



Russian
Science
Foundation

XXXI Symposium on Bioinformatics and Computer-Aided
Drug Discovery
2024



Pitirim Sorokin
SYKTYVKAR STATE UNIVERSITY

CHRONOBIOTICSDB V.2 AI

КАК АГЕНТНЫЙ ИНСТРУМЕНТ ДЛЯ ПОДБОРА ФАРМАКОЛОГИЧЕСКОЙ
ТЕРАПИИ РАССТРОЙСТВ СНА У ПАЦИЕНТОВ КАРДИОЛОГИЧЕСКОГО СТАЦИОНАРА



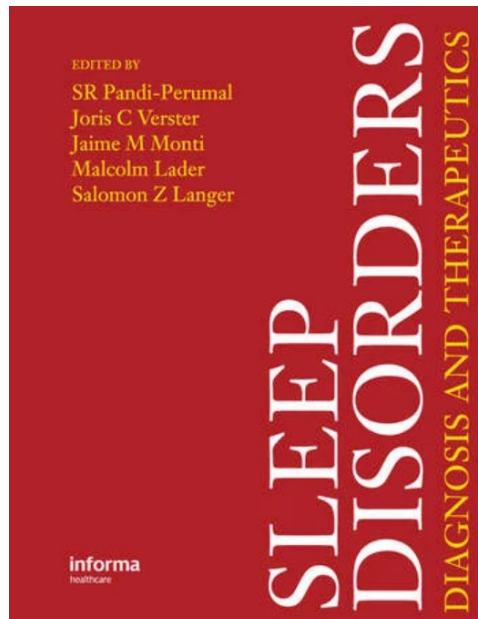
I. Solovev, D. Golubev, N. Kotelina, A. Yagovkina, R. Vetoshikin

*Pitirim Sorokin Syktyvkar State University, Medical Institute,
Laboratory of Translational Bioinformatics and Systems
Biology, Syktyvkar, Russian Federation*

DEFINITION

- Chronobiotic refers to a substance that has the ability to alter the phase of the circadian time system, thereby re-establishing and synchronizing circadian rhythms that have been disrupted in the short or long term.

From: Sleep Disorders [2019], Rethinking the use of hypnotics for treatment of insomnia in the elderly [2021]



EXPERT OPINION ON PHARMACOTHERAPY
2021, VOL. 22, NO. 8, 953–957
<https://doi.org/10.1080/14656566.2021.1900116>



EDITORIAL



Rethinking the use of hypnotics for treatment of insomnia in the elderly

Dieter Kunz^{a,b}

^aClinic for Sleep- & Chronomedicine, St. Hedwig Hospital, Berlin, Germany; ^bCharité – Universitätsmedizin Berlin, Institute of Physiology, Berlin, Germany

ARTICLE HISTORY Received 18 August 2020; Accepted 4 March 2021

KEYWORDS Elderly; hypnotic; insomnia; sleep

1. Introduction

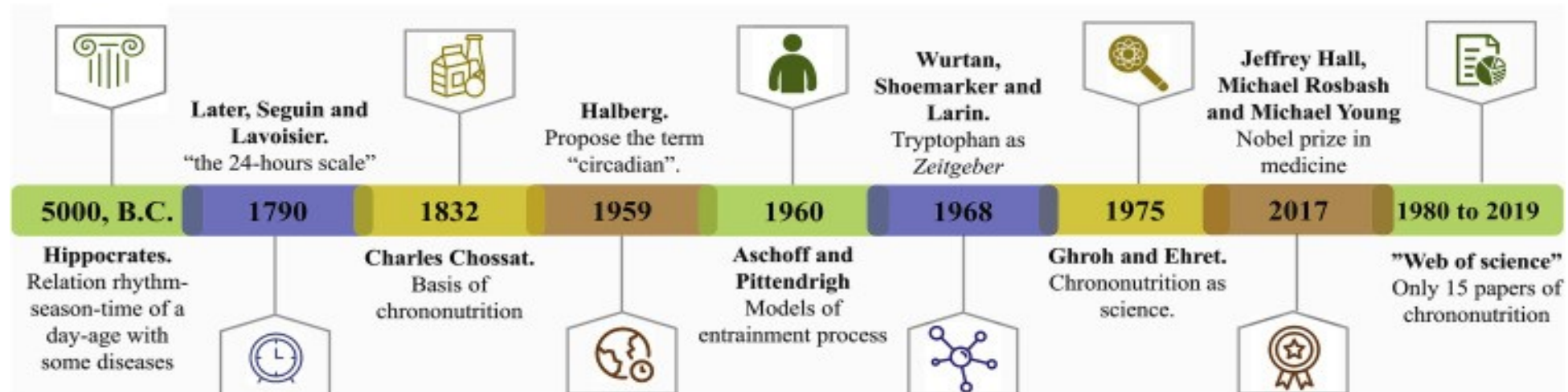
In all living creatures, a predetermined period of endogenously driven motor inactivity occurs during the 24-h day [1,2]. Mostly, this period coincides with the time creatures could be in danger; for example, species that use their eyes to detect enemies are in danger during the dark night. Another evolutionary fact is that during this time of inactivity, creatures respond only to individually relevant, learned events. In humans, for instance, a mother is more likely to awaken at the slightest whisper from her new-born child than to a loud noise, whereas the father sleeping next to her may react in the

