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5-ARYL-7,8,9,10-TETRAHYDRO-5*H*-TETRAZOLO[1,5-*a*]THIOPYRANO[3,2-*d*]PYRIMIDINE 6,6-DIOXIDES – A NEW HETEROCYCLIC ENSEMBLE *via* MCR APPROACH

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Abstract

Tetrazoles are found broad applications in numerous fields such as in medicine, biochemistry, pharmacology, and in industry. Considering our continued interest in new azaheterocycles based on *β*-ketosulfones in this work a three-component heterocyclization of dihydro-2*H*-thiopyran-3(4*H*)-one-1,1-dioxide, 1*H*-tetrazol-5-amine, and aromatic aldehydes under microwave irradiation was studied. Regardless of the reaction conditions, 5-aryl-7,8,9,10-tetrahydro-5*H*-tetrazolo[1,5-*a*]thiopyrano[3,2-*d*]pyrimidine 6,6-dioxides were isolated as sole reaction products in good to excellent yields. To the best of our knowledge mentioned azaheterocycles are novel and previously not reported heterocyclic ensemble. Proposed structures were confirmed by spectral methods. Considering druglikeness we can conclude that compounds match parameters for Lipinski, Ghose, Veber, Egan and Muegge rules, and also correspond to the V class of acute toxicity. *In silico* screening of the biological profile of new derivatives showed adequate ADMET properties along with high (60 % and more) probability levels of activity against such pathogens/diseases as *Candida albicans*, *Alphis gossypii*, *Tripomastigote Chagas*, *Tcruzi amastigota*, *Tcruzi epimastigota* etc.

Keywords: azaheterocycles; sulfones; 5-aminotetrazole; microwave irradiation; multicomponent reactions (MCR).

5-АРИЛ-7,8,9,10-ТЕТРАГІДРО-5*H*-ТЕТРАЗОЛО[1,5-*a*]ТІОПІРАНО[3,2-*d*]ПІРИМІДИН 6,6-ДІОКСИДИ – СИНТЕЗ НОВОГО ГЕТЕРОЦИКЛІЧНОГО АНСАМБЛЮ З ВИКОРИСТАННЯМ МУЛЬТИКОМПОНЕНТНОЇ ХІМІЇ

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Анотація

Тетразоли знаходять широке застосування в багатьох галузях, таких як медицина, біохімія, фармакологія та промисловість. Враховуючи наш постійний інтерес до нових азагетероциклів на основі β-кетосульфонів, у цій роботі трикомпонентна гетероциклізація дигідро-2Н-тіопіран-3(4Н)-он-1,1-діоксиду, 1Н-тетразол-5-аміну та ароматичного альдегідів під впливом мікрохвильового опромінення. Незалежно від умов реакції 5-арил-7,8,9,10-тетрагідро-5Н-тетразоло[1,5-а]тіопірано[3,2-d]піримідин 6,6-діоксиди були виділені як єдині продукти реакції. від хороших до відмінних урожаїв. Наскільки нам відомо, згадані азагетероцикли є новими гетероциклічними ансамблями, про які раніше не повідомлялося. Запропоновані структури підтверджені спектральними методами. З огляду на лікарську схожість можна зробити висновок, що сполуки відповідають параметрам правил Ліпінського, Гозе, Вебера, Егана та Мюгге, а також відповідають V класу гострої токсичності. Скринінг in silico біологічного профілю нових похідних продемонстрував адекватні властивості ADMET разом із високими (60 % і більше) рівнями ймовірності активності проти таких збудників/захворювань, як Candida albicans, Alphis gossypii, Tripomastigote Chagas, Tcruzi amastigota, Tcruzi epimastigota тощо.

Ключові слова: азагетероцикли; сульфони; 5-амінотетразол; мікрохвильове опромінення; багатокомпонентні реакції.

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Introduction

Tetrazoles are a major class of heterocycles very important for medicinal chemistry and drug design due not only to their bioisosterism to carboxylic acids and amides, but also to their metabolic stability and other useful physicochemical properties. This scaffold found broad applications in numerous fields such as in medicine, biochemistry, pharmacology, and in industry as materials, *e.g.*, in photography, imaging chemicals, and military. Among FDA approved drugs, that contain tetrazole substituents, 23 compounds possess hypertensive, antimicrobial, antiviral, antiallergic, cytostatic, nootropic, and other biological activities [1]. Given the privilege of the tetrazole heterocycle, it is not surprising that it is currently the subject of hundreds of publications per year (Fig. 1).

