 and D_3 receptor antagonism the compound should have higher affinity to D_3 than to D_2 receptors.

A significant part of the D_3/D_2 competitor compounds are 4-arylpiperazines substituted on the N-1 nitrogen atom with acylamidoalkyl or acylamidocyclohexylethyl groups. In order to explore whether the acylamido group could be successfully substituted with sulfonamido moieties, a series of compounds with the general formula **A** were prepared and tested *in vitro* and *in vivo*.

During the lead optimisation, several compounds were identified that showed high affinity towards dopamine D_2 receptors with relatively higher affinity towards dopamine D_3 receptors. These compounds were orally bioavailable and elicited significant efficacy in the apomorphine-induced climbing test following oral administration.



A

where: Q = aryl, hetaryl, alkyl;
X = N or CH; Y = single bond, CH_2 or O;
Z = H, one or more alkyl, alkoxy, halogen etc.

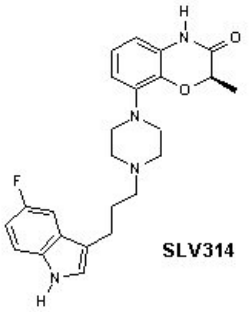
P48

Synthesis, SAR and Biological Properties of 1-heteroaryl-4-[ω-(1H-indol-3-yl)-alkyl]-piperazines, Novel Potential Antipsychotics Combining Potent Dopamine D2 Receptor Antagonism With Potent Serotonin Reuptake Inhibition

P. Smid, H. K. A. C. Coolen, R. van Hes and C. G. Kruse

Solvay Pharmaceuticals Research Laboratories, C.J. van Houtenlaan 36, 1381 CP, Weesp, The Netherlands

A series of novel bicyclic 1-heteroaryl-4-[ω-(1*H*-indol-3-yl)-alkyl]-piperazines was synthesized and evaluated on binding to dopamine D_2 receptors and serotonin reuptake sites. This class of compounds proved to be potent *in vitro* dopamine D_2 receptor antagonists and in addition were highly active as serotonin reuptake inhibitors. Some key representatives showed potent pharmacological *in vivo* activities after oral dosing in both the antagonism of apomorphine-induced climbing and in the potentiation of 5-HTP induced behaviour in mice.



SLV314

Based on the preclinical data, 8-{4-[3-(5-fluoro-1*H*-indol-3-yl)-propyl]-piperazin-1-yl}-4*H*-benzo-[1,4]oxazin-(R)-2-methyl-3-one (**SLV314**) was selected for clinical development. *In vitro* and *in vivo* studies revealed that **SLV314** has favourable pharmacokinetic properties and a high CNS-plasma ratio. Molecular modelling studies showed that the bifunctional activity of **SLV314** can be explained by its ability to adopt two different conformations fitting either the dopamine D_2 receptor pharmacophore or the serotonin transporter pharmacophore.

1) Smid, P.; Coolen, H. K. A. C.; Keizer, H. G.; van Hes, R.; de Moes, J.-P.; den Hartog, A. P.; Stork, B.; Plekkenpol, R. H.; Niemann, L. C.; Stroomer, C. N. J.; Tulp, M. Th. M.; van Stuivenberg, H. H.; McCreary, A. C.; Hesselink, M. B.; Herremans, A. H. J.; Kruse, C. G. *J. Med. Chem.;* **2005**; *48*(22); 6855-6869.

P49

Asymmetric Synthesis of Enantiomerically Pure Milnacipran Analogs

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University of Oslo

Depression is a mental condition related to an imbalance of one or more neurotransmitters [1]. Improvement in efficacy, onset of action, and absence of side effects are major goals in the developent of new antidepressants. Milnacipran (**5**, Ar=Ph) is a commercially available antidepressant drug that shows affinity for the serotonin and norepinephrine transporters [2]. During the present work it has been used as a lead compound in the development of a series of analogs. Both entiomers of the 2-(aminomethyl)-1-aryl-*N*,*N*-diethylcyclopropanecarboxamide hydrochlorides (**5**) were prepared in a four-step synthesis from the corresponding arylacetonitriles (**1**), the first step being an asymmetric synthesis in a reaction with enantiomerically enriched epichlorohydrin.

