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Regiospecific coupling of dehydroacetic acid and hydrazines leading to bioactive heterocycles

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ABSTRACT

The reaction of dehydroacetic acid with hydrazines provides two types of pyranopyrazoles and a bipyrazole. Earlier studies typically missed the detection or isolation of one or more products and did not investigate their ratio systematically. Consequently, current literature data suggest that virtually same reaction conditions led to different products. In this work, we therefore attempted to investigate the effect of reaction conditions and reactants to the distribution of the products such as pyrano [4,3-*c*]pyrazole-4(1*H*)-one, pyrano [2,3-*c*]pyrazole-4(1*H*)-one, and 1′*H*,2*H*-[3,4′-bipyrazole]-5′-ol. Product ratio, reaction rate and the conversion depended on the applied solvent and the acidic additive. Optimized conditions allowed us to expand the limited chemical space of these pyranopyrazoles by enumerating a virtual library synthetically sampled by pilot building blocks. Finally, the biological activity of the isolated compounds was confirmed against the non-receptor tyrosine phosphatase SHP2.

1. Introduction

Heterocyclic compounds are abundant in nature and are essential for life. They are found among the building blocks of DNA, RNA and proteins, and play key roles in cellular processes [1]. Due to their synthetic accessibility and their impact on both ligand interactions and ADMET properties, heterocycles became essential building blocks of bioactive molecules [1–3]. Bemis and Murcko examined drug molecules containing rings in the current database of Comprehensive Medicinal Chemistry [4]. Based on their graph theory based analysis, 32 different ring systems account for 50% of known drugs. Lipkus et al. performed a statistical analysis of organic compounds found in the CAS database and concluded that approximately 10% of the skeletons provide the basis for 80% of the compounds [5]. More recently, Ertl et al. analysed 1.35 million ChEMBL molecules by cheminformatics and found unique rings in only 2% of them [6]. This aligns with our hypothesis, that the vast chemical spaces of synthetically accessible heterocycles are poorly sampled by the most popular representatives. Therefore, any attempts that explore the uncharted part of this space might facilitate the discovery of new ring systems and their potential applications. Our research group was committed to expand the chemical space of ring systems that also initiated this project [7,8]. In this study we aim at developing reasonable synthetic routes to a pair of rare pyranopyrazoles and investigate them as synthetic building blocks or starting points for

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application in medicinal chemistry.

Pyranopyrazoles contain a pyrazole ring that is the tenth most common ring in medicinal chemistry [6] and has been a subject of constant interest among researchers due to their widespread use in the pharmaceutical industry [9]. It serves as a scaffold for various drugs with anticancer (darolutamide), antiparkinson (anle138b), antimicrobial (pyrazofurin), anticoagulant (apixaban), antidepressant (granisetron) and anti-inflammatory (celecoxib) activity (Fig. 1) [10–13]. Some 2-pyrone and condensed derivatives also have biological activities, in particular *anti*-HIV (tipranavir), anticancer (rasfonin), antimicrobial (fusapyrone) and anti-Alzheimer (CP2) effects (Fig. 1) [14]. Therefore, it was interesting for us to explore the chemistry and potential biological activity of compounds formed by the condensation of these ring types.

The preparation of bipyrazoles or pyranopyrazoles from dehydroacetic acid (**1**) with hydrazines (**2**) was previously investigated, however, despite of the similar conditions isolated products and their distribution were often contradictory (Scheme 1, Scheme 2).

The first reports were published in the dawn of the last century reacting dehydroacetic acid with phenylhydrazine in ethanol under reflux leading to two different pyranopyrazole (**3,4**) and a bipyrazole (**5**) [15,16]. Yields were not disclosed and the proposed structures were not proven, only elemental analysis was reported. After several decades, however, new attempts emerged at this reaction providing only two products: pyrano [4,3-*c*]pyrazole (**3**) and the bipyrazole (**5**) were successfully isolated and characterized. Depending on the reaction conditions, diverse yields were obtained, and again, similar conditions led to different products. In particular, heating one equivalent of **2** in ethanol led to pyrano [4,3-*c*]pyrazole (**3**) derivative with good yield (79%, R = Ph) [17] (Scheme 1, **entry 1**). Adding 2 eq. hydrazine (**2**) in acetic acid [18] or triethylamine (TEA) [18], only the bipyrazole (**4**) was observed (Scheme 1, **entries 2–3**). Changing the solvent to dimethoxyethane (DME) only the bipyrazole (**5**) was observed (Scheme 1, **entry 4**) [19].

In addition to the direct formation of pyrano [4,3-*c*]pyrazole **(3)**, there is another option for the ring closure in a two-step process. First, DHA (**1**) reacts with one equivalent of aryl-; or alkylhydrazine leading to corresponding hydrazone (**6**) [19–23] that can be converted to both pyranopyrazoles **3**,**4** and also to bipyrazole **5** (Scheme 2). Adding HCl and using DME at room temperature led to the pyrano [4,3-*c*]pyrazole (**3,** R = CH_3) (Scheme 2, **entry 1**) [19]. Reaction with aryl-hydrazines at higher temperatures, however, yielded the mixture of **3** and **5** (R = 4-Cl-C_6H_5) with poor yields (18% and 17% in order) (Scheme 2, **entry 2**) [19]. Using catalytic amount of *para*-toluenesulfonic acid (*p*TSA) in xylene led to mixture of two pyranopyrazoles (**3,4;** R = Ph) with mediocre production (Scheme 2, **entry 3**) [19], but using 1 equivalent in toluene produced exclusively pyrano [4,3-*c*]pyrazole (**3**) with acceptable yields (67%, R = Ph) (Scheme 2, **entry 4**) [22]. Using acetic acid,