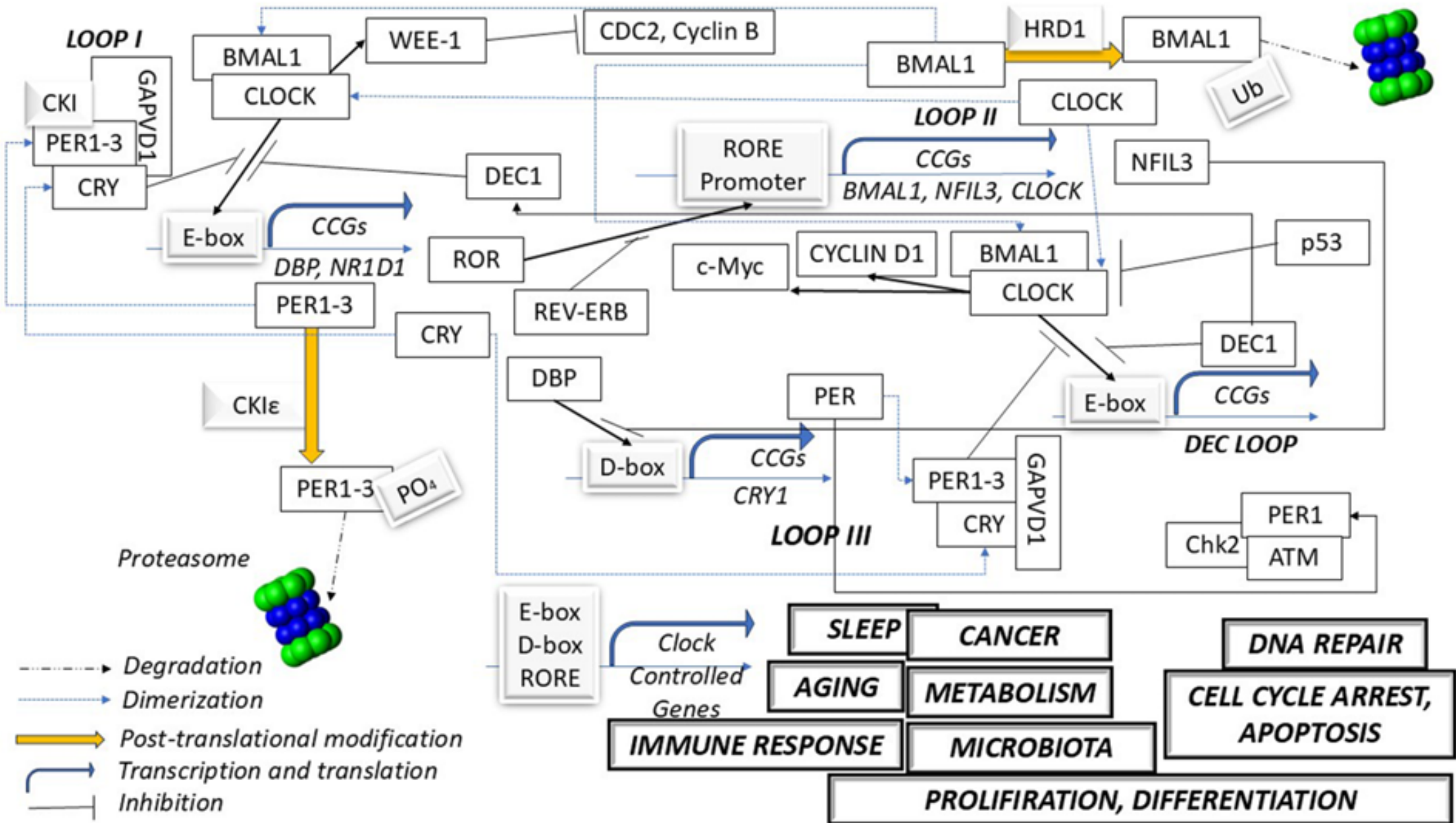
sleep period differs in length from individual to individual, sleep stages in healthy subjects occur in a stereotypic pattern. The complexity in particular of the neural mechanisms behind these coordinated processes cannot be overestimated [3,4]. Changes in any of these processes during sleep result in specific disturbances and functional deficits that can lead to impaired well-being, performance and health [5,7–9].

A common belief is that humans need less sleep as they age. No evidence for this exists, however. Indeed, it is more likely that age-related disorders (co)affecting the nervous system, as well as psychotropic medications, spoil the quality of sleep, leading to an increased need for sleep time in order to

