

Perspective

New Spiro[cycloalkane-pyridazinone] Derivatives with Favorable Fsp³ Character

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Abstract: The large originator pharmaceutical companies need more and more new compounds for their molecule banks, because high throughput screening (HTS) is still a widely used method to find new hits in the course of the lead discovery. In the design and synthesis of a new compound library, important points are in focus nowadays: Lipinski's rule of five (RO5); the high Fsp³ character; the use of bioisosteric heterocycles instead of aromatic rings. With said aim in mind, we have synthesized a small compound library of new spiro[cycloalkane-pyridazinones] with 36 members. The compounds with this new scaffold may be useful in various drug discovery projects.

Keywords: Friedel–Crafts reaction; Grignard reaction; Fsp³ character; pyridazinones; spiro[cycloalkane-pyridazinone]; hydrazine

1. Introduction

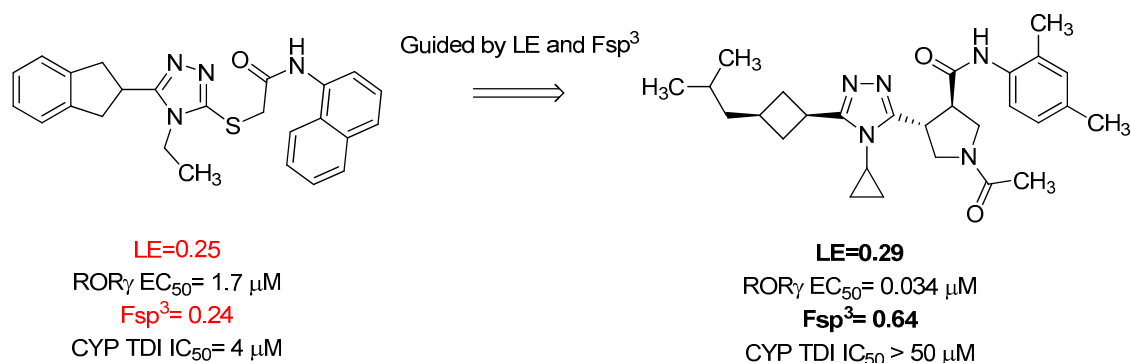
There are various methods used to find a hit that will later be a lead compound in the development of a new drug, a new chemical entity. Nowadays the most up-to-date methods are, e.g., computer aided drug design and the fragment-based techniques. High-throughput screening (HTS) [1,2] is a widely used method, which needs a large number of compounds. The large companies which are interested in the development of originator pharmaceutical products have their own molecule banks, with possible extensive compound libraries. In the building up of a compound library, the advantageous physicochemical parameters of the compounds, the so called ADME (absorption, distribution, metabolism, excretion) parameters, are very important aspects. Large companies do not allow one to put new compounds with disadvantageous parameters or with known toxicity into their molecule banks.

After the publication of Lipinski's "rule of five" (RO5) [3–5], more and more attention was paid to the physicochemical parameters of the drug candidate molecules. According to Lipinski's rules, it is advantageous from the points of view of solubility and permeability if the number of H-bond donors is less than 5, the number of H-bond acceptors is less 10, the calculated logP (P = octanol–water partition coefficient, clogP) is under 5, and the molecular mass is lower than 500. LogP provides valuable information about the lipophilic/hydrophobic property of the molecule which strongly influences the absorption of the substance, its interaction with the receptor, its metabolism, and its toxicity.

Later, other important properties were studied. Veber et al. [6] suggested that the polar surface area should be smaller than 140 Å² and the number of rotatable bonds should be ten or less in an ideal case. The fulfillment of these two criteria provides the opportunity for good oral bioavailability. Today these parameters are routinely studied to predict the drug candidates' pharmacokinetics and ADME profiles [3]. Over the past decade there has been an increasing practice of creating structurally more complex molecules which are closer to natural materials and provide an opportunity to produce new types of compounds.

Lovering et al. [7,8] defined the complexity with the saturation of molecules. Saturation allows the formation of molecules with more complex structures and the expansion of the structural versatility of the compounds without significant increases in molecular weight. It was also supposed that increasing Fsp^3 character may improve the physicochemical properties of the molecules which contribute to clinical success. Lovering and his coworkers [7,8] introduced the definition of the Fsp^3 character, which is an important parameter to characterize the drug-likeness. Fraction of sp^3 carbons means: $Fsp^3 = \text{number of carbons with } sp^3 \text{ hybridization} / \text{total number of carbon atoms}$. Thousands of compounds which reached a phase of drug research (research phase, Phase I–III, drugs) were selected from GVK BIO Biosciences' database and analyzed by their sp^3 character. From the data obtained, it was concluded that the average Fsp^3 character was 0.36 for research compounds and it increased to 0.47 for drugs. This growth trend was observed in all phases of drug research. The degree of saturation also affects the physical properties of the compounds. With increasing sp^3 character, the water solubility increases and the melting point decreases. This way, one is more likely to produce compounds which have favorable ADME parameters, which increases their chances of becoming clinical candidates [7,8].