The synthesized compounds were tested for affinity for the serotonin, norepinephrine and dopamine transporters.

P50

Synthesis and Pharmacological Evaluation of New 1-Aryl- 3-[(4-benzyl)piperidine-1-yl]propane Derivatives

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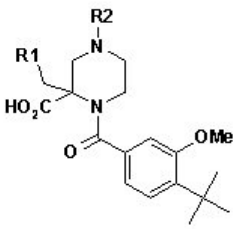
Major depression disorder (MDD) poses a significant health problem and one of the most frequent illnesses in the world affecting people of all gender, ages and backgrounds. Pharmacotheraphy of depression has been successful, but improvements in response rates, remission rates, side effects, compliance and faster onset of therapeutic action have become prime objectives in drug development.

Selective serotonin (5-HT) reuptake inhibitors (SSRIs) have less severe side effects than first generation drugs, tricyclic antidepressants (TCA), and nonselective monoamine oxidase inhibitors (MAOI) and are the most widely prescribed antidepressants in several countries. In a search toward new and efficient antidepressants, a series of 1-aryl-3-[(4-benzyl)piperidine-1-yl]propane derivatives were synthesized and the structures of the compounds have been elucidated by spectral methods. Common structural skeletons of the designed compounds are given below.



[1] Poordad F. Expert Opin. Emerging Drugs (2003), 8: 9-25.

[2] Burton G. et al. Bioorg. Med. Chem. Lett. (2005) 15: 1553-6.

Antivirals

P51

Lead Optimisation of Acylpyrrolidines (C4 6-membered heterocycles) - Novel Inhibitors of Hepatitis C NS5B Polymerase

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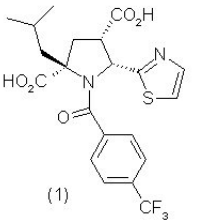
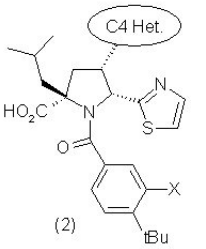
Hepatitis C Virus (HCV) is a positive, single strand RNA virus of the Flaviviridae family. It is estimated that HCV currently infects 170 million people, 3% of the world population [1]. Compounds such as (2*S*,4*S*,5*R*)-2-(2-methylpropyl)-5-(1,3-thiazol-2-yl)-1-{[4-(trifluoromethyl)phenyl]carbonyl}-2,4-pyrrolidinedicarboxylic acid (1) have been shown to exhibit potent activity against HCV NS5B RNA-dependent RNA polymerase [2].





We present some approaches to lead optimisation of this series, with particular focus on 6-membered heterocycle replacements at the C4 position (2), including their synthesis, biological activities and pharmacokinetic profiles.

[1] WHO. Weekly Epidemiology Record (1997), 72, 65.

[2] Burton G. et al. Bioorganic & Medicinal Chemistry Letters (2005), 15, 1553-6.

P52

Structure Based Optimisation of Acylpyrrolidines (Benzamide SAR) - Novel Inhibitors of Hepatitis C NS5B Polymerase

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Hepatitis C Virus (HCV) is a positive, single strand RNA virus of the Flaviviridae family. It is estimated that HCV currently infects ~3% of the world population [1]. Approximately 70% of infected patients go on to develop chronic liver disease, including fibrosis, cirrhosis and liver cancer, making HCV the leading cause for liver transplants. The current gold standard treatment is combination therapy using PEG-interferon-a (1.5mg/kg weekly) and ribavirin (800-1200mg/day) but has limited success rates and a severe side effect profile [2-3]. There is therefore a strong impetus to develop new, more effective drugs to combat this disease.

A potential target for small molecule inhibitors of HCV is the viral NS5B Polymerase. High throughput screening of the GSK compound collection identified a novel class of NS5B inhibitors, the acyl pyrrolidines (AP's) [4]. Structure based approaches to the successful potency optimisation of this lead will be presented, focussing in particular on the benzamide portion of the molecule.

[1] WHO. Weekly Epidemiol. Record (1997), 72, 65.

[2] F. Poordad. Expert Opin. Emerging Drugs (2003), 8, 9-25.