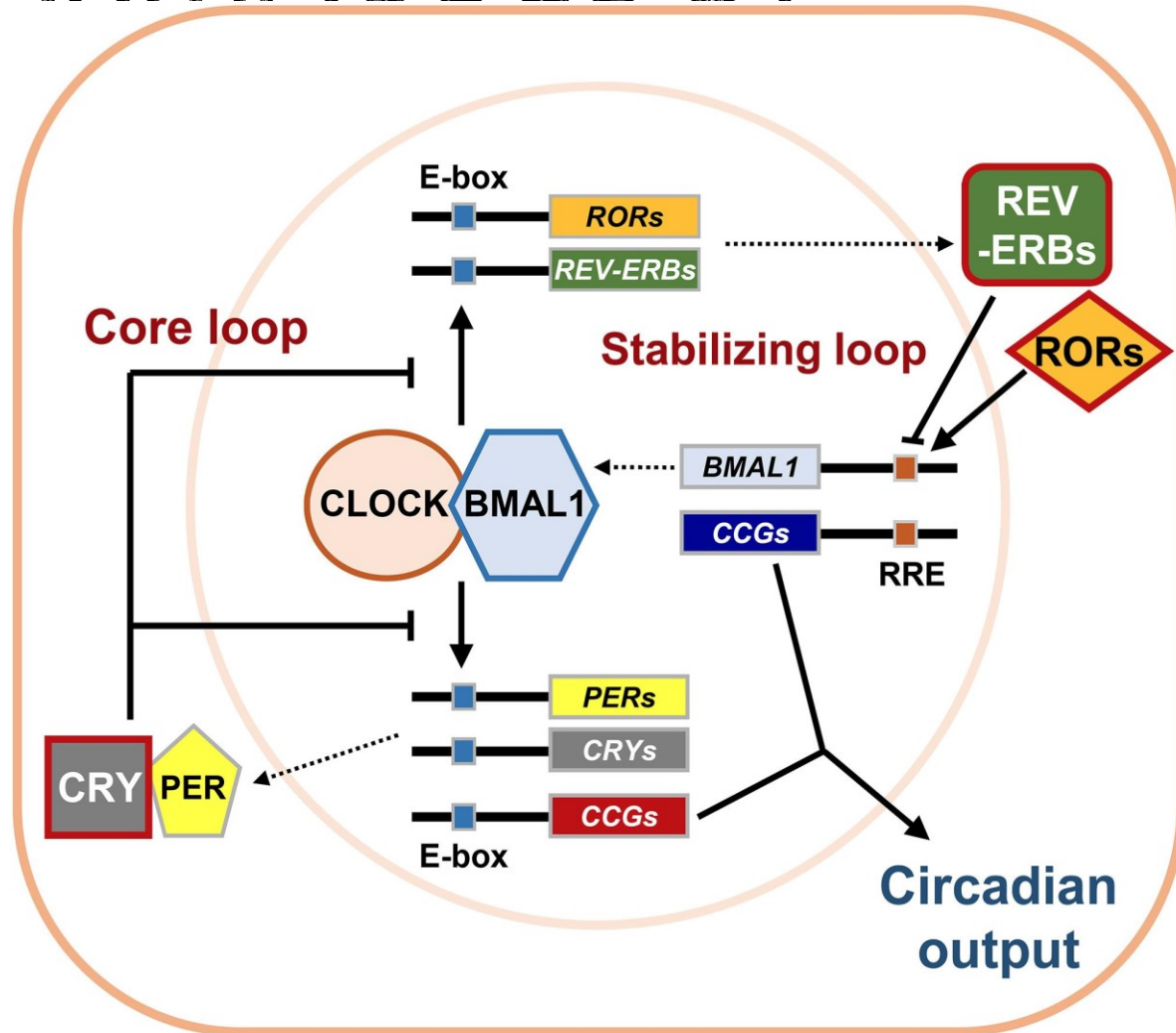
HISTORY AND ACTIVITY

- Chronobiotics are drugs, both experimental and used in medical practice, constituting a rather heterogeneous group of substances that can modify the parameters of the circadian rhythm of fluctuations in various physiological and biochemical parameters, such as the expression of the “clock” genes themselves in organisms-models and cell cultures or the expression of clock-controlled genes.
- The class of chronobiotic drugs has been known for more than 50 years, since the properties of the hormone melatonin were discovered and described in detail in the clinic. Chrononutrition was also defined as science only in 1975.





CIRCADIAN CORE CLOCK AND ITS PHARMACOLOGY



CRYs

- Natural ligand: None
- Stabilizer/activator: KL001 & derivatives
- Inhibitor: KS15

REV-ERBs

- Natural ligand: Heme
- Agonist: GSK4112, SR9009/9011, GSK2945
- Antagonist: SR8278

RORs

- Natural ligand: Oxysterols (α/γ), Retinoic acids (β)
- Agonist: SR1078, Nobiletin
- Inverse agonist: T0901317, SR1001

CLASSIFICATIONS OF CHRONOBOTICS

By Pharmacological Class inside Chronobiotics group:

- **Agonists:** Molecules that activate circadian clock components, such as melatonin receptor agonists (e.g., ramelteon), which promote sleep by mimicking the natural rise in melatonin during the evening.
- **Antagonists:** Compounds like orexin receptor antagonists that block wake-promoting pathways, used for insomnia treatment.
- **Gene Modulators:** These include agents that influence the expression of circadian genes, such as those modulating *PER* or *BMAL1* function.

By Target: Chronobiotics can be classified by their molecular targets, including:

- Central clock proteins (BMAL1, CLOCK, PERs, CRYs, RORs, REV-ERBs, CKs, etc)
- Hormonal and other Receptors, such as melatonin receptors (MT1 and MT2) and orexin receptors (ORX1 and ORX2), which are critical for sleep-wake regulation, ligands, such as melatonin and cortisol, which play systemic roles in rhythm regulation.

By Structure: Chronobiotics can also be grouped by their chemical structure:

- Small molecules, like melatonin and synthetic analogs.
- Peptides (oligopeptides), polypeptides (antibodies and other small proteins), including hormone analogs or signaling molecules.
- Nucleic acids, like RNA-based drugs that target circadian gene expression or viral gene therapies.

By Function: This classification includes substances based on their functional effects on circadian rhythms:

- **Phase-shifters:** Substances like light or melatonin that can advance or delay circadian rhythms.
- **Sleep-inducers:** Agents that promote sleep onset or duration, like sedative hypnotics.
- **Metabolic regulators:** Chronobiotics that influence metabolic rhythms, potentially beneficial in conditions like obesity and type 2 diabetes.

Biomeditsinskaya Khimiya, 2024 vol. 70, issue 6, pp. 381–393.

REVIEW

©Solovev, Golubev

CHRONOBOTICS: CLASSIFICATIONS OF EXISTING CIRCADIAN CLOCK MODULATORS, FUTURE PERSPECTIVES

I.A. Solovev, D.A. Golubev*

Pitirim Sorokin Syktyvkar State University, Medical Institute,
Laboratory of Translational bioinformatics and systems biology,
55 Oktyabrsky ave., Syktyvkar, Komi Republic, 167001 Russia; *e-mail: i@ilyasolovev.ru

PROBLEM



NO DATA

- There is no source of knowledge on chronobiotics powered with specialised AI-assistant which may consult both researchers and medical specialists

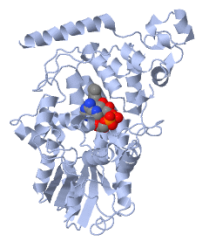


SOLUTION

Creation of the world first AI-powered updated database of chronobiotic compounds (circadian rhythm modulators) and organization of access to it is an urgent fundamental task of chronobiology, chronomedicine and pharmacoinformatics (bioinformatics).

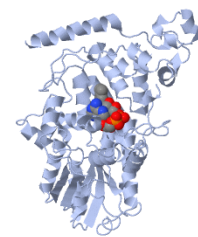
AIM

The purpose of the study is to create a relational database of chronobiotics "ChronobioticsDB" with AI assistant (AI-chronopharmacologist consultant, chronobiotics chemistry analyst/ researcher). In perspective: generative AI for synthesis of chronobiotics' formulae with desired biological activities and targets.

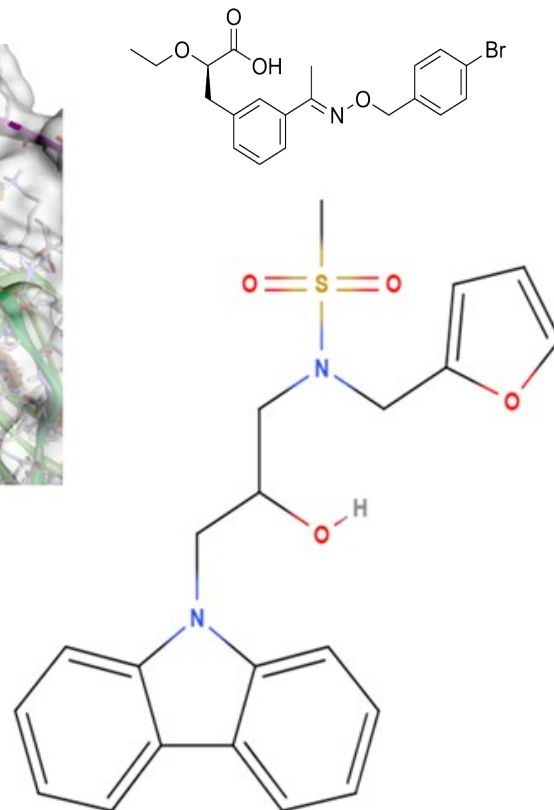
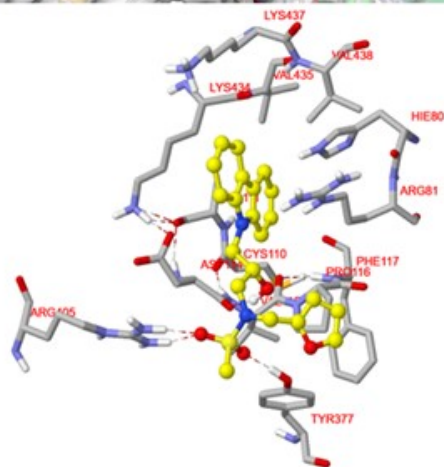
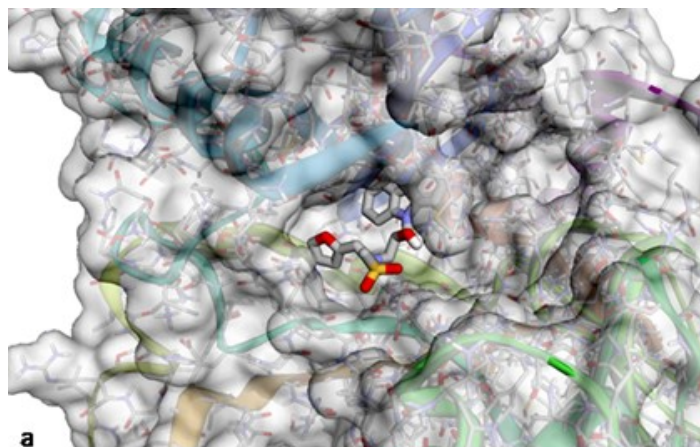