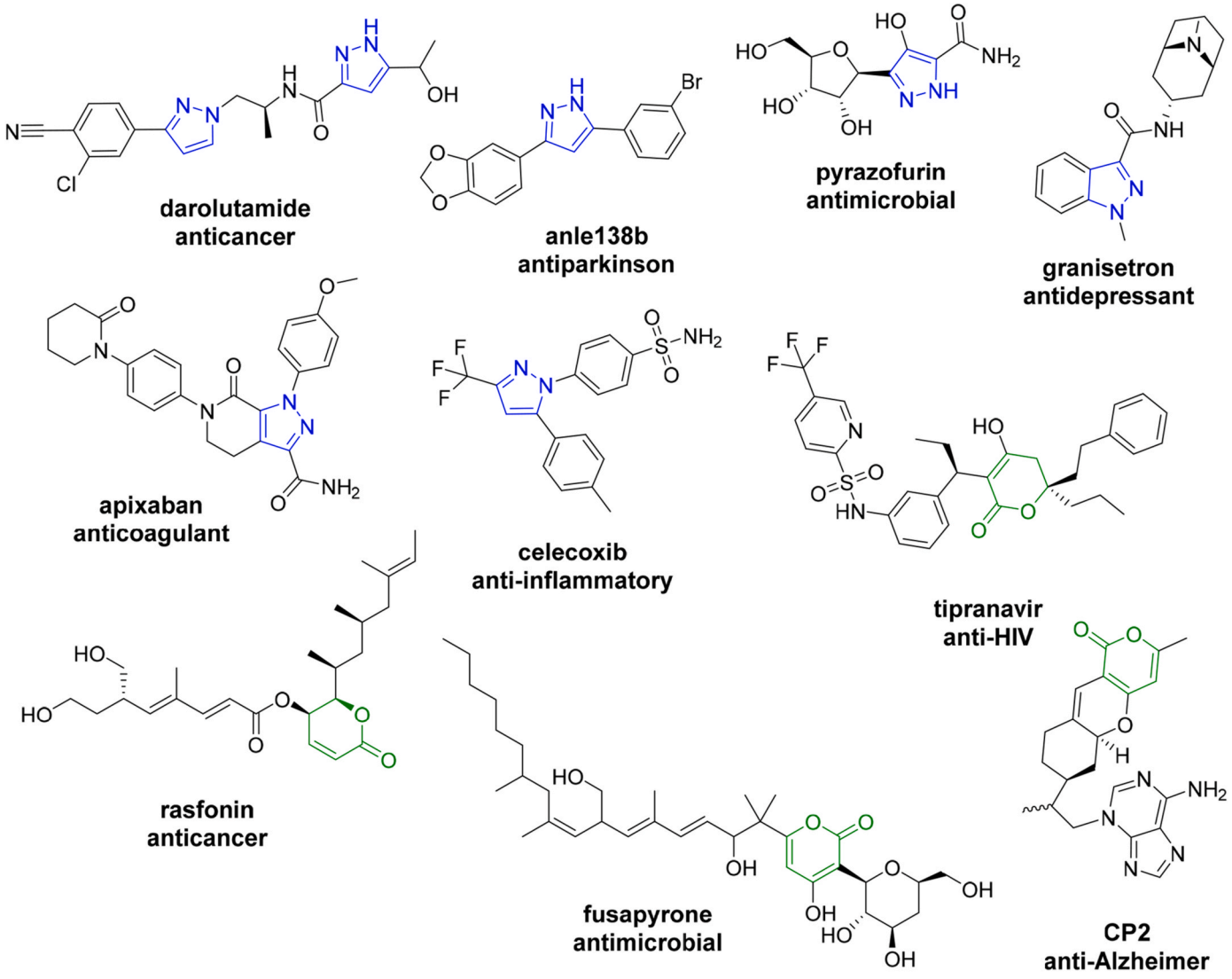
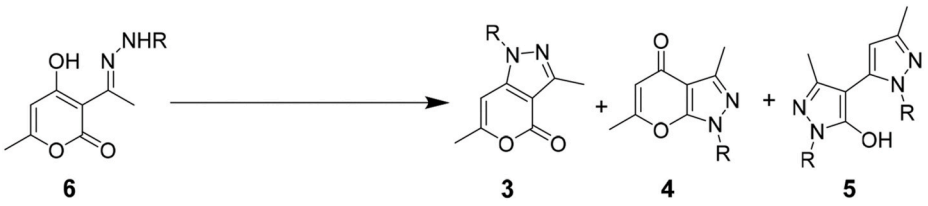


Fig. 1. Bioactive compounds containing pyrazole (blue) and pyrone (green) rings.

				R	
1.	EtOH, Δ, 3-4 h	70-79%	—	aromatic (3)	[17]
2.	acetic acid, 6h, Δ	—	74%	2-imino-2*H*-chromene-3-carbonyl	[18]
3.	ethanol, TEA, 12 h, Δ	—	82%	3-methyl-1*H*-pyrazolyl	[18]
4.	DME, rt or Δ, 40-91 h	—	33-38%	aliphatic (2)	[19]

Scheme 1. Previous reactions of DHA (**1**) and hydrazines (**2**). Number of reported derivatives in parentheses.



					R	
1.	HCl, DME, rt, 23 h	73 %	—	—	aliphatic (1)	[19]
2.	$RNHNH_2$, HCl, DME, 49 h, Δ	18 %	—	17 %	aromatic (1)	[19]
3.	*p*TSA, xylene, 12 h, Δ	33%	30%	—	aromatic (1)	[19]
4.	*p*TSA, toluene, 6 h, Δ	43-64 %	—	—	aromatic (7)	[22]
5.	1.) acetic acid, 1-2 h, Δ 2.) H_2SO_4,acetic acid, Δ	—	70-85%	—	aromatic (3)	[20;23-26]

Scheme 2. Previous reactions starting from DHA hydrazone (**6**). Number of reported derivatives in parentheses.

and after that sulfuric acid in two steps the reaction provided pyrano [2,3-*c*]pyrazole-4(1*H*)-one (**4**) selectively with good yields (70%; 74%, R = Ph) [20,23–26].

