Professor Branko Stanovnik

A Tribute

Professor Branko Stanovnik was born in Brezovica (near Ljubljana) on August 11, 1938. He studied chemistry at the Faculty of Chemistry and Chemical Technology, University of Ljubljana, Slovenia. In November 1963, he defended his Ph.D. thesis entitled "Thion-thiol tautomerism of some heterocyclic systems" under the supervision of Professor Miha Tišler. This was also the beginning of a long-term and very fruitful co-operation with Professor Tišler, which lasted for over 30 years. Next year, he was promoted to the position of Assistant Professor (Docent). In 1964, the Canadian government awarded him a postdoctoral grant and he spent one year (1964–1965) as a postdoctoral fellow at the Atlantic Regional Laboratory of National Research Council of Canada in Halifax, working in the team of Professor Gavin McInnes on the influence of Lewis acids on the Diels-Alder reaction. Upon his return from Canada, he continued his research at the Faculty of Chemistry in Ljubljana, where he was promoted to the position of Associate Professor (1967), and Full Professor (1972) as a permanent position.

Professor Stanovnik has been invited by numerous universities, academies, companies, and other scientific societies and research institutions to lecture about his research work. As a Visiting Professor or Visiting Fellow he has been invited on several lecturing tours, in Great Britain (1971) organised by the British Council, in the USA (1974 and 1976) organized by the National Academy of Sciences (Washington) under the inter-academic exchange program. A collaborative project with the University of Salt Lake City (Utah) on ^{13}C nmr, started on the basis of this exchange program. He also toured France (1976) on the invitation of the Ministry of Foreign Affairs of France; Australia (1978) on the invitation of John Curtin School of Medical Research (Canberra) and in Republic of South Africa (1992). He has also been a plenary or

invited speaker at numerous international symposia and conferences. He has given over 60 plenary and invited lectures at international conferences and symposia and over 150 lectures at various universities, academies, and industrial research laboratories.

Professor Stanovnik was elected Visiting Fellow at the Australian National University, Canberra (1978), Fellow of the Royal Society of Chemistry, London, UK (1984), Full Member of European Academy of Sciences and Arts (Academia Scientarium et Artium Europaea, 1991), Associated Member of the Slovenian Academy of Sciences and Arts (SASA, 1991) and Full Member of SASA (1995), Honorary Member of Hungarian Chemical Society (1998), and Inaugural Honorary Member of the Florida Center for Heterocyclic Compounds (1998). As a person, who has never been politically engaged, he was elected a Member of the Scientific Advisory Board for the Prohibition of Chemical Weapons, Haag, The Netherlands (1998). He also won numerous awards, recognitions, plaques, and diplomas from various universities, institutes, companies, and other institutions, such as the Boris Kidrič Fund Award for Science (1972), Boris Kidrič Award and Medal for Science (1977), Boris Kidrič Fund Award for Innovations (1981 and 1989), and Honorary Medal and Diploma, Technical University Bratislava, Czechoslovakia (1975), and others.

He is a member of many scientific, mostly chemical, societies, such as the International Society of Heterocyclic Chemistry, the Slovenian Chemical Society, the Chemical Society (London), the Swiss Chemical Society, the Federation of European Chemical Societies (FECS), the American Chemical Society, and others. In this connection, he also served or still serves at various boards and committees of the above mentioned scientific societies. Since 1999, he has been Head of Department of International Relations and Scientific Cooperation of SASA and representative of SASA in various international relations. He is a Chairman of the Editorial Board of Acta Chimica Slovenica (formerly Vestnik Slovenskega kemijskega društva), a Member of Advisory Board of Croatica Chemica Acta, Progress in Heterocyclic Chemistry, Journal of Heterocyclic Chemistry, Advances in Heterocyclic Chemistry, and a Member of the Board of Arkivoc. Besides, he was or still is a member of international scientific committees of several congresses, symposia, and conferences including: 8th International Symposium on Organic Sulphur Chemistry (1978), 6th Yugoslavian Symposium on Pure and Applied Chemistry (1979), Yugoslavian Symposia on Organic Chemistry (1981–1989), Congresses of Yugoslavian Students (1981–1983), International Congresses of Heterocyclic Chemistry, International Symposia on the Chemistry and Pharmacology of Pyridazines, 6th European Symposium on Organic Chemistry (1989), European Colloquia on Heterocyclic Chemistry (ECHC), 11th European Symposium on Fluorine Chemistry (1995), Blue Danube Symposia on Heterocyclic Chemistry, Graz-Ljubljana-Trieste Symposia on Organic Chemistry, (TRISOC), and Slovenski kemijski dnevi (Slovenian Chemical Days).