[3] J. Hutchinson et al. N. Engl. J. Med. (1998) 339, 1485-1492.

[4] G. Burton et al. Bioorg. Med. Chem. Lett. (2005),15, 1553-1556.

P53

2'-C-Methyl-cytidine and 2'-C-methyl-uridine as antiviral agents: 3'-C-sugar modified derivatives

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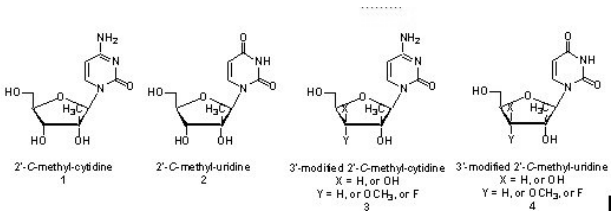
* Laboratoire Coopératif Idenix-CNRS-Université Montpellier II, Case Courrier 008, Université Montpellier II, Place Eugène Bataillon, F-34095 Montpellier Cedex 5, France. ** Laboratoire de Chimie Médicinale Idenix, Cap Gamma, 1682 rue de la Valsière, F-34184 Montpellier Cedex 4, France

Recently, it was discovered that 2'-*C*-methyl-cytidine (**1**) and 2'-*C*-methyl-uridine (**2**) are potent inhibitors of the replication of several RNA viruses in cell culture [1]. Encouraged by these results, and as part of our anti-hepatitis C program, we decided to perform a structure-activity relationship (SAR) study focused on the evaluation of modifications at the 3'-position of the sugar moiety on **1** and **2**.

Therefore, several hitherto unknown 3'-*C*-modified-2'-*C*-methyl-ribonucleosides have been synthesized, in both the cytosine (**3**) and the uracil series (**4**) [2].



We will detail herein the chemical syntheses of those 3'-*C*-modified-2'-*C*-methyl-ribonucleosides. Most of them have been synthesized starting from 2'-*C*-methyl-uridine **2**, excepted the 3'-fluoro derivatives which required another strategy based on the use of commercially available uridine.

All the hitherto unknown compounds thus synthesized were tested against a wide range of RNA viruses, including bovine viral diarrhea virus (BVDV), a pestivirus surrogate model of HCV for the evaluation of antiviral agents [3].

[1] (a) Sommadossi, J.-P.; La Colla, P. W.O. PCT Int. Appl. 2001092282, 2001. (b) Sommadossi, J.-P.; La Colla, P. W.O. PCT Int. Appl. 2001090121, 2001.

[2] Pierra, C.; Amador, A.; Badaroux, E.; Gosselin, G.; Storer R. Synthesis of 2'-*C*-methyl-cytidine and 2'-*C*-methyl-uridine derivatives modified on the 3'-position, as potential antiviral agents. Collection of Czechoslovak Chemical Communications; submitted.

[3] Buckwold, V. E.; Beer, B. E.; Donis, R. O. *Antiviral Res.* 2003, **60**, 1.

P54

Synthesis and biological evaluation of some new 4-Thiazolidinones as chemotherapeutic agents

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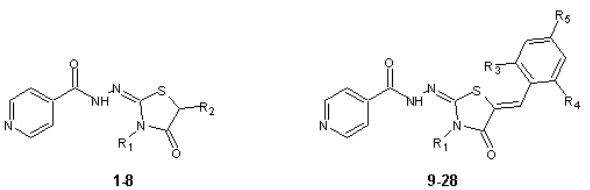
4-Thiazolidinone derivatives have many interesting activity profiles and they have been reported to possess antibacterial [1], antitubercular [2], anti-HIV [3] and anti-cancer [4] properties. Capability of these derivatives to inhibit bacterial enzyme MurB, HIV-1 reverse transcriptase, and COX-2 have been documented. Moreover, reports on antiproliferative activity of some 4-thiazolidinones against prostate and colon cancers make this ring an interesting scaffold for the design of novel chemotherapeutic agents. Therefore we designed and synthesized some novel 4-thiazolidinones **1-8** and their 5-arylidene derivatives **9-28**. Structures of the synthesized compounds were confirmed by the use of IR, ^{1}H-NMR and HR-MS data.