Deeper analysis of the contradictory results can be traced back to the limitations of the ^{1}H NMR and ^{13}C NMR measurements [17,24–26]. Ogawa et al. and Colotta et al. proposed their structures using only ^{1}H NMR and IR [22,23]. However, due to the signals observed at very similar chemical shifts, 1D NMR measurements are typically not sufficient for structure elucidation of the different ring variations, but 2D NMR techniques are required. Therefore, more recently products were characterised with HMBC [18] or ^{1}H{^{1}H} NOE [19] measurements. For a more detailed analysis, see supporting discussion (Supplementary Information and Fig. S1).

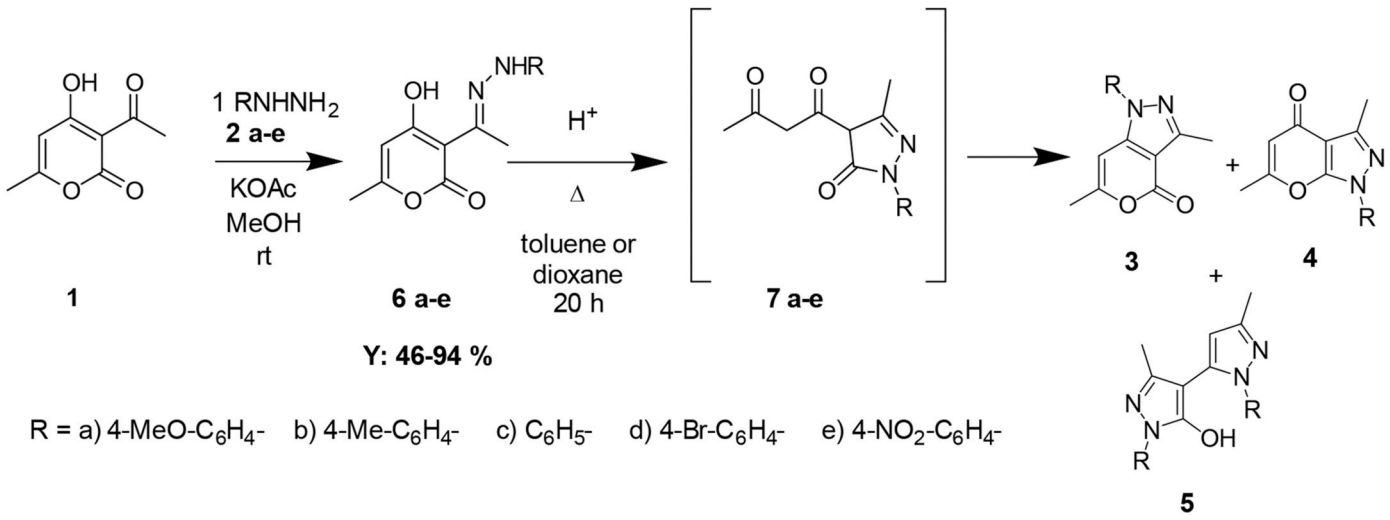
In this work, we attempted to investigate the effect of reaction conditions and reactants to the distribution of pyrano [4,3-*c*]pyrazole-4(1*H*)-one (**3**), pyrano [2,3-*c*]pyrazole-4(1*H*)-one (**4**) and 1′*H*,2*H*-[3,4′-bipyrazole]-5′-ol (**5**) products in the reaction of dehydroacetic acid and phenylhydrazines. Having the optimized conditions for the preparation of both pyranopyrazoles we explored the chemical space of these scaffolds by enumerating a virtual library and testing a range of building blocks for efficient sampling. We believe that the improved synthesis methods and their wide application domain might facilitate using pyranopyrazoles in future medicinal chemistry programs.

2. Results and discussion

Investigating the effect of reaction conditions on the product distribution we selected two solvents, two acidic additives and five differently substituted phenylhydrazines. One of the solvents was the aromatic and hydrophobic toluene with a planar structure and high boiling point of 110 °C. The other solvent was dioxane, a more hydrophilic non-aromatic and non-planar heterocycle with a slightly lower boiling point (101 °C). Tested acidic additives included 4-toluenesulfonic acid monohydrate (*p*TSA, b.p. 261 °C, $pK_a = -2.8$, low water content), 1 M hydrochloric acid (HCl, b.p. ~100 °C, $pK_a = -7$, high water content). Reactions were conducted using four types of aromatic hydrazines such as 4-methoxyphenylhydrazine (**2a**, $pK_a = 5.5$), 4-methylphenylhydrazine (**2b**, $pK_a = 5.4$), phenylhydrazine (**2c**, $pK_a = 5.2$), 4-bromophenylhydrazine (**2d**, $pK_a = 4.9$) and 4-nitrophenylhydrazine (**2e**, $pK_a = 3.8$) to investigate how the substituents influence the reactivity.

As expected, we observed three different products such as pyrano [4,3-*c*]pyrazole-4(1*H*)-one (**3**), pyrano [2,3-*c*]pyrazole-4(1*H*)-one (**4**) and bipyrazole (**5**) next to the starting dehydroacetic acid (**1**) and a diketone (**7**) intermediate (Scheme 3). The reactions were monitored by HPLC-MS and distribution of the products were calculated by the intensity of selected ion chromatogram.

First, we used one or two equivalents of *p*TSA as additive in toluene and dioxane. The observed product distribution was virtually independent to solvent or acid equivalent, but the substituent of the reactant affected the formation of different products (Fig. 2A). In case of **2a-**



Scheme 3. General scheme for the synthesis of pyranopyrazoles and bipyrazoles by the transformation of dehydroacetic acid. The reactions were performed in 20 mg scale in 2 mL solvent.