Alone or with colleagues, he organised several national and international symposia or conferences including: 3rd Yugoslavian Congress on Pure and Applied Chemistry (1972), 5th International Congress of Heterocyclic Chemistry (1975), 3rd Yugoslavian Symposium on Organic Chemistry (1984), 16th European Colloquium on Heterocyclic Chemistry (1994), Graz-

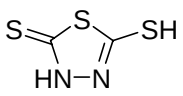
Ljubljana-Trieste Symposia on Organic Chemistry, TRISOC (1985, 1994), 4th International Symposium on the Chemistry and Pharmacology of Pyridazines (1994), and the 8th Blue Danube Symposium on Heterocyclic Chemistry (2000).

Professor Stanovnik was Head of Department of Chemistry and Chemical Technology, Faculty of Natural Sciences and Technology, University of Ljubljana (1967–1969), Head of Department of Organic Chemistry, Faculty of Natural Sciences and Technology, University of Ljubljana (1984–1989), and a vice-Dean of Faculty of Chemistry and Chemical Technology, University of Ljubljana (1992–1997). He was or still is a member of various committees of the University of Ljubljana, such as University Council, Committee for Postgraduate Studies, etc.

Professor Stanovnik is author or co-author of over 550 publications. Among them, there are over 400 original scientific articles and many review articles, book chapters, monographs, and textbooks. As author or co-author he contributed chapters to Advances in Heterocyclic Chemistry, Advances in Pesticide Science, Comprehensive Heterocyclic Chemistry, Comprehensive Organic Functional Group Transformations, Houben–Weyl Methods of Organic Chemistry, Methodum Chimicum, Organic Synthesis: Modern Trends, Progress in Heterocyclic Chemistry, Science of Synthesis: Houben–Weyl Methods of Molecular Transformations, The Chemistry of Heterocyclic Compounds, and Targets in Heterocyclic Systems.

His research interest is mainly oriented to heterocyclic chemistry: synthesis, transformations, and structural investigations of heterocyclic systems, development of new reagents in organic and heterocyclic chemistry, tautomerism of heterocyclic compounds, NMR studies, azido-tetrazolo isomerism, aza-transfer reactions, studies of heterocyclic diazo compounds and diazonium salts, 1,3-dipolar cycloadditions, stereoselective synthesis, chemistry of *N*,*N*-dimethylenaminones, synthesis of functionalized heterocyclic compounds (e.g. heterocyclic amino acids and related compounds), and synthesis of natural product analogues.

His early work was focused on the chemistry of sulphur containing heterocyclic compounds with thioamide structural element: synthesis, reactivity, (ring) transformations, and thion-thiol tautomerism of mercaptoheterocycles. Studies of thion-thiol tautomerism showed that heterocyclic thioamides could exist either in the thion or in the thiol tautomeric form, although at that time it was generally accepted that a thioamide group in heterocyclic systems existed only in the thion (thiolactam) form. This phenomenon has been proven in the case of 2,5-dimercapto-1,3,4-thiadiazole (**1**) and 3,6-dimercaptopyridazine (**2**) having one of the thione group in the thiolactim and the other one in the thiolactam form.