M. Hansson et al. studied the relationship between molecular hit rates in HTS and molecular descriptors. They established that ClogP and Fsp^3 had the largest influences on the hit rate [9]. This inspired researchers to synthesize new compound with high Fsp^3 character. For example, after a HTS study, Hirata and coworkers [10] developed a new series of ROR γ inhibitors, which was guided by Fsp^3 character and ligand efficiency (LE). Both of them are important drug-likeness metrics. With a careful design, the authors could improve the metabolic stability and reduce the CYP inhibition of their orally efficacious ROR γ inhibitors (Scheme 1).



Scheme 1. Development of a new series of ROR γ inhibitors guided by LE and Fsp^3 .

M. H. Clausen et al. published another example for the synthesis of compounds with high Fsp^3 character [10,11]. They established a library of fluorinated Fsp^3 -rich fragments for ^{19}F -NMR based screening in fragment based drug discovery (FBDD), which is one of the most important methods of searching for a lead in drug discovery. The synthesized 115 fluorinated fragments gave valuable hits against four diverse protein targets in ^{19}F -NMR screening.

Normally, the 3D descriptors perform better in lead-compound searches than 2D descriptors, such as Fsp^3 or logP. D. C. Kombo et al. [12] showed the importance of the 2D and 3D molecular descriptors for clinical success. They studied the MDL Drug Data Report (MDDR) database; the compounds were monitored from the preclinical phase to the market. According their experience, these shape-based 3D molecular descriptors predicted the success or withdrawal from the market of a compound at preclinical or Phase I stage better than logD or Fsp^3 .

J. H. Nettles and coworkers [13] used 2D and 3D molecular descriptors for target fishing connecting the chemical and biological space. They compared the 2D and 3D molecular descriptors for prediction of the biological targets. This method was based on the similarity to reference molecules of the biologically active compounds in a chemical database with 46,000 compounds. They concluded that 2D molecular descriptors were more successful in target prediction, while the 3D molecular descriptors

seemed to be better in cases of singletons, which showed low structural similarity to other molecules in the database. It is worth combining both 2D and 3D descriptors.

Ritchie and coworkers [14] studied the role of the number of aromatic rings in the compound's developability. The effects of aromatic ring number on various developmental parameters were analyzed, such as water solubility, lipophilicity, serum albumin binding, CyP450 inhibition, and hERG inhibition. They concluded that the presence of fewer aromatic rings in an oral drug candidate is beneficial in regard of developability. In addition, the presence of more than three aromatic rings in a molecule correlates with poor prospects in the development, thereby reducing the chances of successful drug discovery. Further analyzes [15] have also shown that the replacement of an aromatic ring with a bioisoster heteroaromatic ring has a good effect on development. This can explain why the number of approved drugs with heteroaromatic rings is rising.

The expansion of the chemical space is another important point of view when building up a new compound library. In spite of the fact that spirocycles have been published for sixty years, this compound family remained at the periphery of drug discovery earlier [16]. Nowadays there are a few drugs on the market or under development [17–21]. The natural product Griseofulvin has antifungal activity [22]. The steroid derivative spironolactone is used for the treatment of fluid retention, edema, and symptoms of heart failure (Figure 1) [23]. Recently the FDA approved the calcitonin gene-related peptide receptor antagonist ubrogepant for the acute treatment of migraines [24]. The spiro moiety usually has high Fsp³ character and its advantage is that it makes possible greater three-dimensionality than the aromatic rings. Y-J. Zheng and C. M. Tice collected interesting examples wherein spirocyclic scaffolds were applied in drug discovery [25].