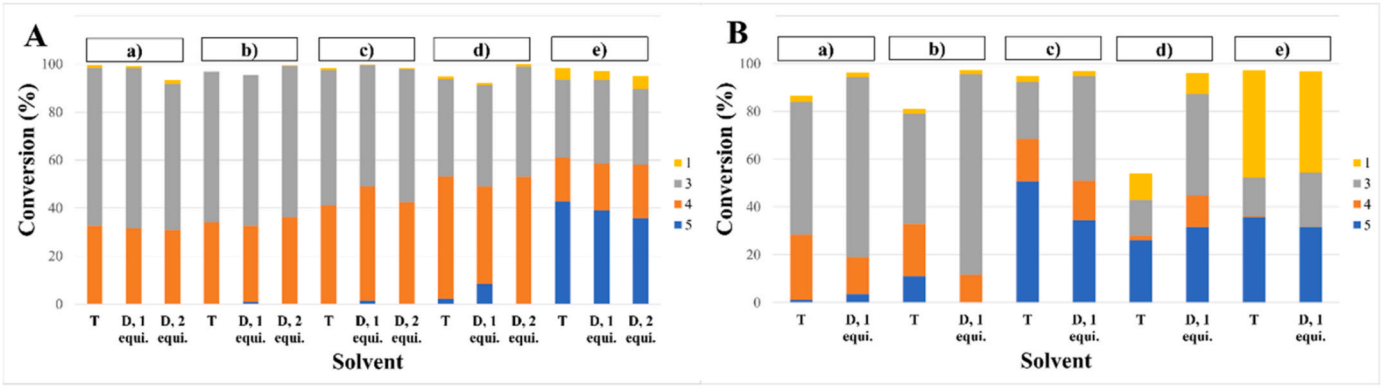


Fig. 2. Conversion and product distribution of the experiments with A) *p*TSA, B) HCl as a function of solvent, acid content and hydrazine.

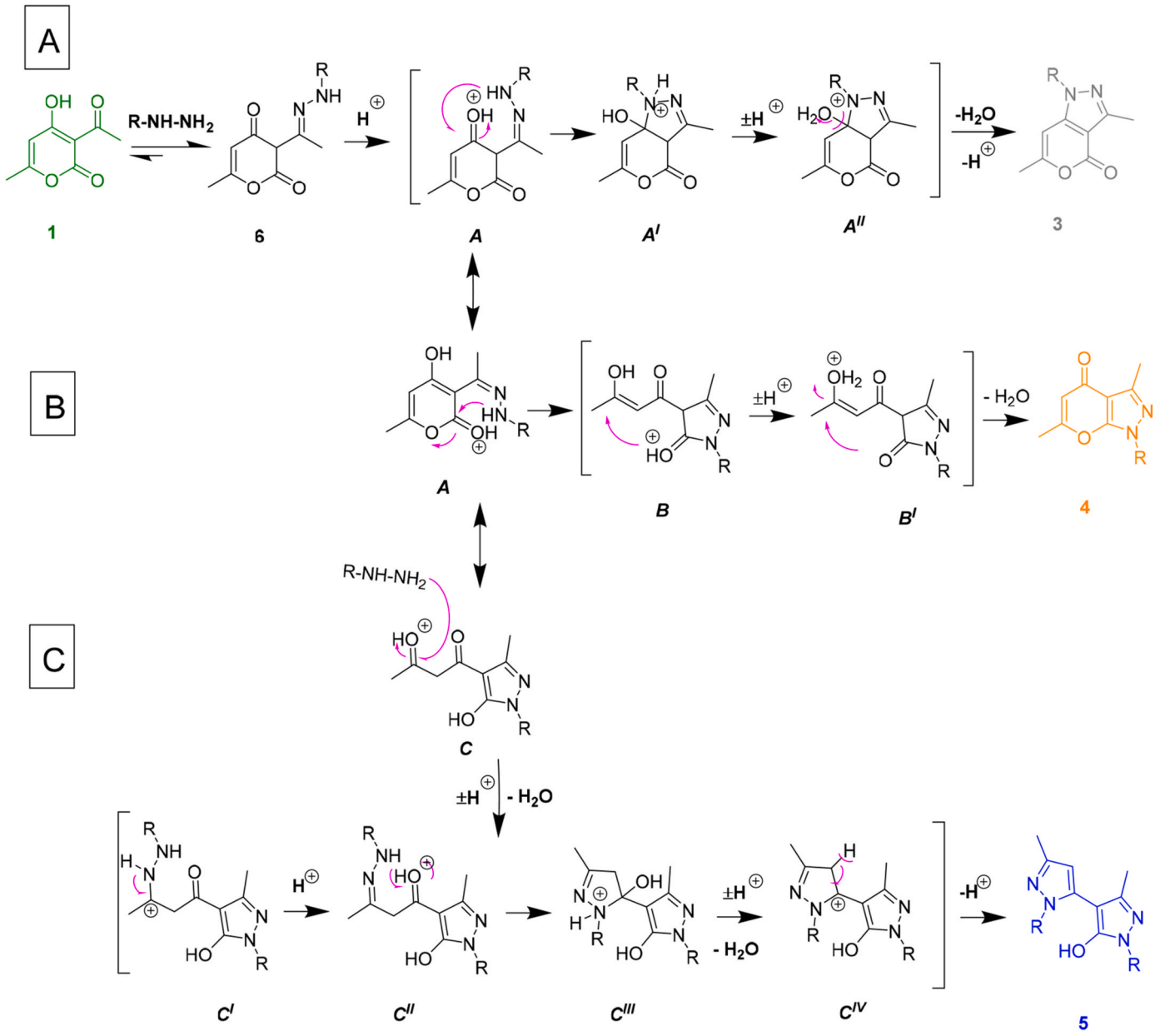
d hydrazines, products **3** and **4** were formed in an average of 40-67% and 31-53%, respectively. With the increase of electron withdrawal effect, heterocycle **4** became somewhat more dominant (Fig. 2A/a-d). In the case of the strongly electron withdrawing nitro substituent (**2e**) next to **3** and **4** (34% and 20% in average, respectively) bipyrazole **5** was formed as the main product (39% in average, Fig. 2A/e). These results suggest that in case of an organic acidic additive with low water content mostly the electronic effect of the phenyl substituent determines the distribution of the formed heterocycles.