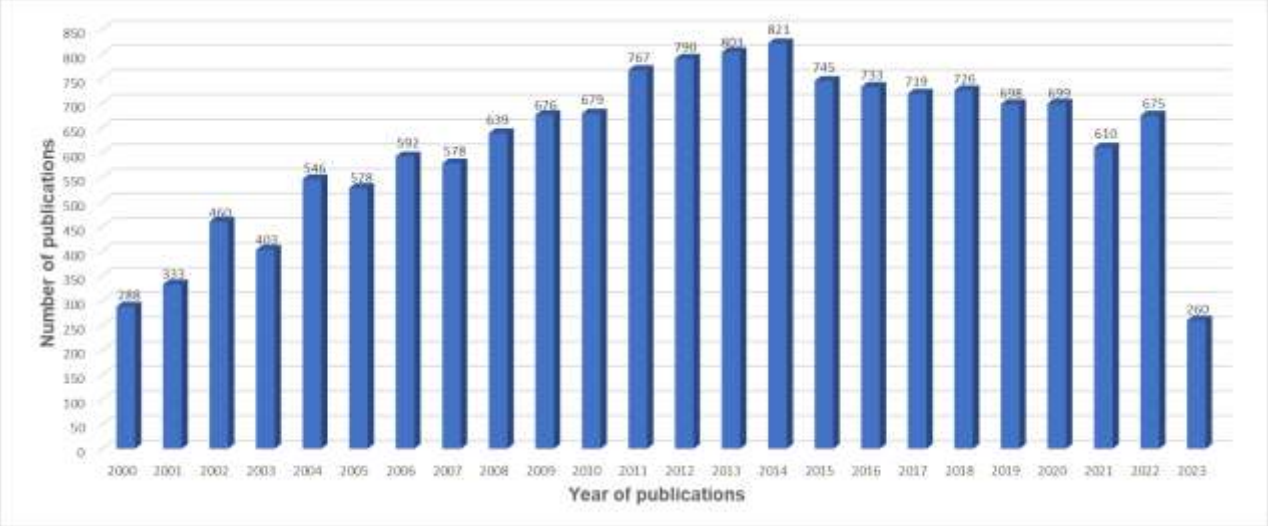


Fig. 1. Number of publications containing "tetrazole(s)" in the title, abstract and/or keywords of the articles plotted against the publication year as analyzed by Scopus (14768 articles in total between 2000 and June 2023)

Considering our continued interest in new heterocycles based on *β*-ketosulfones [2–7], in this work, we have tried to combine the high biological potential of tetrazoles and sulfones by placing these fragments together. Literature survey showed many successful cases of using 1*H*-tetrazol-5-amine in the synthesis of azaheterocycles (mostly dihydrotetrazolo-pyrimidines) based on 1,3-diketones or their synthetic equivalents and aromatic aldehydes (**Fig. 2**). Thus, to the best of our knowledge desired 5-aryl-7,8,9,10-tetrahydro-5*H*-tetrazolo[1,5-*a*]thio-pyrano[3,2-*d*]pyrimidine 6,6-dioxides are novel and previously not reported heterocyclic ensemble.

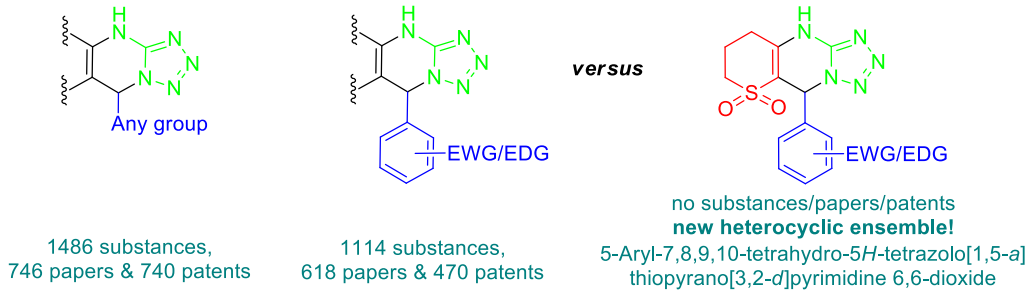


Fig. 2. Number of substituted dihydrotetrazolopyrimidines synthesized from 1*H*-tetrazol-5-amine as analyzed by Reaxys (June 2023)

Importantly, multicomponent reaction (MCR) chemistry offers convergent access to multiple tetrazole scaffolds providing the three important elements of novelty, diversity, and complexity [8-10]. On the other hand, a number of interesting cases of heterocyclization of dihydro-2*H*-thiopyran-3(4*H*)-one-1,1-dioxide 1 into various azaheterocycles were designed recently [11] (Fig. 3A). As an additional confirmation of the relevance of our study, we present the structures of well-known drugs, including sulfone and tetrazole subunits, which have already won their place in the pharmacological market (Fig. 3B).