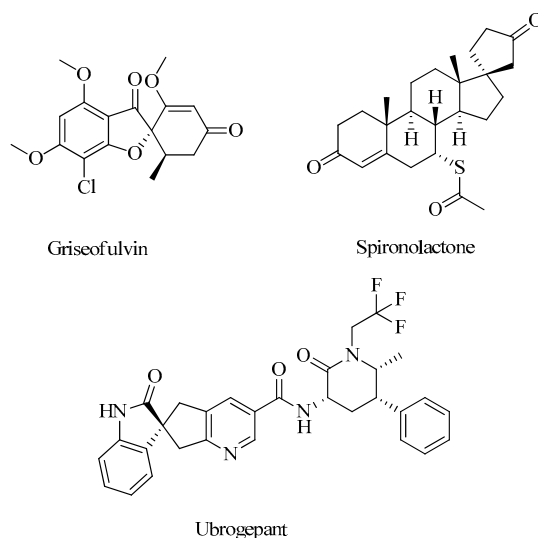


Figure 1. Drugs with spirocyclic scaffolds.

A further way to improve the physicochemical properties of the compounds is to replace the phenyl or pyridyl rings with bioisoster rings containing two nitrogens: pyridazine, pyrimidine, or pyrazine. This increases the drug-likeness of the molecules, and generally the ADME profile, log P values, solubility, and absorption are more favorable [26]. For example, pyridazin-3(2H)-one is a valuable structural moiety which can be a good starting point for drug research projects [27]. The pyridazine ring can be easily functionalized in various positions, making it an attractive synthetic building block for the preparation of new compounds [28]. Various structural modifications on the ring system containing the pyridazinone unit have resulted in compounds with favorable biological activity [29]. Over the past few decades, many papers and patents have been published on bioactive pyridazines and pyridazinones, which have been utilized in almost all therapeutic fields with various mechanisms of action [30,31]. For example, the antihypertensive hydralazine (Apresoline) is used to treat high blood pressure and heart failure [32]. The calcium sensitizer levosimendan is effective

in congestive heart failure [33]. The antihypertensive bemoradan is an inhibitor of cardiac muscle cyclic AMP phosphodiesterase (PDE), which explains its cardiotonic effect [34]. The monoamine oxidase inhibitor minaprine [35,36] has an antidepressant effect. The tricyclic pipofezine (Azafen or Azaphen) [37] acts as a serotonin reuptake inhibitor. It was launched as an antidepressant in the 1960s and it is still on the market today. Emorfazone [38], as a nonsteroidal anti-inflammatory agent, has analgesic effects. See Figure 2 for said examples.

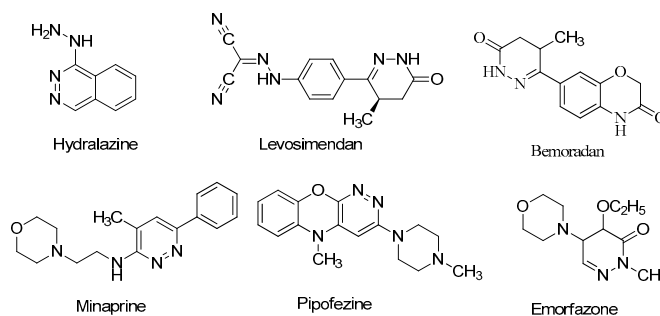


Figure 2. Antihypertensive, antidepressant, and anti-inflammatory pyridazinone derivatives.

Imazodan [39], Amipizone [40], Zardaverine [41], and Indolidan [42] are used in veterinary medicine. Pimobendan [43] belongs to a group of selective phosphodiesterase (PDE3) inhibitors used to treat heart problems of dogs (Figure 3).

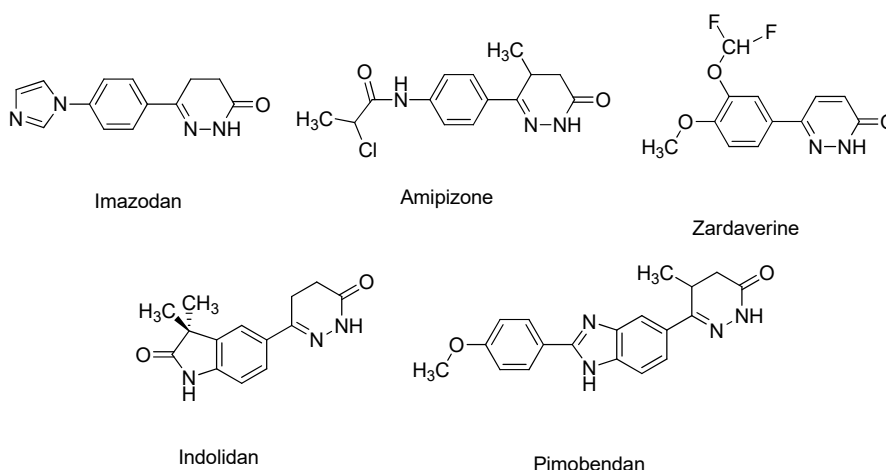


Figure 3. Pyridazinone derivatives in veterinary medicine.