Next, we used hydrochloric acid that is a stronger acid and contains a large amount of water. In this case only the electron donating **2a,b** hydrazines led to pyranopyrazoles, preferring **3** over **4** (56/46%:27/22% in toluene and 76/84%:15/12% in dioxane). Electron withdrawing substituents decreased the conversion as indicated by the unreacted dehydroacetic acid (**1**). A mixture of **3c,d**, **4c,d** and **5c,d** was observed for **2c** and **2d** (15-44%; 2-18%; 26-51% in order). Nitrophenylhydrazine (**2e**) led mostly to bipyrazole **5e** (32-36%) together with DHA (42-46%), which can be explained by the limited stability of hydrazone **(6e)** under these conditions (Fig. 2B/e). In summary, using HCl with stronger EWG groups results in the formation of bipyrazole (**5**) along with compound **3**.

Reactions carried out in dioxane proceeded with good conversion (85-100 %). Using *p*TSA the formation of pyranopyrazoles is preferred and the electron withdrawal influences the distribution between **3** (EDG) and **4** (EWG). By increasing the acid strength and electron withdrawing substituent effects, we experienced the increased formation of bipyrazoles (**5**). In the most acidic medium, compound **4** becomes the minor product, and pyranopyrazole **3** can be synthesized with a higher selectivity. In the case of the strongest electron withdrawing substituent and acidity, a larger amount (40-50%) of DHA (**1**) appears, which can be explained by the hydrolysis of hydrazone **(5)** (Fig. 2A/e; B/e).

According to the proposed mechanism (Scheme 4) pyrano [4,3-*c*] pyrazole-4(1*H*)-one **(3)** is formed when the hydrazone NH attacks the carbon of the α,β-unsaturated carbonyl group, followed by a cyclization and a water release (Scheme 4A). For the other two products, the hydrazone NH attacks the lactone carbonyl, at which point the ring opens to form the pyrazolone/hydroxypyrazole (**B/C**). The reaction can then proceed in two ways, either in an intramolecular cyclization or a second reaction with a hydrazine present. In the first case a proton shift is followed by the reaction between the oxygen of the pyrazolone and the protonated enol and a subsequent water release leads to the formation of the new lactone ring (Scheme 4B). In the second case, a reaction of the diketone with another hydrazine gives the bipyrazole (Scheme 4C).

According to the proposed mechanism, acid additive ensures the proper protonation of the carbonyl groups in cyclizations and enhances water elimination at the final step. In the case of *p*TSA and **a-d** hydrazones pathways **A** and **B** proceed more rapidly. Pathway **A** might be sterically preferred, while in pathway **B** for hydrazines **a-d** there is no -M effect (mesomeric effect) that softens the nucleophilicity of the oxygen reacting more readily with the enol carbon to form heterocycle **4**.



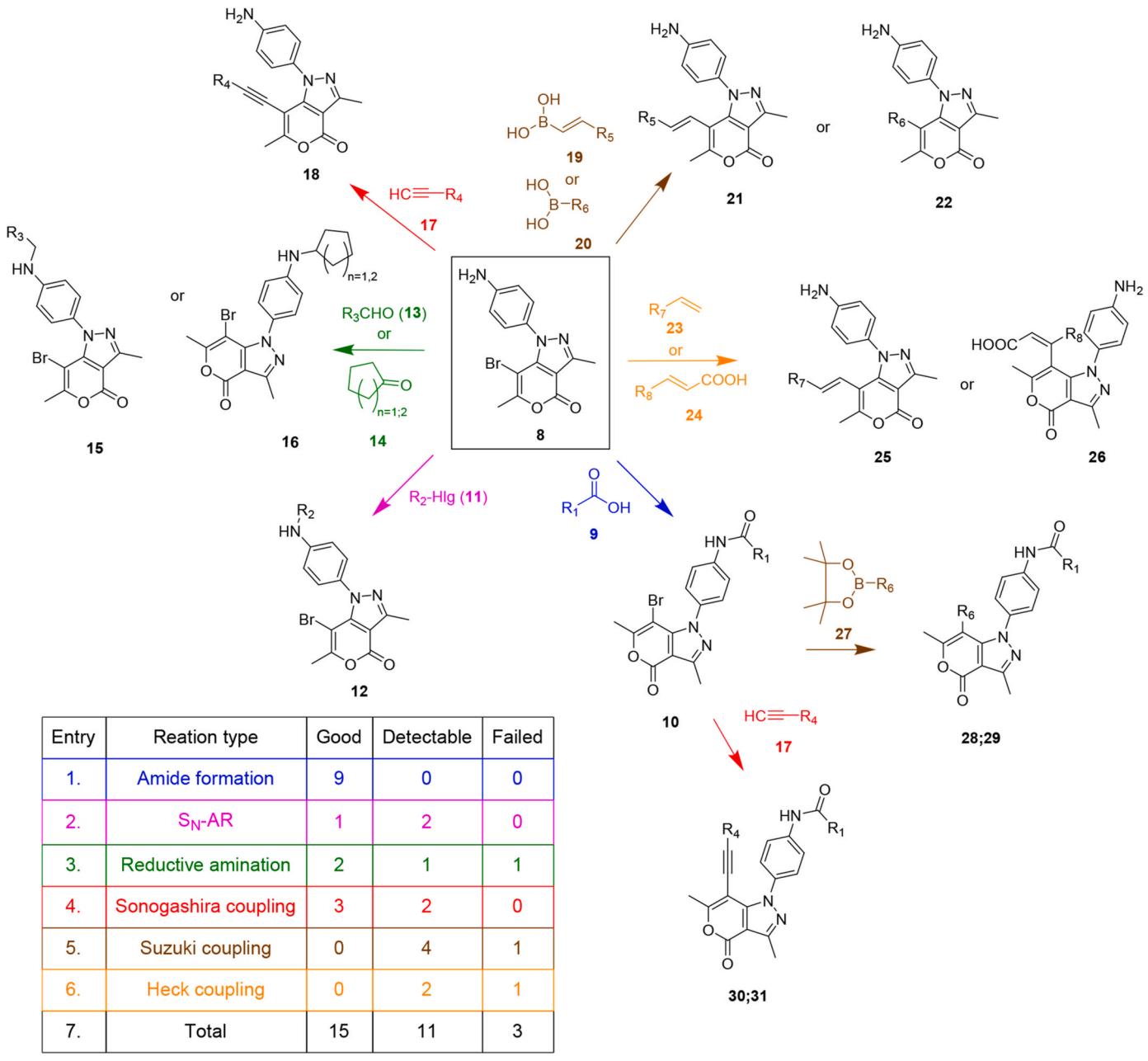
Scheme 4. Proposed mechanism for the formation of the pyranopyrazole and bipyrazole structures.