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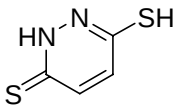
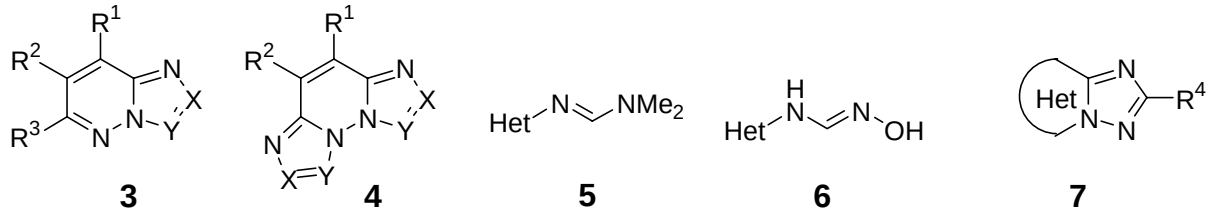


2

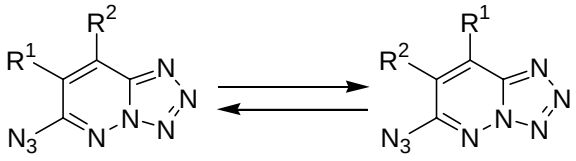
Another field of heterocyclic chemistry, which his early research was devoted to, is the chemistry of azolo fused azines with a bridgehead nitrogen atom and related tri- and polycyclic

systems, such as, for example, fused pyridazine derivatives **3** and **4**. Many new synthetic methods for preparation of such azaindolizines were developed. Reactivity of these heteroaromatic systems, which are isoelectronic with indole, was also investigated: the site of protonation and quarternisation, homolytic alkylations and arylations, nucleophilic substitutions including tele-substitutions, ring opening, additions, *N*-oxidations, etc. In particular, *N*,*N*-dimethyl-*N*'-heteroarylamidines **5** and *N*-heteroarylamide oximes **6** were shown to be useful synthetic intermediates for the preparation of heterocyclic systems. For example, cyclodehydration of *N*-heteroarylamide oximes made [1,5–*x*]-fused 1,2,4-triazoles **7** with a bridgehead nitrogen atom available in 3 steps from the corresponding 3-aminopyridazines.



3 **4** **5** **6** **7**

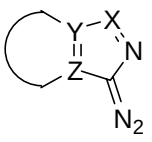
In connection with azoloazines with bridgehead nitrogen atom, studies on azido-tetrazolo isomerism of 6-azidotetrazolo[1,5–*b*]pyridazine derivatives with general formulas **8** and **9** should be highlighted. The research in this field gave, in addition to previous literature data, new and interesting results with respect to synthetic applicability as well as the effects which control the azido-tetrazolo isomerisation including energy of activation and enthalpy of isomerisation.



8 **9**

The chemistry of heterocyclic diazo compounds, which were (contrary to the corresponding diazonium salts) practically unknown in that time, was another interesting area of his research which started in 1970-ies. These studies were focused on the chemistry of α-diazoazoles, heterocyclic α-diazoketones, and their fused analogues of general formulas **10** and **11**. Aza-transfer reactions, coupling reactions, photochemical reactions, Wolff rearrangements, synthesis of heterocycles, and other consequent synthetic applications, which were studied, offered access to a variety of nitrogen substituted compounds and fused heterocycles, including polyazasteroids **12**. Consequently, this study established heterocyclic diazo compounds as useful synthons. Just recently, when various α-amino substituted fused 4-azinones and 2-pyranones became easily available from alkyl 2-acylamino-3-dimethylaminopropenoates, he returned to the chemistry of heteroaryldiazonium salts. Many interesting results have also been obtained in this series. So far,

'ring switching' transformations, aza-Wolff rearrangements, and coupling reactions of heteroaryldiazonium salts with the general formula **13** have been published.



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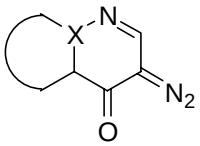

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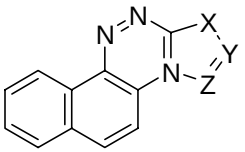

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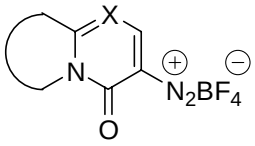