The pyridazine-containing fused ring system may have valuable biological activity. Zopolrestat is used as an aldose reductase inhibitor to treat diabetic neuropathy and nephropathy [44]. The melanin concentrating hormone 1 (MCHC-1) antagonist thienopyridazinones [45] showed in vivo anorectic properties. The pyrazolo-pyrimidinopyridazinones exhibit potent and elective phosphodiesterase 5 (PDE5) inhibitory activity [46]. KK 505 is used as an anti-asthma agent [47] (Figure 4).

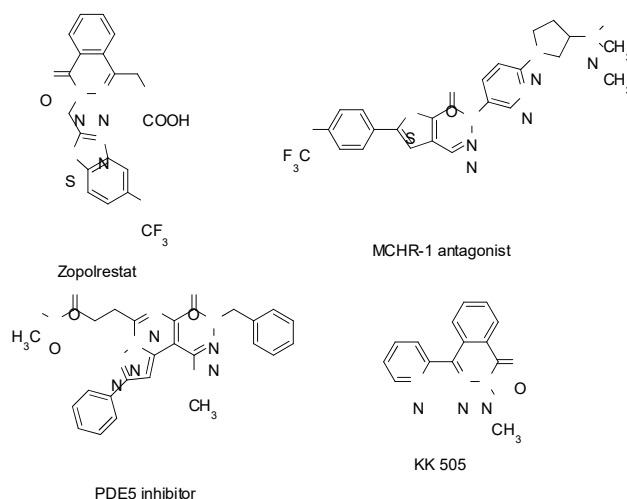


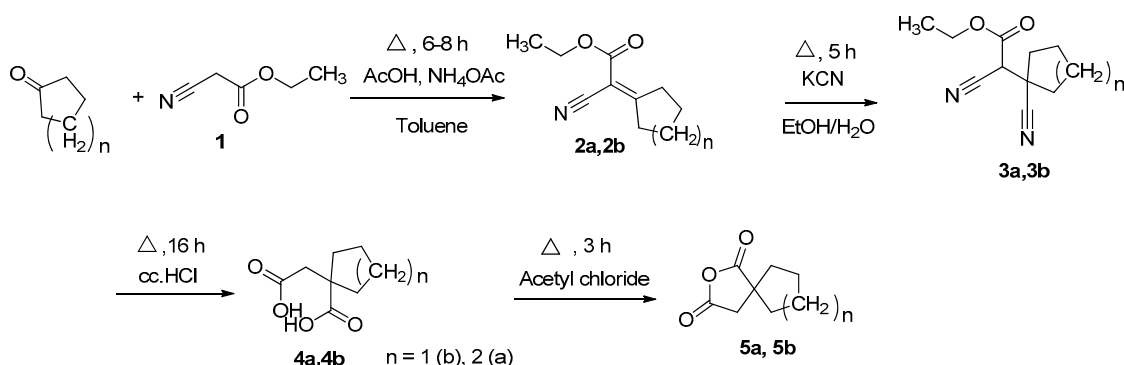
Figure 4. Biologically active pyridazinones.

2. Synthesis of Spiro[cycloalkane-pyridazinone] Derivatives

Taking into account the expected bioactivity of the pyridazine derivatives and their favorable physicochemical parameters, our attention turned to this family of compounds. Considering the advantages of compounds with high F_{sp^3} character, we have designed a compound library with a spiro[cycloalkane-pyridazinone] scaffold instead of the usual phenyl-pyridazinone derivatives.

2.1. Synthesis of the Starting Materials

The preparation of our starting materials 2-oxaspiro[4.5]decane-1,3-dione and 2-oxaspiro[4.4]nonane-1,3-dione was performed according to methods known in the literature, optimizing them [48,49]. In the first step, starting from cyclohexanone or cyclopentanone, we performed Knoevenagel condensation in the presence of ethyl 2-cyanoacetate (**1**) followed by the addition of a cyanide group. The nitrile groups were hydrolyzed with concentrated hydrochloric acid. The anhydride formation from the cycloalkyl dicarboxylic acids (**4a**, **4b**) was also examined with two reagents: acetic anhydride and acetyl chloride. The cyclization with acetyl chloride was clearly more favorable as the desired spirocyclic anhydrides formed at lower temperatures and with higher yields (**5a**, **5b**) (Scheme 2).