However, in the case of the nitro derivative **e**, the reactivity of intermediate **B** is reduced due to the -M effect of the nitro group, thus oxygen becomes a harder nucleophile. The aromatization of the hydroxypyrazole ring is also stabilizing and the protonated ketone is open for the addition of the second hydrazine reactant leading to the preferred bipyrazole **(5)** product (Scheme 4C).

2.1. *Test reactions for utilization of pyranopyrazoles as building blocks*

One of the most powerful technologies to expand the chemical space around a particular scaffold is enumerating and sampling a virtual library [27–31]. To achieve this goal we brominated and then reduced compound **3e** to obtain **8.** This compound has two different groups for further functionalization that open new pathways for expanding the related chemical space. First, we generated a virtual chemical library using Mcule's enumeration algorithm ARCHIE [30], using 6 reaction types frequently used by medicinal and synthetic chemistry due to their robustness [32–34]. Next, we performed overall 29 test reactions including acylation, S_NAr-functionalization, reductive amination, Suzuki-, Heck- and Sonogashira couplings all followed by LC-MS. It should be noted that the these reactions were not optimized, but rather general conditions were tested [30,35–42]. This approach is typically used by vendors trying at most 2-3 reaction conditions for one example without deeper optimization [30]. During the development of virtual molecules for early-stage drug discovery, price and lead time are crucial factors.

The summary of these results is shown in Scheme 5 and Table S1. All amide formations showed good conversion (Scheme 5, **entry 1**; Table S1, **entries 1–9**). Similar good conversions were detected for the S_NAr reactions (Scheme 5, **entry 2**; Table S1, **entries 10–12**) and reductive aminations (Scheme 5, **entry 3**; Table S1, **entries 13–16**) that worked with 43% success rate. In the case of C-C couplings, however, we observed that the reaction is more sensible to steric effects. Sonogashira coupling with acetylenes with 5-membered aromatic substituents performed better than those with larger 6-membered substituents (Scheme 5, **entry 4**; Table S1, **entries 17–19, 28–29**). Suzuki coupling (Scheme



Entry	Reation type	Good	Detectable	Failed
1.	Amide formation	9	0	0
2.	S_N-AR	1	2	0
3.	Reductive amination	2	1	1
4.	Sonogashira coupling	3	2	0
5.	Suzuki coupling	0	4	1
6.	Heck coupling	0	2	1
7.	Total	15	11	3

Scheme 5. Summary of the test reactions analysed by LC-MS.

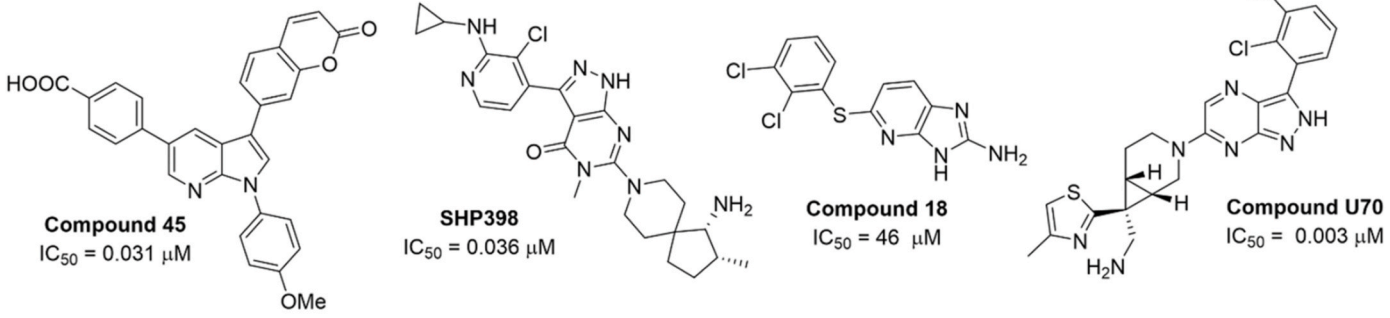
5, **entry 5**; Table S1, **entries 20–22, 26–27**) with vinyl boronic acid (**18**) show better reactivity than with aryl boronic acids (**19**) due to the distance between the lactone ring and the aryl group. When it comes to the Heck coupling (Scheme 5, **entry 6**; Table S1, **entries 23–25**) the vinyl derivative showed the highest conversion, while the two acrylic acids displayed reduced reactivity presumably due to steric effects. We performed four 2-step syntheses to reach more complex molecules starting from **10h** and **10i** (Table S1, **entries 26–29**). Based on these reactions the brominated amine (**8**) can be modified through both of its functional groups, starting with an acylation and followed by cross-couplings. During these first screenings there was no room for deep exploration of reaction conditions for each synthesis, so reactions that do not show at least a minimum progress might be abandoned at the early stage and be replaced with other molecules in further studies. These investigations aimed to demonstrate the usefulness of the building blocks to synthesize novel structures for screening purposes or to use DEL approaches [43] or fragment-based discovery [44].