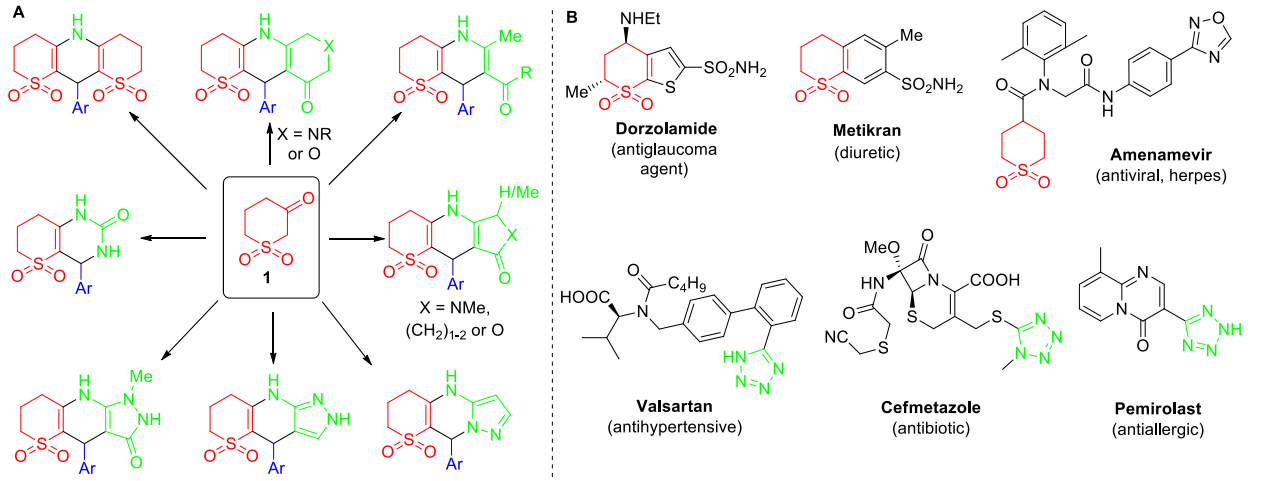
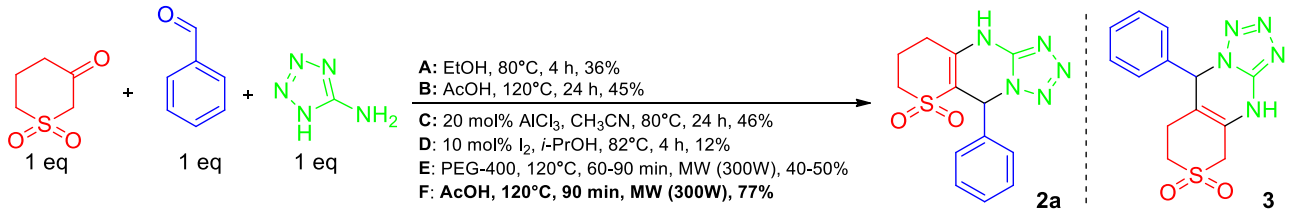


Fig. 3. Selected cases of heterocyclization of *β*-ketosulfone 1 *via* MCR approach leading to azaheterocycles (A) and marketed drugs containing sulfone and tetrazole subunits (B)

Results and discussion

Our strategy for the preparation of the desired 5-aryl-7,8,9,10-tetrahydro-5*H*-tetrazolo[1,5-*a*]thiopyrano[3,2-*d*]pyrimidine 6,6-dioxides **2** was quite straightforward and relied on MCR approach. The study commenced with optimization of the reaction conditions between equimolar amounts of ketosulfone **1**, benzaldehyde and 1*H*-tetrazol-5-amine (Scheme 1). We tried several known and suggested by us conditions for this chemistry. It was found that testing published protocols for this type of heretocyclization using 1*H*-tetrazol-5-amine *e.g.* $AlCl_3$-catalysis in acetonitrile [12] or I_2-catalysis in isopropyl alcohol [13] yielded the desired product **2a** in only 12–46 %. We, of course, turned our attention to classical MCR approach under microwave irradiation (300W). Using PEG-400 as a high boiling solvent [14], gave only 40-50 % of the desired product, but using acetic acid and decreasing the reaction time to 90 min led to significantly better outcome (77 % yield).