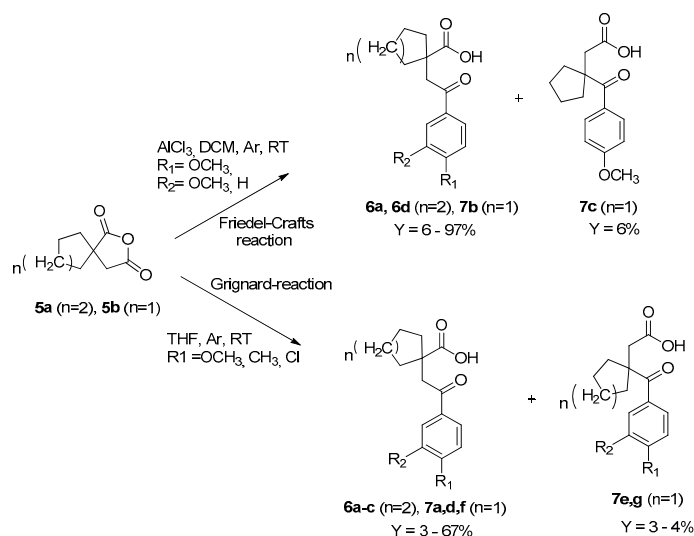
Scheme 2. Synthesis of starting materials.

2.2. Friedel–Crafts and Grignard Reactions

In course of the synthesis of our pyridazinone derivatives, we prepared first the isomeric γ -oxocarboxylic acids containing 1,1-disubstituted cycloalkanes from the starting compounds (**5a**, **5b**) and variously substituted benzene derivatives by Friedel–Crafts reaction (Scheme 4). This was done according to a patented process in which 2-oxaspiro[4.4]nonane-1,3-dione was reacted with (**5b**)

1,2-dimethoxybenzene in the presence of AlCl_3 [50]. In our work, eight new isomeric γ -oxocarboxylic acids containing 1,1-disubstituted cycloalkanes were prepared. Compounds **6b** and **6c** were obtained only in very low yields because the electrophilic aromatic substitution favors electron-rich groups. Furthermore, in the Friedel–Crafts reaction of compound **5b** with anisole, in addition to the main product **7b**, **7c**—a by-product with an isomeric structure—was also identified.

Another way to prepare isomeric γ -oxocarboxylic acids containing 1,1-disubstituted cycloalkanes is via the Grignard reaction [51]. This was used in cases where only low yields could be achieved in Friedel–Crafts reactions, for example, in cases with less active reagents, such as toluene and chlorobenzene. Grignard reactions were performed in tetrahydrofuran with *p*-tolyl magnesium bromide and (4-chlorophenyl) magnesium bromide, under inert conditions. For compounds **6b** and **6c** the yield was improved. Furthermore, for compounds **7a** and **7f**, molecules with isomeric structures (**7e** and **7g**) were also isolated and identified (Scheme 3) (Table 1).



Scheme 3. Friedel–Crafts and Grignard reaction.

Table 1. Fsp^3 values of γ -oxocarboxylic acids.

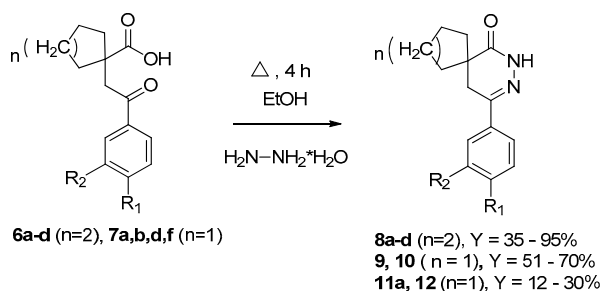
Starting Material	R ¹	R ²	Product	Fsp^3	LogP	CLogP
5a	OCH ₃	H	6a	0.50	2.91	3.4955
5a	CH ₃	H	6b	0.50	3.53	3.7746
5a	Cl	H	6c	0.46	3.60	4.0642
5a	OCH ₃	OCH ₃	6d	0.53	2.79	3.17319
5b	CH ₃	H	7a	0.47	3.11	3.2156
5b	OCH ₃	H	7b	0.47	2.50	2.9365
5b	OCH ₃	H	7c ¹	0.47	2.50	2.9365
5b	OCH ₃	OCH ₃	7d	0.50	2.37	2.61419
5b	CH ₃	H	7e ¹	0.47	3.11	3.2156
5b	Cl	H	7f	0.43	3.18	3.5052
5b	Cl	H	7g ¹	0.43	3.18	3.5052

¹ Isomeric structure.