R_1 = CH_3, C_2H_5, $CH_2CH=CH_2$, $CH_2C_6H_5$; R_2 = H, CH_3 ; R_3, R_4, R_5 = H, Cl, F, OCH_3

All compounds **1-28** were evaluated in vitro against HIV-1 (IIIB) and HIV-2 (ROD) strains in MT-4 cells, as well as other selected viruses such as bovine viral diarrhoea virus (BVDV), yellow fever virus (YFV), HSV-1, HSV-2, Vaccinia virus, Vesicular stomatitis virus, Coxsackie virus B4, RSV, Parainfluenza-3 virus, Reovirus-1, Sindbis virus and Punta Toro virus using HeLa, Vero, HEL and E_6SM cell cultures. The synthesized compounds **1-28** were also screened for their cytotoxic properties on HEK 293 cells and anti-cancer effects against HeLa (cervic cancer), Hep-3B (hepatocellular carcinoma) cell lines. To find effects of anti-cancer and

cytotoxic properties, the CellTiter 96® AQueous Non-Radioactive Cell Proliferation Assay is applied.

[1] Bonde C.G., Gaikwad N.J., *Bioorg. Med. Chem.* **12** (2004) 2151–2161.

[2] Küçükgüzel S.G., Oruç E.E., Rollas S., Şahin F., Özbek A., *Eur.J.Med.Chem.* **37** (2002) 197–206.

[3] Rao A., Balzarini J., Carbone A. et.al., *Antiviral Research* **63** (2004) 79–84.

[4] Ottanà R., Carotti S., Maccari R. et.al., *Bioorg.Med.Chem.Lett.* **15** (2005) 3930–3933.

P55

Identification and development of 2-(3-bromophenyl)-6-[(2-hydroxyethyl)amino]-1H-benzo[de]isoquinoline-1,3(2H)-dione as inhibitor of HCV NS5B Polymerase

S. Malancona, B. Attenni, S. Avolio, J. Martin Hernando, V. Summa, U. Koch, S. Di Marco, E. Rydberg, A. Carfì, S. Altamura, G. Migliaccio, J. Ontoria, M. Rowley, F. Narjes

IRBM-MRL Rome, via Pontina Km 30.600, 00040 Pomezia (Rome), Italy

The Hepatitis C virus (HCV), a (+)-strand RNA virus, is the major causative agent of non-A non-B hepatitis and infects nearly 3% of the world population. The viral encoded HCV non-structural proteins are attractive targets for antiviral therapy as they have been shown to play an essential role in the replication of the virus. In particular, the RNA dependent RNA polymerase, located in the non-structural 5B region of the viral polyprotein, is essential for viral replication. NS5B is not expressed in uninfected cells favoring the development of selective and non-toxic inhibitors, which makes NS5B inhibition an attractive target for the treatment of viral infection.

Compound **(1)** with nanomolar activity on NS5B polymerase of the major genotypes 1 and 2 was identified in the HTS assay. Optimization of the lead compound was developed in order to gain in *vivo* potency, to solve possible problems of cytotoxicity and to improve the PK profile. The details of the work will be reported together with mechanistic studies and X-ray analysis of the inhibitor bound to NS5B polymerase of both genotypes 1 and 2.

[2] Sudo K, Matsumoto Y, Matsushima M, et.al., *Biochem Biophys Res Commun* **238** (1997) 643–647.

[3] Lee G, Piper DE, Wang Z, et.al. *J.Mol.Biol*. **357** (2006) 1051-1057.

[4] Tatar E, Küçükgüzel I, De Clercq E, et.al. *2nd International Meeting on Medicinal and Pharmaceutical Chemistry*, Antalya - TURKEY, P10, 10-14 October 2004.