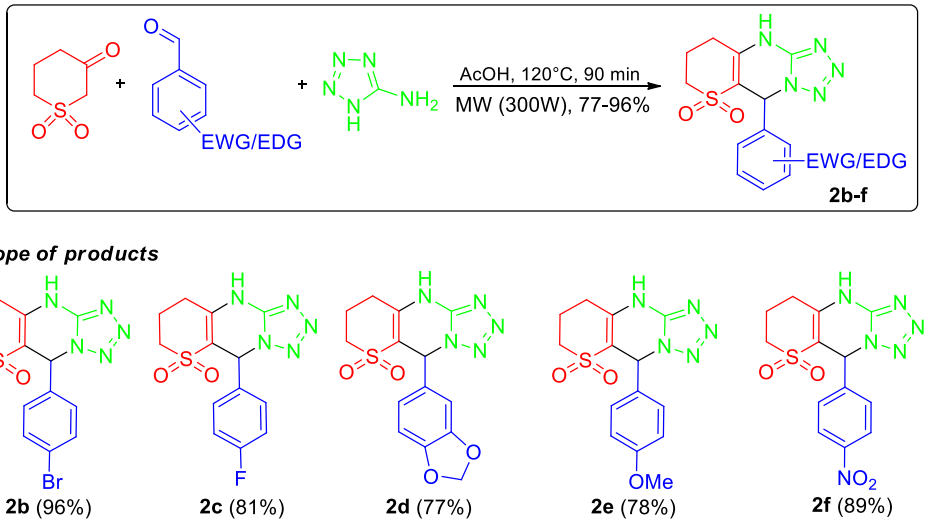


Scheme 1. Optimization of the reaction conditions

We also consider the possibility of the formation of an alternative regioisomer **3**, but we have not found any evidence of its formation. Regardless of the reaction conditions, 5-phenyl-7,8,9,10-tetrahydro-5*H*-tetrazolo[1,5-*a*]thiopyrano[3,2-*d*]pyrimidine 6,6-dioxide **2a** was isolated as reaction product and its structure was confirmed by spectral methods.

Having the optimized conditions in hands, we further explored the scope of current protocol using aromatic aldehydes containing electron withdrawing (EWG) and donating (EDG) groups. All aldehydes gave good to excellent yields for final products **2b-f** (Scheme 2).

These conclusions were made on the basis of spectral analysis data. ^{1}H NMR spectra of the reaction products **2a-f** exhibited the following signals: characteristic resonances for the aromatic ring protons (6.91–8.23 ppm), a singlet for Ar–CH proton (6.71–7.01 ppm), a broad singlet for pyrimidine NH group (11.32–11.52 ppm), complicated signals for three consecutive CH_2 groups of sulfone fragment (2.28–3.31 ppm), and appropriate signals for substituents in aromatic rings.



Scheme 2. Scope of products 2b-f

This set of signals can clearly correspond to depicted above heterocycles. A representative sample of ^{1}H and ^{13}C NMR spectra in the case of compound **2a** showed in Figure 4.