Jmol

SOURCE OF INSPIRATION FOR DATABASE: CRYPTOCHROMES AND THEIR INHIBITORS

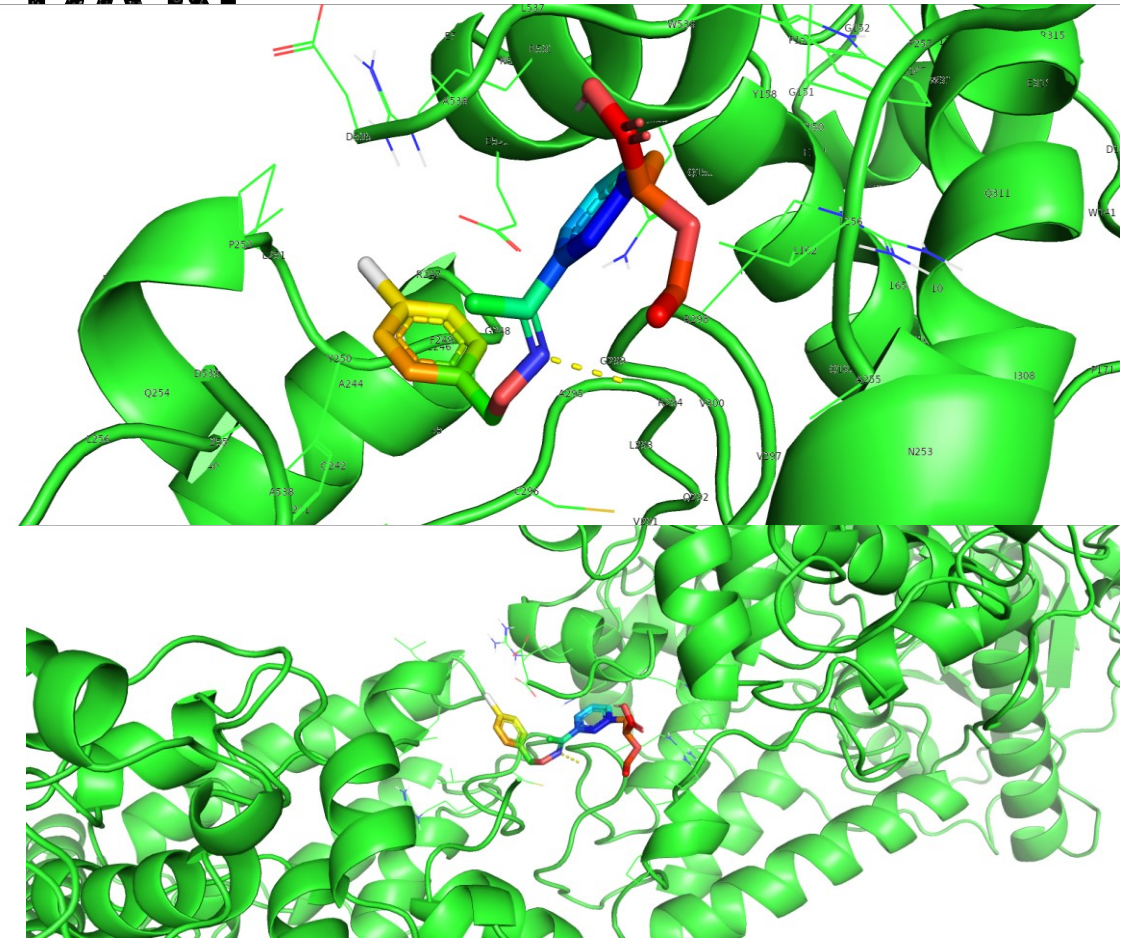
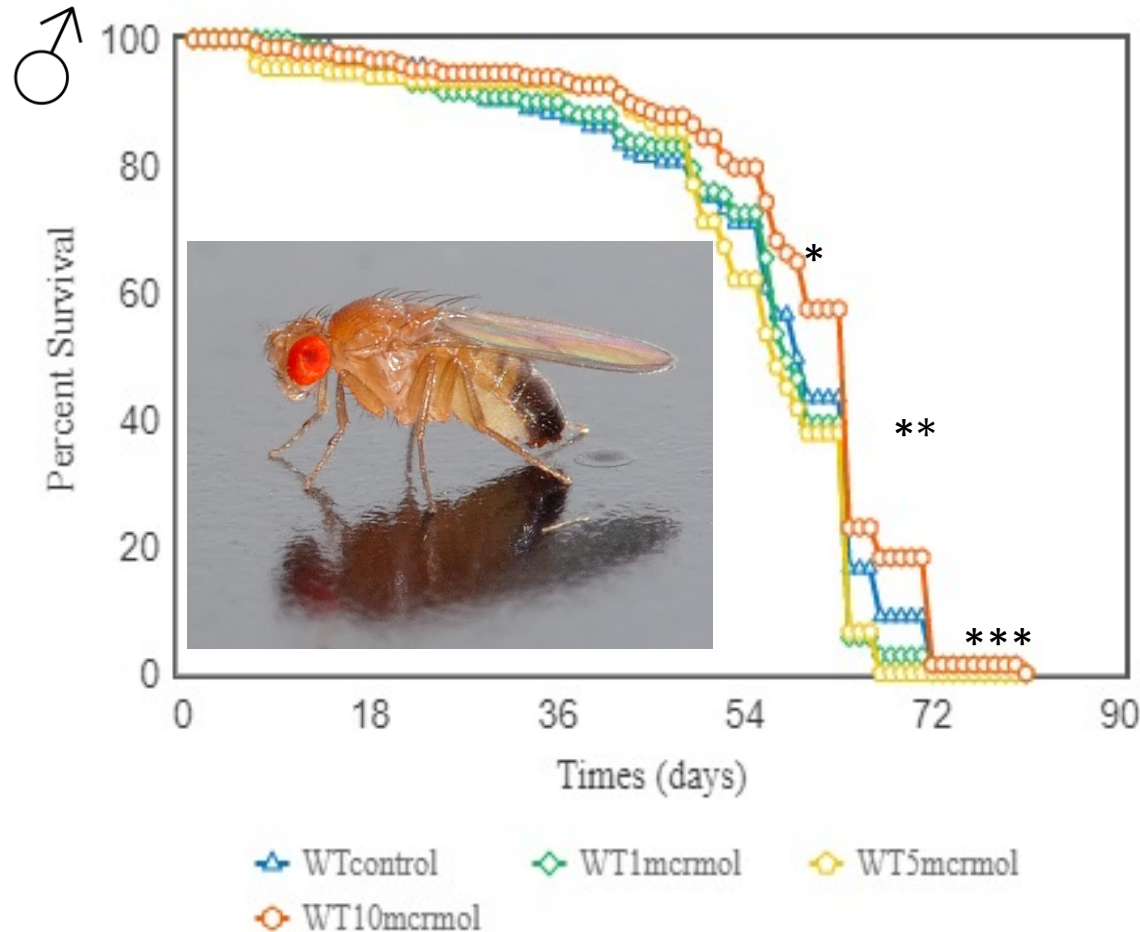