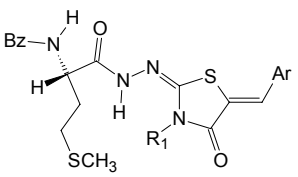
L56

Evaluation of Novel 4-Thiazolidinone Derivatives as Inhibitors of Hepatitis C Virus NS5B and SARS-CoV polymerase

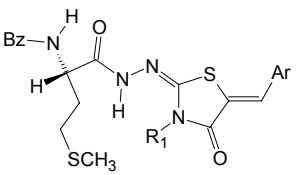
Neerja Kaushik-Basu[1], Alain Bopda-Waffo[1], Amartya Basu[1], Ye Chen[1], Tanaji T. Talele[2], Esra Tatar[3] and İlkay Küçükgüzel3

[1]Department of Biochemistry and Molecular Biology, UMDNJ-New Jersey Medical School, 185 South Orange Avenue, Newark, NJ 07103 ; [2]Dept. of Pharmaceutical Sciences, College of Pharmacy & Allied Health Pofessions, St. John's University, Jamaica, NY 11439 ; [3]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Marmara University, Haydarpasa, 34668 İstanbul, Turkey

Among the human pathogens, positive strand RNA viruses such as the Human Immunodeficiency virus (HIV), Hepatitis C virus (HCV) and the SARS coronavirus (SARS-CoV) continue to pose formidable public health challenges. Preventative strategies such as vaccines against these viral infections are currently unavailable and effective anti-viral therapeutics has yielded limited success. Thus, efforts are ongoing to develop novel and improved treatment strategies. Two viral enzymes, namely the viral proteases and their polymerases/ replicases have received attention as antiviral targets, with considerable success being acheived with HIV-RT and its protease. A similar strategy employing nucleoside and non-nucleoside analogues as potential candidate drugs is being investigated against NS5B, the HCV replicase and NSP12, the SARS replicase. Recent studies have documented 2,3-diaryl-1,3-thiazolidin-4-one derivatives as a new class of non-nucleoside reverse transcriptase inhibitors (NNRTIs), that proved to inhibit HIV-1 replication [1]. Thiazolidine derivatives have been reported to inhibit HCV protease [2] whereas, there is only one report on anti-RdRp activities of these compounds against HCV and SARS replicase [3]. In a quest to identify novel compounds targeting these viral replicase, we evaluated a new series of N-{1-[[2-(3-substituted-4-oxo-1,3-thiazolidin-2-ylidene)hydrazino]carbonyl-3-(methylthio)-propyl}benzamide **1-4** and N-{1-[[2-[5-benzylidene)-3-substituted-4-oxo-1,3-thiazolidin-2-ylidene]hydrazino]carbonyl-3-(methylthio)propyl}benzamide **5-20** derivatives [4]. In vitro NS5B RdRp inhibition analysis with compounds **1-20** was performed to determine their IC_{50} values. Molecular docking of the derivatives with the lowest IC50 values was also carried out to reveal binding mode of the compounds.



1-4



5-20

[1] Rao A., Balzarini J., Carbone A., et.al., Zappalà M. Antiviral Research 63 (2004) 79–84.

[2] Sudo K, Matsumoto Y, Matsushima M, et.al., Biochem Biophys Res Commun 238 (1997) 643–647.

[3] Lee G, Piper DE, Wang Z, et.al. J.Mol.Biol. 357 (2006) 1051-1057.

[4] Tatar E, Küçükgüzel I, De Clercq E, et.al. 2nd International Meeting on Medicinal and Pharmaceutical Chemistry, Antalya - TURKEY, P10, 10-14 October 2004.

P57

Some novel thioureas derived from 4-aminobenzoic acid hydrazones as potential antiviral and antitubercular agents

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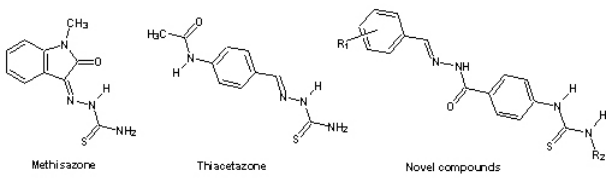
Thiacetazone which possesses a thiosemicarbazone structure, has been reported as a tuberculostatic agent. Methisazone was one of the first antiviral compounds used in clinical practice. This drug plays an important role as a prophylactic agent against several viral diseases. Various hydrazide-hydrazone derivatives have also been reported to exhibit antitubercular and antiviral activities. Sriram and co-workers have recently reported antitubercular activity of several thiourea derivatives obtained from isonicotinoyl hydrazone [1].