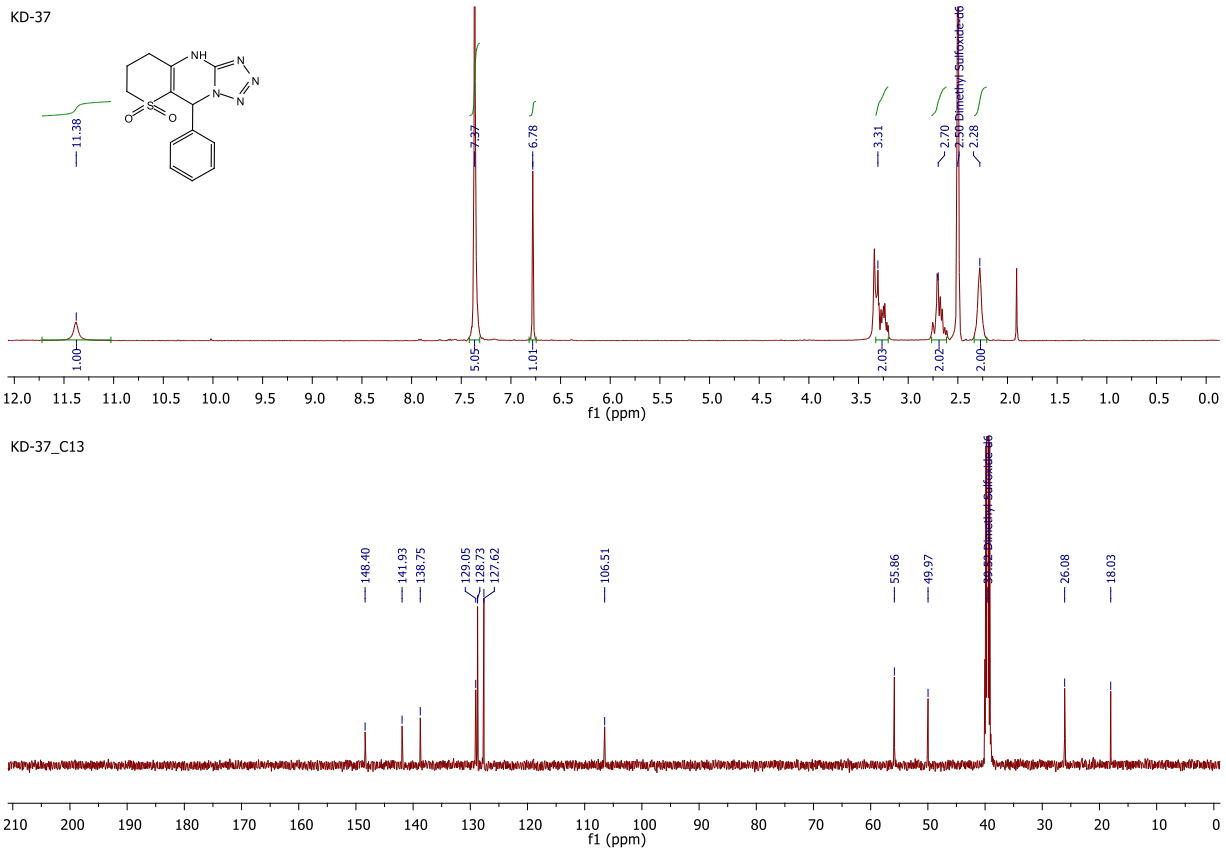
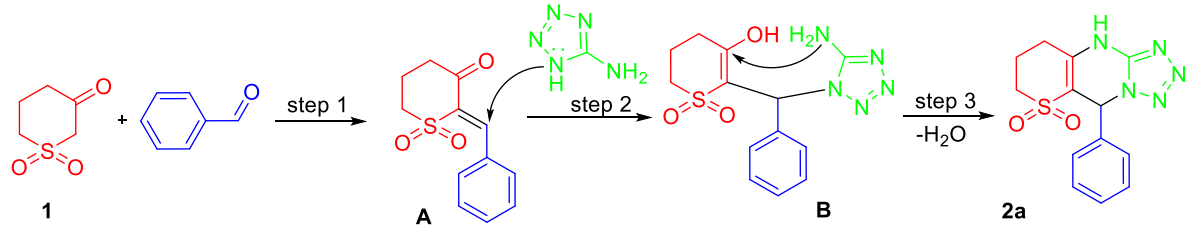


Fig. 4. ^{1}H (*up*) and ^{13}C (*down*) NMR spectra of compound 2a (DMSO-d_6, 500MHz for ^{1}H and 126MHz for ^{13}C nuclei)

Considering literature precedents [14] and our experimental results, the plausible reaction scheme includes three major steps (Scheme 3). Step 1 involves the Knoevenagel condensation (product A) when benzaldehyde reacts with *β*-ketosulfone **1**. In step 2 nucleophilic aminotetrazole attacks the electrophilic benzylic carbon atom to give B by simple hydroamination reaction. The final step 3 involves the thermal dehydration followed by cyclization to give final product **2a**. In the overall reaction mechanism, acetic acid acts as catalyst and high boiling solvent simultaneously.