2.2. *Biology*

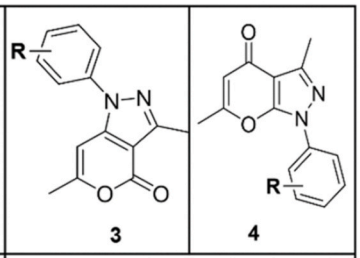
Demonstrating the biological relevance of the pyranopyrazole scaffold we tested our molecules against a challenging oncology target, SHP2 phosphatase that showed affinity towards bicyclic nitrogen heterocycles at both its orthosteric and allosteric sites (Fig. 3A)[45–48]. SHP2 is a member of a human protein phosphatases (PTPs) encoded by the PTPN11 proto-oncogene [49]. This enzyme controls the activation of several intracellular signalling pathways such as receptor tyrosine kinase, MAPK, JAK-STAT, PI3K-Akt, PD-1-PD-L1 and mTOR [50]. Mutations and/or overexpression of SHP2 have been associated with genetic developmental diseases and cancers [51].

We used our established *in vitro* biochemical assay in that SHP2 is allosterically activated upon binding of *bis*-tyrosyl-phosphorylated peptides to its Src Homology 2 (SH2) domains. This activation step results in the release of SHP2's auto-inhibitory interface, thereby activating the PTP domain and enabling substrate recognition and catalytic

A



B



Cmp.	R	inhibition in 100 μM (%)	
a	4-MeO	**80%**	7%
b	4-Me	2%	9%
c	H	not active	not active
d	4-Br	not active	not active
e	4-NO_2	4%	12%
f	4-NH_2	6%	not active
g	4-Cl	not active	not active
h	4-F	**72%**	18%
j	3-Me	not active	not active
k	3-MeO	3%	not active
l	3-NO_2	**74%**	37%
m	3-NH_2	8%	6%
n	2,3-diCl	not active	14 %

C

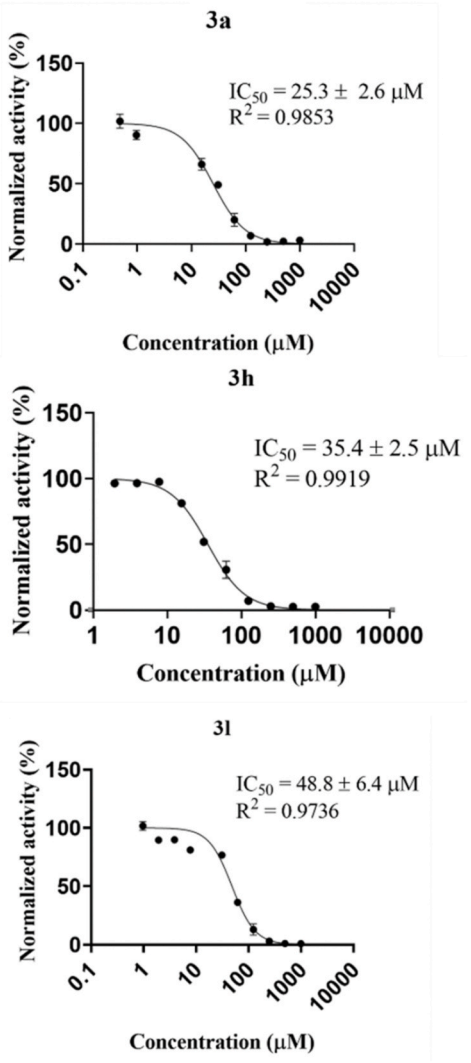


Fig. 3. (A) SHP2 inhibitors. (B) Inhibition of SHP2 by compounds **3a-n** and **4a-n** measured by *in vitro* biochemical assay. (C) IC_{50} curves of compounds **3a**, **3h** and **3l**.

activity. Three compounds (**3a,h,l**) showed >50% inhibition at 100 μM (Fig. 3B). The IC_{50} curves for these hits were determined and IC_{50}s were between 25 and 49 μM that is acceptable for a starting point coming from a non-rationally chosen set of heterocycles (Fig. 3C).

We aimed to identify the potential binding site and from the orthosteric and allosteric sites the tunnel site seemed to be the most promising considering the docking poses and docking scores generated by computational modelling (Table S2). We then measured compounds on the isolated catalytic domain and found no activity (data not shown), suggesting allosteric binding. In Fig. 4A the X-ray crystallographic analysis of Compound U70 is shown (PDB: 8CBH) [48]. The ligand forms hydrogen-bonds with Thr108, Glu110, Phe113 and Glu250 residues, and there is an interaction with Thr219 through a water molecule. Finally, there is a π–cation interaction between the dichlorophenyl ring and Arg111. We docked our active molecules using this structure (PDB: 8CBH) and based on the docking poses, we presume that compound **3a** forms a hydrogen bond through the pyrano carbonyl oxygen with the Thr218 residue, and the pyrazole ring can form an aromatic interaction with His114 (Fig. 4B). On the other hand, by the other two compounds (**3h, 3l**) we obtained a rotated pose compared to **3a**, and hydrogen bond