Jmol



CRYPTOCHROME INHIBITOR KS15 (0,1% DMSO) EXTENDS DROSOPHILA

I I E E S D A N



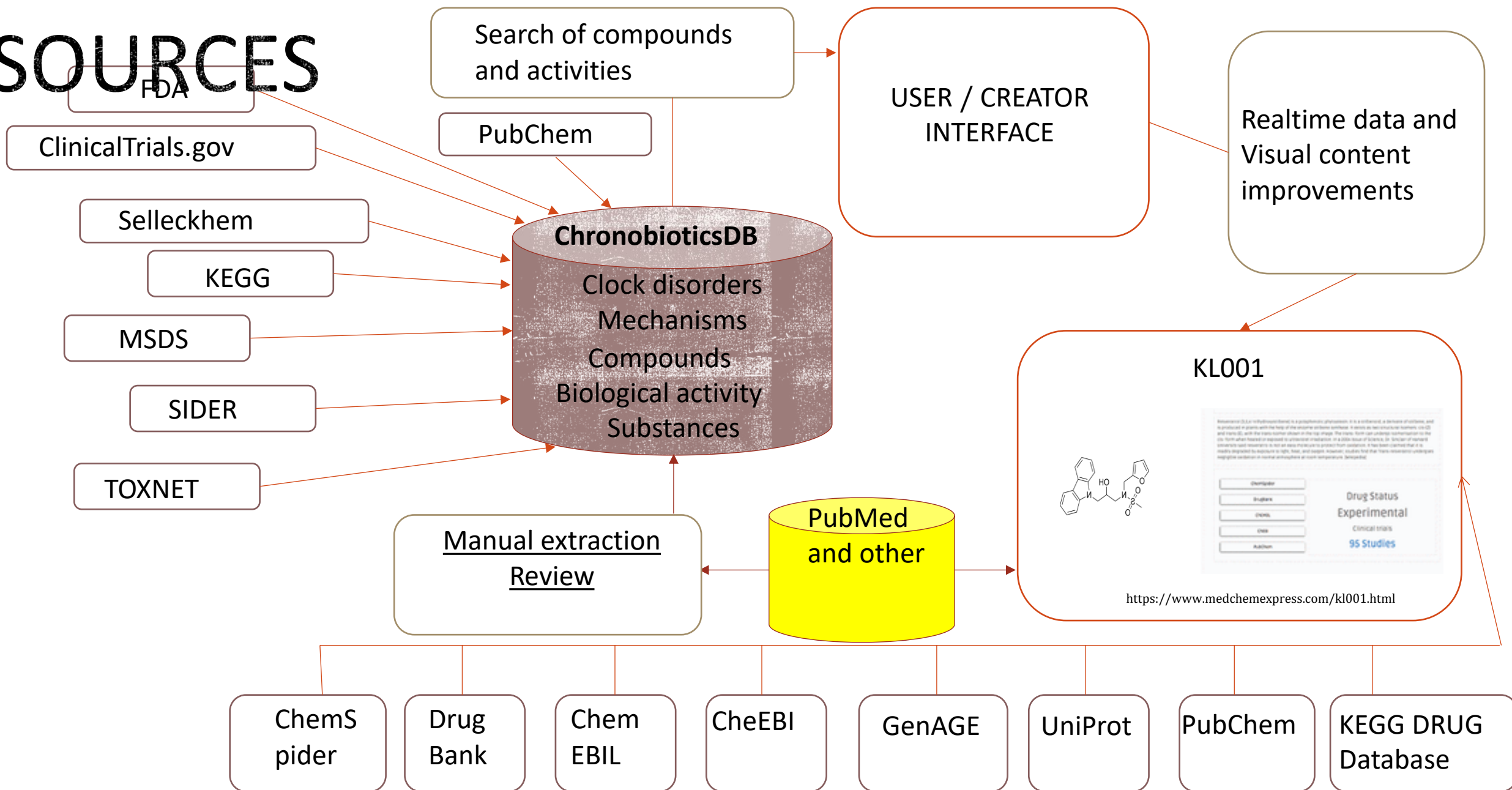
*- $p < 0.01$, according to χ^2 ; **- $p < 0.01$ (Gehan-Breslow-Wilcoxon); ***- $p < 0.05$ Wang Allison test.

Solovev, I.A., Shaposhnikov, M.V., Moskalev, A.A. (2021) *Clocks & Sleep*, 3, 429-441.