Scheme 3. Proposed scheme for the formation of the product 2a.

In silico screening of the biological profile. Being inspired by the aforementioned results, we have evaluated *in silico* the biological profile of compounds **2a-f** using SwissADME (http://www.swissadme.ch) [15], ProTox-II (https://tox-new.charite.de) [16], and MolPredictX (https://www.molpredictx.ufpb.br) [17] tools. Chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET), play key roles in drug discovery and development. A high-quality drug candidate should not only have sufficient efficacy against the therapeutic target, but also show appropriate ADMET properties at a therapeutic dose. Considering druglikeness we can conclude that compounds **2a-e** and partially **2f** match parameters for Lipinski [18], Ghose [19], Veber [20], Egan [21] and Muegge [22] rules. Only nitro-derivative **2f** violates Veber and Egan rules. The estimation of octanol-water partition coefficient (lipophilicity) studies as of Log $P_{octanol/water}$ (given as consensus Log $P_{o/w*}$ an average of five predictions calculated *via* SwissADME tool) for our set of compounds is in the range 0.47–1.80. The topological polar surface area (TPSA) is another important descriptor of the appropriate physicochemical space for oral bioavailability and should be in the range 20 Å^2–130 Å^2. For the tested compounds the value is in the range 98–117 Å^2 (except compound **2f**). All compounds are soluble or moderately soluble in water, have high gastrointestinal (GI) absorption (except compound **2f**), good bioavailability score (0.55), no BBB permeability and no alerts for PAINS filter (*Table 1*).

The prediction of compound toxicities is an important part of the drug design development process. Computational toxicity estimations are not only faster than the determination of toxic doses in animals but can also help to reduce the amount of animal experiments. *In silico* prediction of LD_{50} values were performed by ProTox-II software. These data correspond to the V class of acute toxicity which may be harmful if swallowed ($2000 < LD_{50} \leq 5000$). MolPredictX is a web tool that allows the scientific community to obtain biological activities predictions of molecules. To our delight we found high (60 % and more) probability levels of activity against the following pathogens/species/diseases: *Candida albicans*, *Alphis gossypii*, *Tripomastigote Chagas*, *Tcruzi amastigota*, *Tcruzi epimastigota etc*. For more details see Table.

Table

Predicted druglikeness properties of the synthesized compounds 2a-f

Compd	Lipophi-licity Log $P_{o/w}$	Predicted toxicity, mg/kg	Topological surface area, Å	Biological profile
2a	1.17	2025	98.2	*Candida albicans* (100 %), *Alphis gossypii* (100 %), *Tripomastigote Chagas* (60 %), *Tcruzi amastigota* (80 %), *Tcruzi epimastigota* (60 %)
2b	1.80	2025	98.2	*Sars-COVID* (60 %), *Candida albicans* (100 %), *Alphis gossypii* (100 %), *Tripomastigote Chagas* (60 %), *Tcruzi amastigota* (80 %), *Tcruzi epimastigota* (60 %), *Tcruzi trypomastigota* (100 %)
2c	1.49	2025	98.2	*Candida albicans* (100 %), *Salmonella* (60 %), *Leishmania braziliensis* (60 %), *Alphis gossypii* (100 %), *Alzheimer – NADPH* (100%), *Promastigote Ldonovani* (100%), *Tripomastigote Chagas* (100%), *Tcruzi amastigota* (100%), *Tcruzi trypomastigota* (100%)

Continuation of the table

2d	1.04	2100	116.6	*Sars-COVID* (80 %), *Candida albicans* (100 %), *Alphis gossypii* (100 %), *Leishmania major* (80 %), *Promastigote Ldonovani* (60 %), *PTR L major* (100 %), *Tcruzi amastigota* (100 %), *Tcruzi epimastigota* (60 %), *Tcruzi trypomastigota* (100 %)
2e	1.17	2100	107.4	*Candida albicans* (80 %), *Alphis gossypii* (100 %), *Tripomastigote Chagas* (60 %), *Tcruzi amastigota* (80 %), *Tcruzi epimastigota* (60 %), *Tcruzi trypomastigota* (100 %)
2f	0.47	2025	144.0	*Candida albicans* (100 %), *Alphis gossypii* (100 %), *Tripomastigote Chagas* (60 %), *Tcruzi amastigota* (100 %), *Tcruzi epimastigota* (60 %), *Tcruzi trypomastigota* (60 %)