As a continuation of our previous efforts on 4-aminobenzoic acid hydrazones [2] and thiourea derivatives [3], a series of novel thioureas, in which hydrazide-hydrazone and disubstituted thiourea moieties were incorporated in one structure, have been synthesized starting from 4-amino-*N*'-[(substitutedphenyl)methylene]-benzohydrazide for evaluation of their antitubercular and antiviral potency. All synthesized compounds were screened in vitro against HIV-1 (IIIB) and HIV-2 (ROD) strains in MT-4 cells, as well as other selected viruses. In vitro antimycobacterial activity of novel compounds against *Mycobacterium tuberculosis* H37 Rv were also evaluated using the BACTEC 460 Radiometric system.

[1] Sriram D, Yogeeswari P, Madhu K. Synthesis and in vitro antitubercular activity of some 1-[(4-sub)phenyl]-3-(4-{1-[(pyridine-4-carbonyl)hydrazono]ethyl}phenyl)thiourea. *Bioorg Med Chem Lett 2006*; 16 : 876-878.

[2] Küçükgüzel ŞG, Rollas S, Küçükgüzel I, Kiraz M. Synthesis and antimycobacterial activity of some coupling products from 4-aminobenzoic acid hydrazones. *Eur J Med Chem* 1999; 34 : 1093-1100.

[3] Küçükgüzel İ, Küçükgüzel ŞG, Rollas S, Kiraz M. Some 3-Thioxo/alkylthio-1,2,4-triazoles with a substituted thiourea moiety as possible antimycobacterials. *Bioorg Med Chem Lett* 2001; 11 : 1703-1707.

P58

Synthesis and antiviral activity of some novel thioureas derived from N-(4-nitro-2-phenoxyphenyl)-methanesulfonamide

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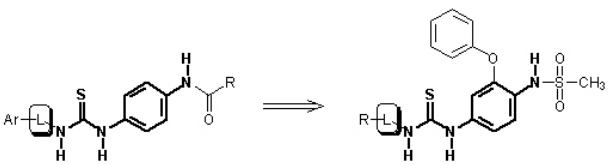
HIV infection and AIDS represent one of the first diseases for which the discovery of drugs was performed entirely via a rational drug design approach. Current treatment regimens are based on the use of two or more drugs from more classes of inhibitors termed highly active antiretroviral therapy (HAART). Some thiourea compounds were reported to be non-nucleoside inhibitors (NNIs) of the reverse transcriptase (RT) enzyme of the human immunodeficiency virus (HIV) **[1]**. High throughput screening studies revealed that certain bis(aryl)thioureas carrying an amide functionality, as exemplified by structure shown below, could be considered as inhibitors of herpes viruses such as HSV, CMV and VZV [2].

These findings encouraged us to go further with our



ongoing studies on thiourea derivatives [3]. Therefore, a novel series of 1-[4-(methanesulfonamido)-3-phenoxyphenyl]-3-alkyl/aryl thioureas were designed by modification of bis(aryl)thioureas. The intentional modifications were : *i.* introduction of alkyl and aryl groups at **R** position ; trying several linkers (**L**) ; *ii.* introduction of a phenoxy ring ; *iii.* replacement of aroylamido group with methanesulfonamido functionality.

All synthesized compounds **1-16** have been screened in vitro against HIV-1 (IIIB) and HIV-2 (ROD) in MT-4 cells, as well as other selected viral strains (such as HSV, CMV, VZV). Comparative results in terms of structure-activity relationships will be discussed in detail.

[1] Ludovici DW, Kukla MJ, Grous PG, Krishnan S, Andries K, de Bethune MP, Azijn H, Pauwels R, De Clercq E, Arnold E, Janssen PA. *Bioorg Med Chem Lett.* 2001;**11** : 2225-2228.

[2] Bloom JD, Dushin RG, Curran KJ, Donahue F, Norton EB, Terefenko E, Jones TR, Ross AA, Feld B, Lang SA, Di Grandi MJ. *Bioorg Med Chem Lett* 2004; **14** : 1703-1707.

[3] Küçükgüzel İ, Küçükgüzel ŞG, Rollas S, Kiraz M. *Bioorg Med Chem Lett* 2001; **11** : 1703-1707.