MATERIALS AND METHODS

- Django programming framework as a key tool, JAVA as facultative
- PostgreSQL as a database management system
- The ChronobioticsDB is filled using PubMed data on chronobiotics which are manually extracted from articles and annotated
- The cards of chronobiotics are filled manually using key sources
- Local LLM deployment (64 GB GPUs running Q3 quantized models)
- PostgreSQL and Django interface integration of the model
- ChronobioticsDB full-text articles mark up
- Training of local LLM on the material of ChronobioticsDB
- Testing of the

DATA SOURCES



RESEARCH DESIGN

1.0 TRAIN and TEST LAB HARDWARE RELEVANT ASSISTANT MODELS additionally teaching them chronopharmacology on a server (Ryzen 9 CPU, 128Gb RAM, 64gb vRAM GPU)

1.1. WizardLM2 8x22B

1.2. DeepSeek v2 Lite

1.3 Large models at lower quantisations:

Tencent Hunyuan 235B: This model can be run on systems with 128GB RAM.

A Q3 quantization is possible and may provide good quality of answers.

Possibly the progressive local models will be tested

1.3.1 Llama 3 70B

1.3.2 Qwen 2 72B

2. Deployment of the best overtrained LLM with dataset model locally and give access via the recourse Chronobiotic.ru to the scientific community



ChronobioticsDB: The Database of Drugs and Compounds Modulating Circadian Rhythms

Laboratory of Translational Bioinformatics and Systems Biology, Medical Institute, Pitirim Sorokin Syktyvkar State University, Oktyabrsky Prospekt 55, 167000 Syktyvkar, Russia; denismeatboy@gmail.com (D.A.G.); zedgoliz@mail.ru (A.I.Y.); nkotelina@gmail.com (N.O.K.)

Abstract

Chronobiotics represent a pharmacologically diverse group of substances, encompassing both experimental compounds and those utilized in clinical practice, which possess the capacity to modulate the parameters of circadian rhythms. These substances influence fluctuations in various physiological and biochemical processes, including the expression of core “clock” genes in model organisms and cell cultures, as well as the expression of clock-controlled genes. Despite their chemical heterogeneity, chronobiotics share the common ability to alter circadian dynamics. The concept of chronobiotic drugs has been recognized for over five decades, dating back to the discovery and detailed clinical characterization

Name	SMILES	FDA Status	Effects	Targets	Mechanisms	Articles
BLEOMYCIN SULFATE	<chem>CC1=C(N=C(N=C1N)[C@H](CC(=O)N)NC(C@@H)(C(=O)N)N(C(=O)N)[C@H]([C@H](C2=CN=CN2)OC3C(C(C(C(O3)CO)O)OC4C(C(C(C(O4)CO)O)OC(=O)N)O)C(=O)N)[C@H](C)[C@H]([C@H](C(C(=O)N)[C@H](C@H([C@H](C(CO)O)NCCC5=NC(=CS5)C6=NC(=CS6)C(=O)NCCC[S+])C)(CO</chem>	Approved	Circadian rhythm disruption	CLOCK-BMAL1, BMAL1 expression (induction), Dec1 gene expression	Bmal1, de-repressing BMAL1, BMAL1 expression modulation, BMAL1 expression modulation, by an immediate-early induction of Dec1	Tamai, T.K., Nakane, Y., Ota, W., Kobayashi, A., Ishiguro, M., Kadofusa, N., Ikegami, K., Yagita, K., Shigeyoshi, Y., Sudo, M. and Nishiwaki-Ohkawa, T., 2018. Identification of circadian clock modulators from existing drugs. EMBO



List of Chronobiotics



Insert name, formula, SMILES etc.

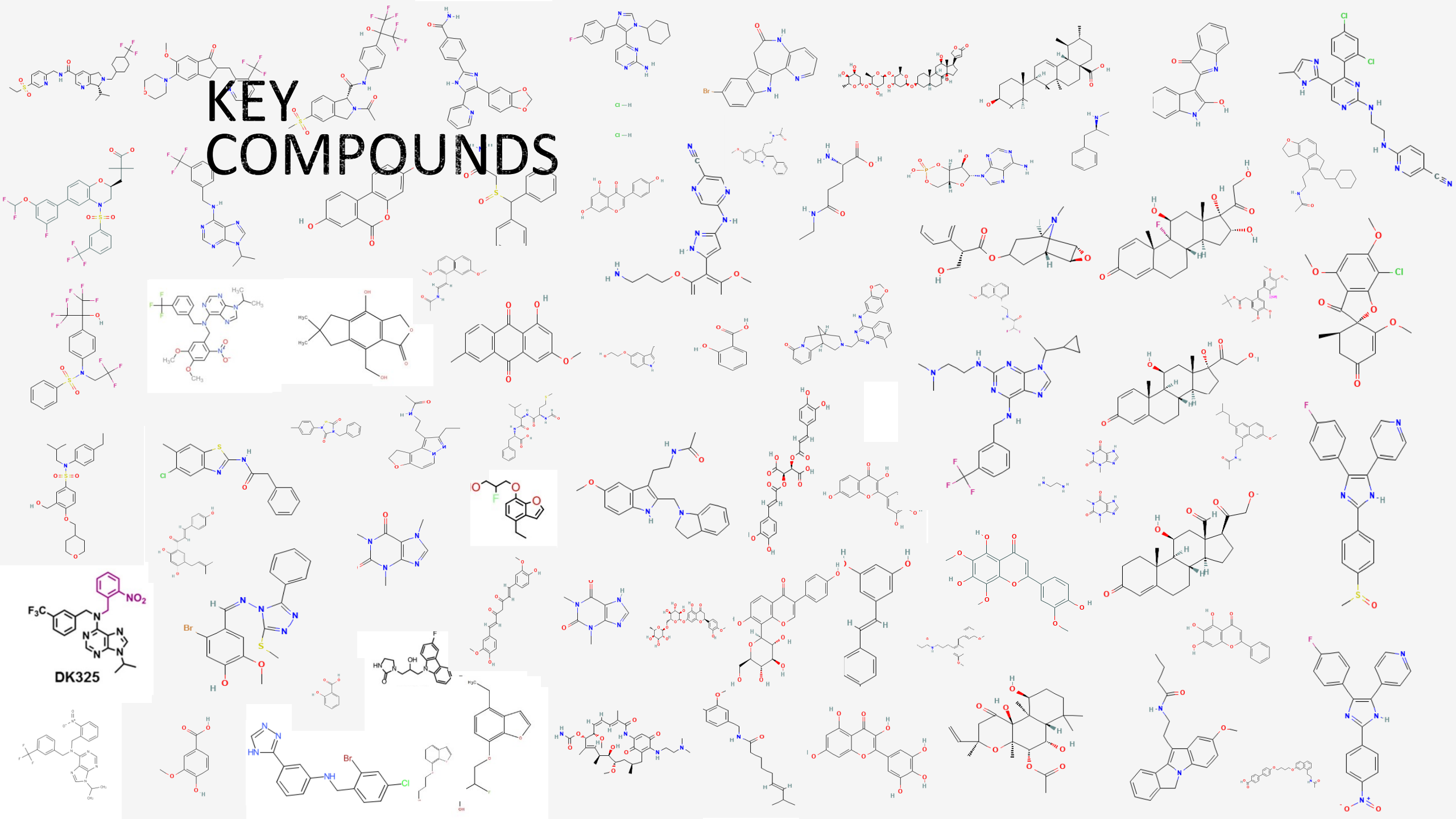
Name	SMILES	FDA Status	Effects	Targets	Mechanisms	Articles
Bavachalcone	<chem>CC1=CCC1=CC(=C(C=C1O)O)C(=O)C=C/C2=CC=C(C=C2)O</chem>	none	Amplitude enhancement in human cells	RORA, RORα	ROR	Dang, Y., Ling, S., Ma, J., Ni, R. and Xu, J.W., 2015. Bavachalcone enhances RORα expression, controls Bmal1 circadian transcription, and depresses cellular senescence in human endothelial cells: Evidence-based Complementary and Alternative Medicine, 2015(1), p.920431.
SB-202190	<chem>C1=CC(=CC=C1C2=NC(=C(N2)C3=CC=NC(=C3)C4=CC(=C(C4)F)O</chem>	Not	Period	p38 MAP	Inhibits p38 MAPK	Hirota, T., Lewis, W.G., Liu, A.C.,