Experimental

All chemicals were supplied by Enamine Ltd. (www.enamine.net). All solvents were purified according to standard methods. Thin layer chromatography (TLC) was carried out using Merck aluminium backed DC 60 F_{254} 0.2 mm precoated plates. Spots were then visualized by the quenching of ultraviolet light fluorescence (λ_{max} 254 nm) and then stained and heated with either anisaldehyde or potassium permanganate solutions as appropriate. ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra were recorded at 126 MHz using Bruker 500 spectrometer. ^{1}H and ^{13}C NMR chemical shifts are calibrated using residual undeuterated DMSO (δ = 2.50 ppm for ^{1}H, 39.52 ppm for ^{13}C). Coupling constants (*J*) are given in Hz, multiplicities are given as s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time-of-flight reflectron experiments.

General method for the synthesis of compounds **2a-f**. A stirred reaction mixture of dihydro-2*H*-thiopyran-3(4*H*)-one **1** (148 mg, 1 mmol), 1*H*-tetrazol-5-amine monohydrate (103 mg, 1 mmol), and aromatic aldehyde (1 mmol) in acetic acid (1 mL) was heated at 120 °C for 90 min under microwave irradiation (300 W). The progress of the reaction was monitored by ^{1}H NMR. After completion the reaction, solvent was evaporated *in vacuo* and the semi-crystalline residue was triturated or recrystallized from isopropyl alcohol where appropriate.

5-Phenyl-5,8,9,10-tetrahydro-7H-tetrazolo[1,5-a]thiopyrano[3,2-d]pyrimidine 6,6-dioxide **(2a).** Yield: 233 mg (77 %), m.p. 218-221°C, light-yellow powder. ^{1}H NMR (500 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 11.38 (1H, br.s, NH), 7.37 (5H, m, H^{Ar}), 6.78 (1H, s, CH), 3.31 (2H, m, CH_2), 2.70 (2H, m, CH_2), 2.28 (2H, m, CH_2). ^{13}C NMR (126 MHz, DMSO-d_6), ppm: 148.40, 141.93, 138.75, 129.05, 128.73, 127.62, 106.51, 55.86, 49.97, 26.08, 18.03. HRMS (ESI-TOF), *m/z*: found 326.0682, calculated for $C_{13}H_{13}N_5O_2SNa$ $[M+Na]^+$ 326.0683.

5-(4-Bromophenyl)-5,8,9,10-tetrahydro-7H-tetrazolo[1,5-a]thiopyrano[3,2-d]pyrimidine 6,6-dioxide **(2b).** Yield: 368 mg (96 %), m.p. 210-213°C, light-yellow powder. ^{1}H NMR (500 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 11.42 (1H, br.s, NH), 7.57 (2H, d, *J* = 8.2 Hz, H^{Ar}), 7.36 (2H, d, *J* = 8.2 Hz, H^{Ar}), 6.81 (1H, s, CH), 3.31 (2H, m, CH_2), 2.69 (2H, m, CH_2), 2.28 (2H, m, CH_2). ^{13}C NMR (126 MHz, DMSO-d_6), ppm: 148.28, 142.10, 138.10, 131.69, 130.03, 122.47, 106.03, 55.36, 49.90, 26.10, 18. HRMS (ESI-TOF), *m/z*: found 403.9788, calculated for $C_{13}H_{12}BrN_5O_2SNa$ $[M+Na]^+$ 403.9787.

5-(4-Fluorophenyl)-5,8,9,10-tetrahydro-7H-tetrazolo[1,5-a]thiopyrano[3,2-d]pyrimidine 6,6-dioxide **(2c).** Yield: 260 mg (81 %), m.p. 260-263°C, light-yellow powder. ^{1}H NMR (500 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 11.39 (1H, br.s, NH), 7.46 (2H, dd, *J* = 8.5 and 5.5 Hz, H^{Ar}), 7.20 (2H, t, *J* = 8.5 Hz, H^{Ar}), 6.82 (1H, s, CH), 3.31 (2H, m, CH_2), 2.70 (2H, m, CH_2), 2.28 (2H, m, CH_2). ^{13}C NMR (126 MHz, DMSO-d_6), ppm: 162.32 (d, $^1J_{C\text{-}F}$ = 245.4 Hz), 148.27, 141.98, 135.03, 130.09 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 115.58 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 106.25, 55.21, 49.98, 26.09, 18.03. HRMS (ESI-TOF), *m/z*: found 344.0585, calculated for $C_{13}H_{12}FN_5O_2SNa$ $[M+Na]^+$ 344.0588.