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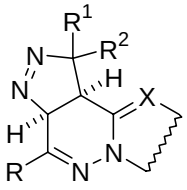
In the early 1980-ies, upon attempted methylation of 3-amino-6-chloropyridazine with excess diazomethane, the product turned out to be the cycloadduct formed upon 1,3-dipolar cycloaddition of diazomethane to the C(4)=C(5) double bond of the pyridazine ring. The result of this experiment was extremely surprising, since in that time 1,3-dipolar cycloadditions to 6-membered heteroaromatics were postulated to be "forbidden" and only a few sporadic examples of cycloadditions to (hetero)aromatic systems were reported in the literature. Thus began an extensive study of 1,3-dipolar cycloadditions of diazoalkanes to pyridazine derivatives which showed that cycloadditions proceed under mild conditions regiospecifically to the C=C double bond giving the CH,CH-dihydro systems **14** as the primary products, which can be isomerised selectively into NH,NH-dihydro **15** and NH,CH-dihydro cycloadducts **16**. The chemistry of these diazoalkane-pyridazine cycloadducts was also studied: sigmatropic rearrangements, oxidative aromatisations, elimination of nitrogen, ring opening, ring contractions and expansions, preparation and transformations of azomethine imines **17**, etc. The latter reactions were also applied to stereoselective synthesis of acyclo *C*-nucleosides. For example, treatment of NH,NH-dihydro cycloadduct with D-ribose in the presence of methyl acrylate furnished the corresponding acyclo *C*-nucleoside **18**.



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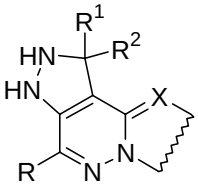

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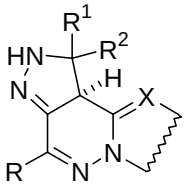

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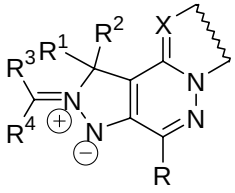

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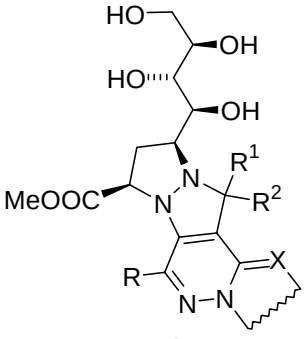
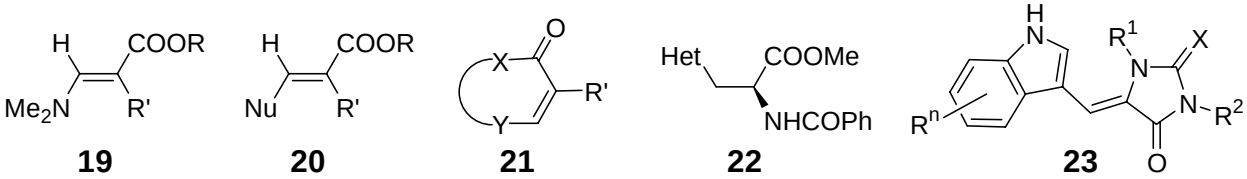


18

In the last 15 years, his research has focused mainly on alkyl 2-substituted 3-(dimethylamino)prop-2-enoates **19** and analogous enaminones, especially 2-(substituted amino) prop-2-enoates as dehydroalanine derivatives. These easily available compounds turned out to be versatile reagents for the preparation of heterocyclic amino and hydroxy acids, their analogs, and related compounds, as well as for the synthesis of a variety of heterocyclic systems, such as

pyrroles, pyrazoles, imidazoles, isoxazoles, oxazoles, pyridines, pyridazines, pyrimidines, pyranones, and their fused ring analogs. The most typical are acid-catalysed reactions of *N*,*N*-dimethylenaminones with *N*- and *C*-nucleophiles and ambident nucleophiles. Under mild conditions, dimethylamine substitution takes place giving access to various *β*-nitrogen and *β*-carbon substituted *α*,*β*-unsaturated carbonyl compounds and carboxylic acid derivatives **20**. For example, various *β*-(hetero)aryl- and *β*-(hetero)arylamino-*α*,*β*-dehydroalanine derivatives can be obtained by dimethylamine substitution in 2-amino substituted propenoates **20** (R' = NHCOR, $NHCH=CR_2$, etc.). At elevated temperatures, ambident nucleophiles react further with the carbonyl group to give five- and six-membered heterocyclic rings of general formula **21**. Important analogues of 3-dimethylaminopropenoates are 3-cyanopropenoates (**20**, Nu = CN), which proved to be useful dipolarophiles for 1,3-dipolar cycloaddition reactions leading to 5-membered heterocycles. Synthetic applications of 3-dimethylaminopropenoates and related enaminones have been extended toward the preparation of functionalised heterocyclic compounds and natural product analogues, such as (*S*)-*β*-heteroarylalanine derivatives **22** and aplysinopsin analogues **23**.