List of Chronobiotics

MT2

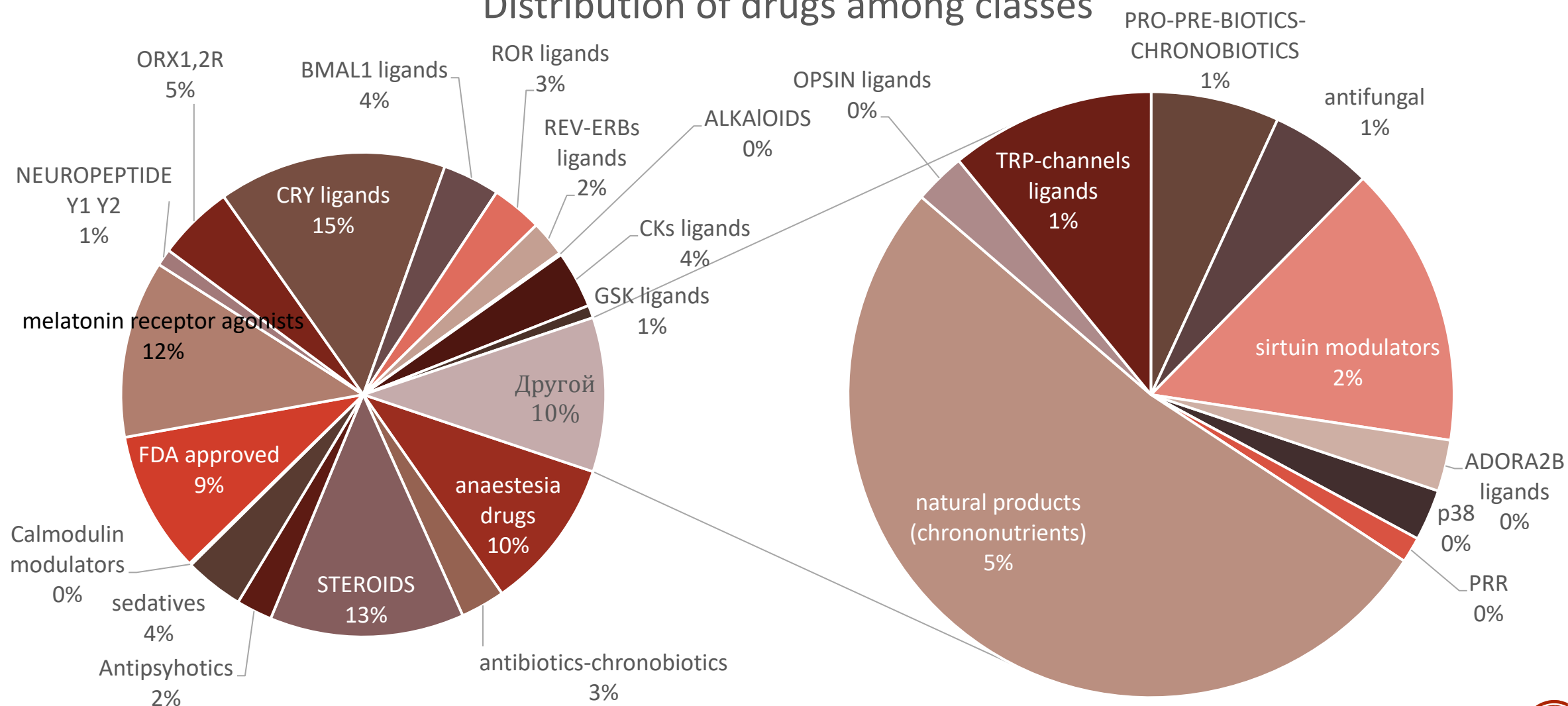
Name	SMILES	FDA Status	Effects	Targets	Mechanisms	Articles
Melatonin	<chem>CC(=O)NCCC1=CN=C2=C1C=C(C)C=C2OC</chem>	Approved	restores normal circadian rhythms	T58921 Peroxisome proliferator-activated receptor gamma (PPAR-gamma) Melatonin receptor PEPT2, GLUT1 HES, Calp, TUBULIN Calcitriol MT3, MT1, MT2 RORa, Mel1C, CAND2 VDR, QR2, MMP9, PEPsin, PR2, mPTP, PEPT1	SIRT1, ROR, Melatonin receptor agonist RORγ binding Antioxidant, Melatonin receptor binding RORγt/RORα inhibitor	Arendt, J. and Skene, D.J., 2005. Melatonin as a chronobiotic. <i>Sleep Medicine Reviews</i> , 9(1), pp.25–39. Pévet, P., Botheorel, B., Slangen, H. and Saboureau, M., 2002. The chronobiotic properties of melatonin. <i>Cell and Tissue Research</i> , 309, pp.183–191. Cardinali, D.P., 2024. Melatonin as a chronobiotic/chronoprotective agent in bone. <i>Doses Involved: Journal of Pineal Research</i> , 76(1), p.e12931.