5-(Benzo[d][1,3]dioxol-5-yl)-5,8,9,10-tetrahydro-7H-tetrazolo[1,5-a]thiopyrano[3,2-d]pyrimidine 6,6-dioxide **(2d).** Yield: 267 mg (77 %), m.p. 206-209°C, light-yellow powder. ^{1}H NMR (500 MHz, DMSO-d_6), *δ*, ppm (*J*, Hz): 11.32 (1H, br.s, NH), 6.91 (3H, m, H^{Ar}), 6.71 (1H, s, CH), 6.02 (2H, d, *J* = 8.5 Hz, OCH_2O), 3.27 (2H, m, CH_2), 2.68 (2H, m, CH_2), 2.28 (2H, m, CH_2). ^{13}C NMR (126 MHz, DMSO-d_6), ppm: 148.21, 147.83, 147.52, 141.92, 132.63, 121.79,

108.15, 107.93, 106.40, 101.40, 55.64, 50.00, 26.13, 18.03. HRMS (ESI-TOF), *m/z*: found 370.0580, calculated for $C_{14}H_{13}N_5O_4SNa$ $[M+Na]^+$ 370.0581.

5-(4-Methoxyphenyl)-5,8,9,10-tetrahydro-7H-tetrazolo[1,5-a]thiopyrano[3,2-d]pyrimidine 6,6-dioxide **(2e).** Yield: 260 mg (78 %), m.p. 208-211°C, light-yellow powder. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm (J, Hz): 11.32 (1H, br.s, NH), 7.30 (2H, d, J = 8.5 Hz, H^{Ar}), 6.91 (2H, d, J = 8.5 Hz, H^{Ar}), 6.73 (1H, s, CH), 3.74 (3H, s, CH_3), 3.27 (2H, m, CH_2), 2.68 (2H, m, CH_2), 2.28 (2H, m, CH_2). ^{13}C NMR (126 MHz, DMSO-d_6), ppm: 159.66, 148.28, 141.68, 130.86, 129.04, 114.01, 106.66, 55.40, 55.14, 49.97, 26.07, 18.03. HRMS (ESI-TOF), *m/z*: found 356.0790, calculated for $C_{14}H_{15}N_5O_3SNa$ $[M+Na]^+$ 356.0788.

5-(4-Nitrophenyl)-5,8,9,10-tetrahydro-7H-tetrazolo[1,5-a]thiopyrano[3,2-d]pyrimidine 6,6-dioxide **(2f).** Yield: 310 mg (89 %), m.p. 211-214°C, yellow powder. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm (J, Hz): 11.52 (1H, br.s, NH), 8.23 (2H, d, J = 8.5 Hz, H^{Ar}), 7.70 (2H, d, J = 8.5 Hz, H^{Ar}), 7.01 (1H, s, CH), 3.26 (2H, m, CH_2), 2.71 (2H, m, CH_2), 2.28 (2H, m, CH_2). ^{13}C NMR (126 MHz, DMSO-d_6), ppm: 148.34, 147.85, 145.35, 142.49, 129.43, 123.91, 105.67, 55.21, 49.97, 26.15, 18.05. HRMS (ESI-TOF), *m/z*: found 371.0531, calculated for $C_{13}H_{12}N_6O_4SNa$ $[M+Na]^+$ 371.0533.

Conclusions

In summary, starting from easily available dihydro-2*H*-thiopyran-3(4*H*)-one-1,1-dioxide we have developed valuable synthetic route to a new heterocyclic ensemble namely 5-aryl-7,8,9,10-tetrahydro-5*H*-tetrazolo[1,5-*a*]thiopyrano[3,2-*d*]pyrimidine 6,6-dioxide. An efficient, multicomponent, green protocol to access this class of azaheterocycles was elaborated. Considering druglikeness we can conclude that compounds match parameters for Lipinski, Ghose, Veber, Egan and Muegge rules. *In silico* screening of the biological profile showed that new derivatives correspond to the V class of acute toxicity and may have high activity against diseases related to these species: *Candida albicans, Alphis gossypii, Tripomastigote Chagas, Tcruzi amastigote* and *Tcruzi epimastigota*.

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