P59

4-Thiazolidinones : A Novel Class of Hepatitis C Virus NS5B Polymerase Inhibitors

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Hepatitis C virus (HCV) and the SARS coronavirus (SARS-CoV), two positive strand RNA virus are human pathogens of considerable medical significance. Therapies against SARS are yet to be developed, while current therapies against HCV are limited in efficacy and have adverse side effects thus necessitating the development of new antiviral agents against these pathogens. HCV and SARS encode replicase proteins termed NS5B and NSP12, respectively, which function as their RNA dependent RNA polymerase (RdRp), and have no functional equivalent in their host thus representing attractive target for therapeutic intervention. In a quest to identify novel compounds targeting these viral replicase, we evaluated a new series of 4-thiazolidinone derivatives (18 compounds) [1, 2] .With the exception of one report [3], the anti-RdRp activities of these compounds against HCV and SARS replicase have not been examined to-date. Our *in vitro* NS5B RdRp inhibition analysis with 2¢,4¢-difluoro-4-hydroxybiphenyl-3-carboxylic acid[2-(5-nitro-2-furyl / substituted phenyl)-4-thiazolidinone-3-yl]amides (6 derivatives) yielded an IC_{50} value ranging from 45-75 micromolar. Pre-incubation of NS5B with RNA, protected the RdRp from inhibition resulting in increase in the IC_{50} value. Molecular docking of the derivative with the lowest IC_{50} value revealed that the biphenyl ring of the inhibitor forms strong hydrophobic interaction with Ile482, and Leu497 of NS5B while its fluorophenyl ring stabilizes in the hydrophobic pocket formed by residues Trp528, Arg422, Tyr477, Met423 and Leu 419. In addition, the carbonyl oxygen of the thiazolidinone derivative forms a strong H-bond (~2.05 Å distance) with the backbone of Ser 476. By contrast, theses compounds lacked specificity for the SARS replicase exhibiting an IC_{50} value of 500 micromolar or above.

[1] Küçükgüzel SG, Oruç EE, Rollas S, et.al. *Eur.J.Med.Chem.* **37** (2002) 197-206.

[2] Küçükgüzel SG, Kocatepe A, De Clercq E, et.al. *Eur.J.Med.Chem.* **41** (2006) 353-359.

[3] Lee G, Piper DE, Wang Z, et.al. *J.Mol.Biol.* **357** (2006) 1051-1057.

P60

Arilthiopyrrole (ATP) derivatives as non-nucleoside HIV-1 reverse transcriptase inhibitors

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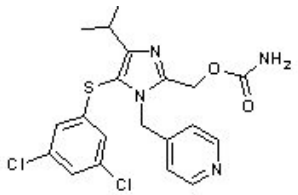
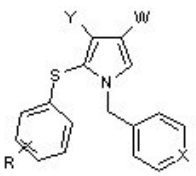
Acquired immunodeficiency syndrome (AIDS) remains a serious global health problem. The rapid emergence of drug resistant HIV strains and the knowledge that HIV cannot be eradicated from the infected body because its persistence in cellular reservoirs, highlight the urgent need for new drugs, which are less toxic and more active against resistant mutants selected by current therapies. Recently, we synthesized novel pyrrole derivatives related to capravirine (S-1153), a potent NNRTIs highly active against a wide range of resistant mutants [1,2]. Herein we reported the SAR studies of novel compounds belonging to the ATP series. The newly synthesized ATPs were found active in the range 0.008-53 ?M and their citotoxicity was generally lower than S-1153.



Capravirine



ATP derivatives

A selected number of derivatives were tested against clinically relevant drug-resistant RT forms carrying K103N and Y181I mutations. Moreover, docking calculations of the most active compounds were also performed to investigate their binding mode into the RT NNBS and to rationalize both SAR and resistance data. In conclusion, ATP derivatives described in this work seem to be interesting NNRTIs, which could be good tools to develop antiviral agents useful in clinical practice against mutated forms of HIV-1.