19 **20** **21** **22** **23**

In connection with Professor Stanovnik's research work, a long-standing and fruitful co-operation with Professor Miha Tišler has already been mentioned. One should also emphasise, that numerous crystal structures of new heterocyclic compounds have been solved by Professors Ljubo Golič, Ivan Leban, Anton Meden, and Dr. Amalija Golobič. One should also acknowledge long-standing friendship, co-operation, and support from Professors Jerald S. Bradshaw, Raymond N. Castle (†1999), and Alan R. Katritzky. He also has many friends at universities and institutes throughout the world.

Until now, Professor Stanovnik has been supervisor to approximately 200 diploma students and 30 PhD students. Many of his former students achieved teaching positions at universities, and leading positions in research laboratories, mostly in the pharmaceutical industry.

Dr. Jurij Svete
Faculty of Chemistry and Chemical Technology, University of Ljubljana, Slovenia

Some selected publications and reviews of Professor Stanovnik where the main areas of his research are summarised

1. **Pyridazines and fused pyridazines:** (a) Tišler M.; Stanovnik, B. "Sulfur Compounds of Pyridazines" In *The Chemistry of Heterocyclic Compounds*; Castle, R. N. Ed.; John Wiley &

Sons: New York, 1973; Vol. 28, pp 755–837. (b) Tišler M.; Stanovnik, B. "Azolo- and Azinopyridazines and Some Oxa and Thia Analogs" In *Condensed Pyridazines Including Cinnolines and Phthalazines* In *The Chemistry of Heterocyclic Compounds*; Castle, R. N., Ed.; John Wiley & Sons: New York, 1973; Vol. 27, pp 761–1056. (c) Tišler M.; Stanovnik, B. "Pyridazines and Their Benzo Derivatives" In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W. Eds., Boulton, A. J.; McKillop, A., Eds.; Pergamon: Oxford-New York, 1984; Vol. 3, pp 1–56. (d) Stanovnik, B. "Pyridazines", "Cinnolines", "Phthalazines", and "Pyridazino[1,2–*a*]pyridazines" In *Hetarenes IV: Six-Membered and Larger Heterorings with Maximum Unsaturation* in *Houben-Weyl Methods of Organic Chemistry*, Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 1997; Vol. E 9a, pp 557–792.

2. **Heterocyclic diazo compounds:** (a) Tišler, M.; Stanovnik, B. "Utility of Heterocyclic Diazo Compounds in Organic Synthesis" *Heterocycles* **1976**, *4*, 1115. (b) Stanovnik, B. "Transformations of Heterocyclic Diazo Compounds" *Rad Jugosl. akad. znan. i umjet., kem.* **1983**, *2*, 163.
3. **Diazoalkane–pyridazine cycloadducts:** (a) Stanovnik, B. *Tetrahedron* **1991**, *47*, 2925. (b) Stanovnik, B.; Jelen, B.; Turk, C.; Žličar, M.; Svete, J. *J. Heterocycl. Chem.* **1998**, *35*, 1187.
4. **Alky 2-substituted 3-(dimethylamino)prop-2-enoates and related enaminones:** (a) Stanovnik, B. "Methyl 2-Benzoylamino-3-dimethylaminopropenoate in the Synthesis of Heterocyclic Systems" In *Progress in Heterocyclic Chemistry*; Suschitzky, H.; Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1993; Vol. 5, pp 34–53. (b) Stanovnik, B. *Molecules*; **1996**, *1*, 123. (c) Stanovnik, B. *J. Heterocyclic Chem.* **1999**, *36*, 1581. (d) Stanovnik, B.; Svete, J. *Synlett* **2000**, 1077. (e) Stanovnik, B.; Svete, J. *Targets in Heterocyclic Systems* **2000**, *4*, 105.