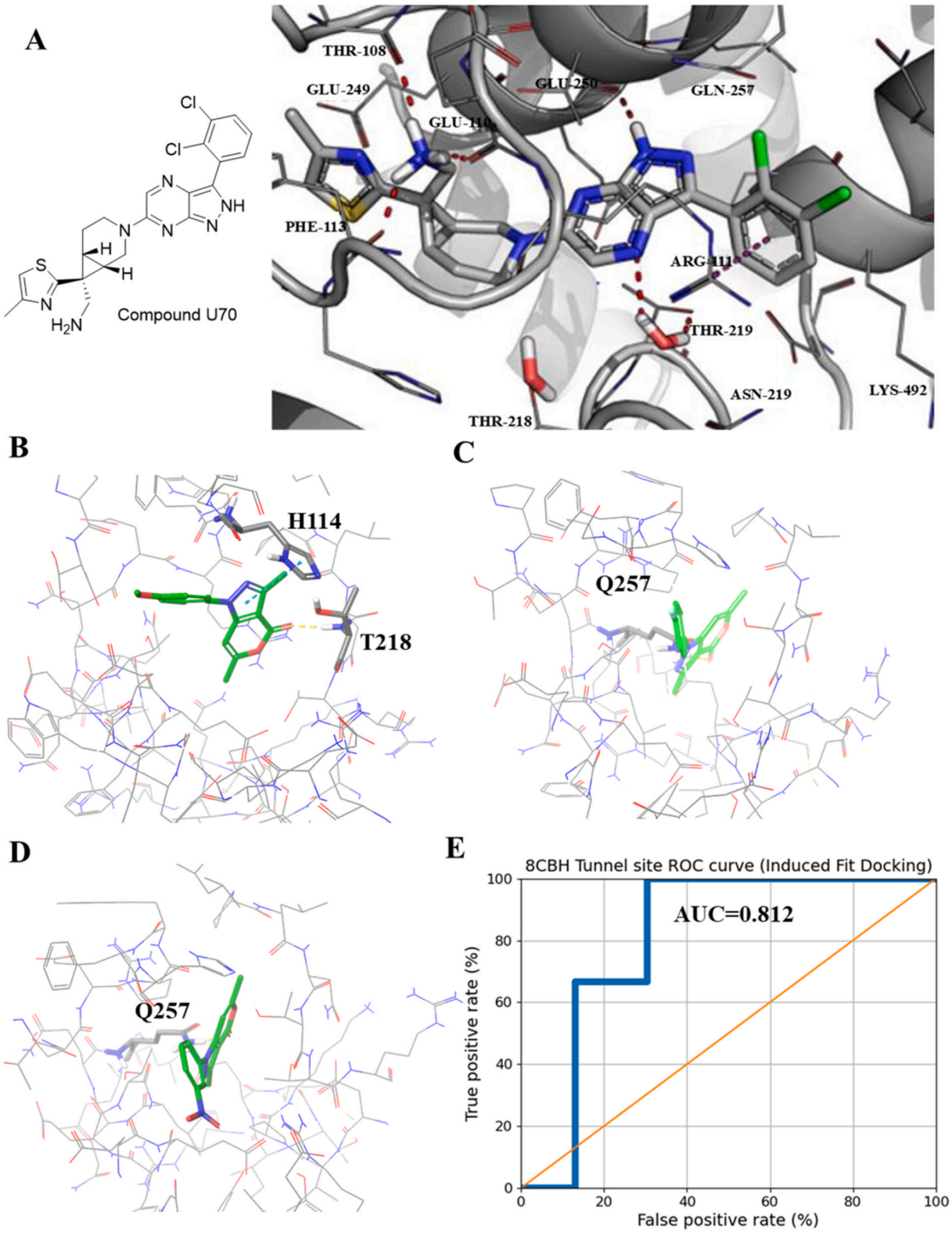


Fig. 4. (A) Binding mode of Compound U70 in the tunnel allosteric site of SHP2 (PDB entry: 8CBH) [48]. (B-D) Docking of compounds **3a**, **3h** and **3l** to the tunnel allosteric site of SHP2, respectively. Yellow dashed line indicates hydrogen bond interaction, blue dashed line indicates aromatic interaction. (E) ROC curve fitting for the 3 active substances.

is presumed with Gln257 through the pyrano carbonyl oxygen (Fig. 4C and D). This difference in the binding poses might explain their different activity. In addition, comparing the active molecules with the inactives we found better docking scores for the active ones (Fig. 4E–Table S2).

3. Conclusions

Investigating the reaction of dehydroacetic acid with hydrazines we established how reaction conditions influence product distribution.

Targeting the l-aryl-3,6-dimethyl-4-oxo-pyrano [4,3-*c*]pyrazole-4(1*H*)-one (**3**) or l-aryl-3,6-dimethyl-4-oxo-pyrano [2,3-*c*]pyrazole-4(1*H*)-one (**4**) heterocycles *para*-toluenesulfonic acid is suggested as the preferable acidic additive. With the increase of electron withdrawing effect of the hydrazine substituents, product **4** becomes more favoured. Significant formation of bipyrazoles (**5**) should be anticipated when strong electron-withdrawing groups are present. Changing the acid additive to aqueous HCl and the hydrazine being more electron-donating, the formation of the other pyranopyrazole product (**3**) becomes more beneficial, but the proportion of bipyrazoles (**5**) is also increasing. Next, we designed a virtual library for pyranopyrazoles and tested the syntheses of the enumerated products using robust reactions and pyranopyrazoles as building block. Out of 29 reactions the desired product was detectable in LC-MS in 26 cases without any optimization, indicating that the building block could be useful for extending the chemical space of these heterocycles. Finally, testing compounds with **3** and **4** type cores against SHP2 we found three active molecules acting in the micromolar range, which can be considered as starting point for medicinal chemistry programs.

CRediT authorship contribution statement

Ágnes Hornyánszky: Writing – original draft, Visualization, Investigation. **Péter Kovács:** Supervision, Conceptualization. **Helga Bereczki:** Investigation. **Noémi Csorba:** Investigation. **Dávid Havasi:** Writing – original draft, Investigation. **Gábor Turczel:** Investigation. **Tibor Viktor Szalai:** Formal analysis. **György Miklós Keserű:** Writing – review & editing, Supervision, Funding acquisition. **Péter Ábrányi-Balogh:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tchem.2026.100159.

Data availability

Data will be made available on request.

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