[1] T. Fujiwara, A.Sato, M. El-Farrash, S. Miki, K. Abe, Y. Isaka, M. Kodama, Y. Wu, L.B. Chen, H. Harada, H.; Sugimoto, M. Hatanaka, Y. Hinuma, Antimicrob. Agents Chemother. 1998, 42, 1340-1345.

[2] R. Di Santo, R. Costi, M. Artico, R. Ragno, S. Massa, M. La Colla, R. Loddo, P. La Colla, A. Pani, Med. Chem. Res. 2002, 11, 153-167.

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Quinolones as potential anti HIV-1 agents targeted at Tat/TAR recognition

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The interaction between Tat and TAR is an attractive target for the development of new antiviral agents against HIV-1. We have recently demonstrated that some aminoquinolones with antiviral activity are able to interact effectively with the provirus LTR in the region where the TAR structure is located, showing in vitro the ability to disrupt the complex with Tat. These encouraging results prompted us to analyse the activity of new quinolones designed rationally to bind the TAR bulge. These compounds are the first of a new series in which the modes of interaction with the nucleic acid and the protein/RNA complex differ significantly from those referring to fluoro- and aminoquinolones bearing the classical keto-carboxylic function. Indeed, the quinolone ring serves as a stacking moiety between base pairs of the nucleic acid and as a scaffold for a phenyl ring mono or o-disubstituted with basic chains, intended to bind electrostatically the phosphate backbone of TAR. The new quinolones are able to interfere with Tat-TAR complex depending on precise structural requirements, as demonstrated by electrophoresis mobility shift assay (EMSA); in our experimental conditions the most active compound showed a better activity than the lead aminoquinolone of the previous series, validating our new approach and prompting the study of new quinolone congeners to fully explore the structural properties of the active drugs and to optimize the pharmacokinetic parameters of these basic compounds.

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Antiviral activity of some (5-chloro-2-oxobenzothiazolin-3-yl) aceto/ propanohydrazide derivatives

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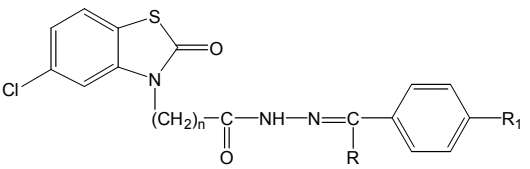
The structural and therapeutic diversity coupled with commercial viability of various molecules have fascinated organic and medicinal chemists for many years[1]. There has been considerable interest in the chemistry of 2-(3H)-benzothiazoles, which is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activity including antimicrobial, antifungal, antituberculosis, anticonvulsant, antiinflammatory and analgesic activities. At the same time, a considerable number of hydrazide/hydrazone derivatives have been reported to demonstrate antiviral activity.

Based on above findings, we synthesized eleven (5-chloro-2-oxobenzothiazolin-3-yl)aceto/propanohydrazide derivatives to test their antiviral activity against DNA and RNA viruses.

The antiviral activities as well as cytotoxicity were tested against *Herpes simplex* (HSV) as DNA virus and *Parainfluenza*-3 *virus* (PI-3) as RNA virus using Vero (African green monkey kidney) and MDBK (Madin-Darby Bovine Kidney) cell line cultures. Acyclovir (16-<0.25μg/ml) and Oseltamivir (32- <0.25μg/ml) were employed in the test as references. Synthesized compounds resulted in antiviral activity at 16-1μg/ml concentration range.



R: H, CH_3
R_1:H, Cl, CH_3, OCH_3

[1] H.S. Gold, R.C. Moellering, N. Engl. *J. Med. Chem*. 335, 1445–1453, 1996.

Cancer

P63

Design and development of lantadenes as antitumor agents

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Lantana plant has encroached upon a large land area in India as well as other parts of the world and imposed a great threat to grazing animals and overall ecology. Eradication of this weed cannot be excepted in the near future by the use of conventional methods. However, this plant has been in use in folk medicine in different parts of the world. During the past few years, a number of chemical compounds have been reported from this plant and have been investigated for their pharmacological properties. Recently, the triterpeniods named lantadenes isolated from lantana leaves have been found to exhibit antitumor activities and therefore, studies for the development of lantadenes as potential antitumor agents will be rational way to utilize this biomass as a resource for drug discovery and development. A number of lantadenes **(Fig.1)**