KEY COMPOUNDS



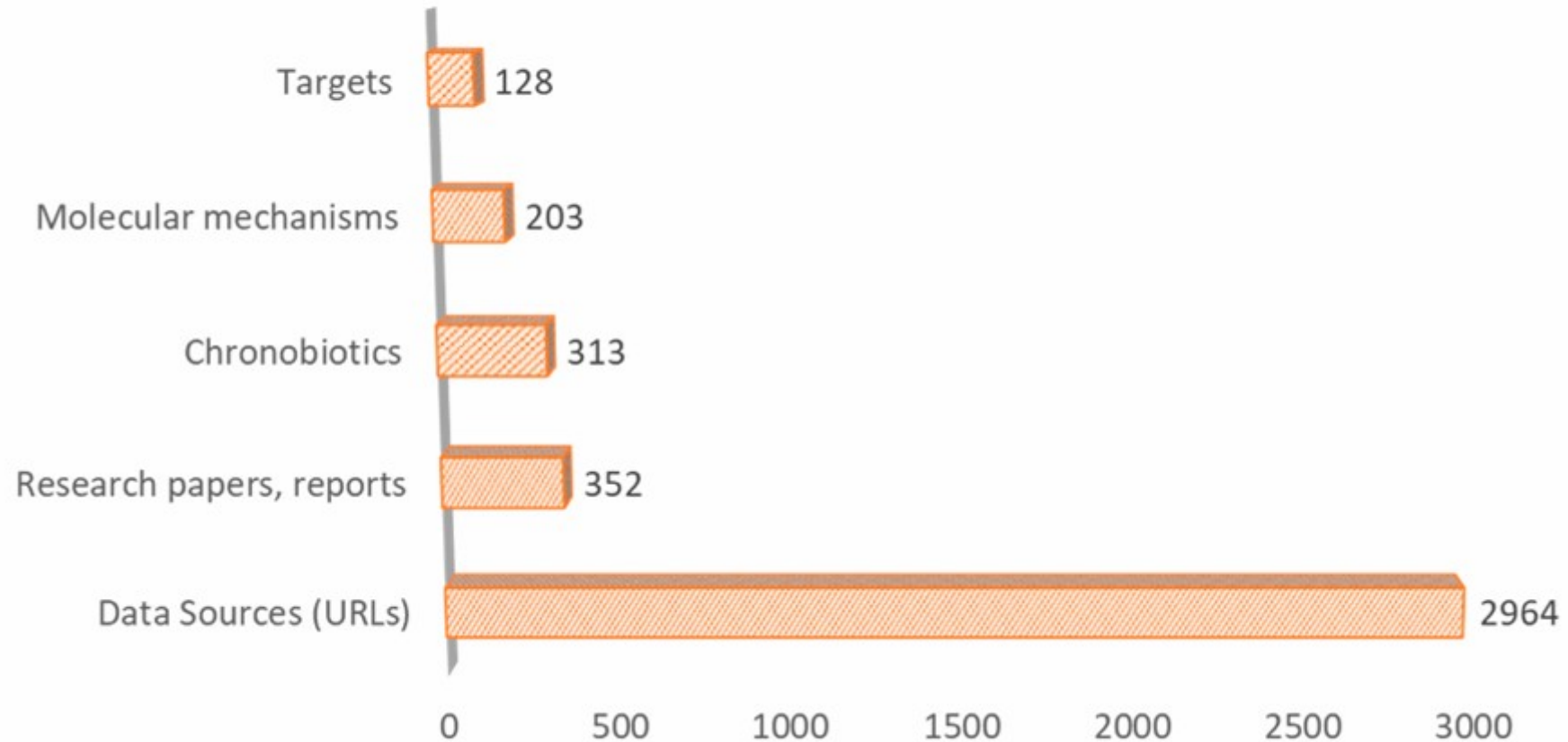
CONTENT OF CHRONOBIOTICSDB

Distribution of drugs among classes



CONTENT

CHRONOBIOTICSDB 2025 STATISTICS



ANALYSIS OF COMPOUNDS IN CHRONOBIOTICSDB (NOT PUBLISHED)

- Ongoing analysis of 300+ structures of chronobiotics in collaboration with Way2Drug platform (Poroikov et al. 2024) is just finished and is under description
- Study of the biological activity spectra of chronobiotics
- Creation of PASS-powered detector of chronobiotic compounds
- Search of novel potential chronobiotics in synthesis-accessible compounds databases in collaboration with IBMC and acad. RAS, prof., Dr. Vladimir Poroikov

CONCLUSION

- The ChronobioticsDB is accessible all over the world since May 2025
- ChronobioticsDB is growing every week (over 3000 sources)
- ChronobioticsDB becomes a key instrument to create a training set for machine learning tool searching for novel chronobiotics of different classes
- In May 2026 ChronobioticsDB v2 AI (trained on full text articles and other sources) as a world first chronobiology expert agent will appear

ACKNOWLEDGEMENTS



**Russian Science
Foundation**

- This work was funded by the Russian Science Foundation Grant “Design of the world's first pharmacological database of circadian rhythm modulators (ChronobioticsDB) and organisation of the access to it” № 24-75-00108

TRANSLATIONAL BIOINFORMATICS AND SYSTEMS BIOLOGY LAB



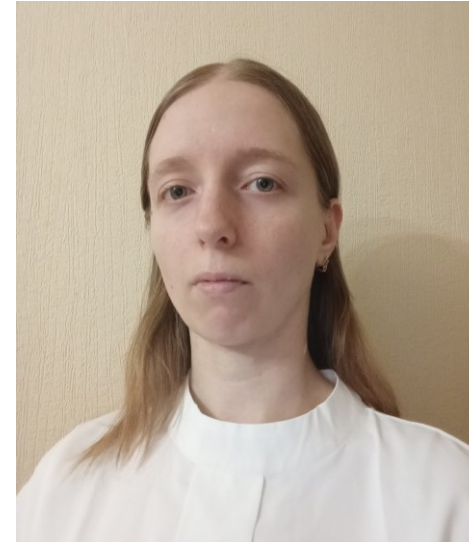
- Dr. Ilya A. Solovev (PhD in Biogerontology, Senior Researcher TBSB lab)



- Dr. Nadezhda O. Kotelina (PhD in Mathematics, Assistant professor of the Applied mathematics department)



- Denis A. Golubev (PhD student Life Sciences, Biogerontology)



- Arina I. Yagovkina (Student, Applied mathematics <https://github.com/YagovkinaA/chronobioticdb>)



GIT-HUB

THANK YOU FOR ATTENTION