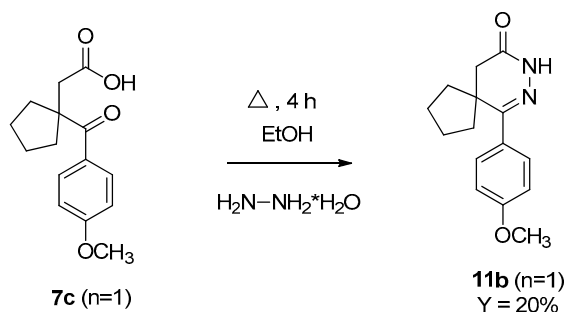
2.3. Formation of Pyridazinone Ring

Pyridazinones were formed from isomeric γ -oxocarboxylic acids containing 1,1-disubstituted cycloalkanes with hydrazine and hydrazine derivatives (methyl- and phenylhydrazine). We used the reaction conditions developed by Van der May et al. [51]. The pyridazinones (**8a–d**) were prepared in good yields. Pyridazinone derivatives (**9**) and (**10**) were also isolated in medium yields (Scheme 4).

In the case of compound **7b**, in addition to the expected structure (**11a**), a compound with an isomeric structure (**11b**) was also isolated and identified by 2D NMR (Scheme 5) (Table 2).



Scheme 4. Ring closure with hydrazine.



Scheme 5. Ring closure of the isomeric compound **7c**.

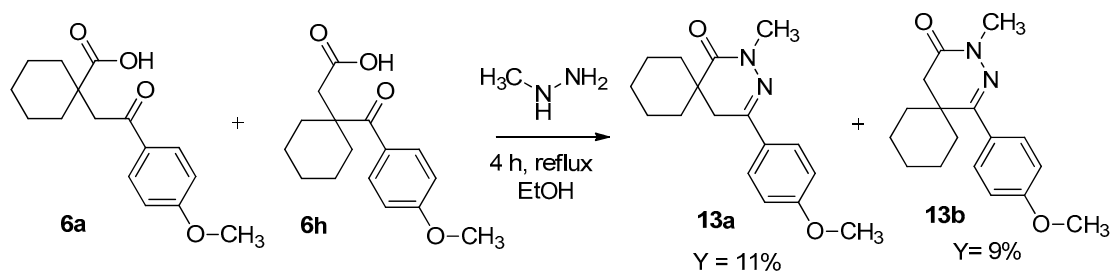
Table 2. Fsp³ values of pyridazinones.

Starting Material	R ¹	R ²	Product	Fsp ³	LogP	CLogP
6a	OCH ₃	H	8a	0.50	2.91	2.753
6b	CH ₃	H	8b	0.50	3.52	3.333
6c	Cl	H	8c	0.47	3.59	3.547
6d	OCH ₃	OCH ₃	8d	0.53	2.78	2.492
7a	CH ₃	H	9	0.46	3.10	2.774
7f	Cl	H	10	0.43	3.17	2.988
7b	OCH ₃	H	11a	0.46	2.49	2.194
			11b ¹	0.46	2.49	2.194
7c	OCH ₃	OCH ₃	12	0.50	2.36	1.933

¹ Isomeric structure.

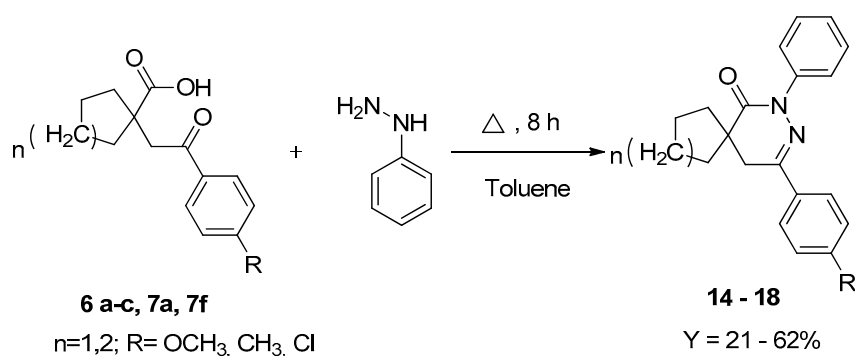
2.4. N-Substituted Pyridazinone Derivatives

N-substituted pyridazinone derivatives were formed with methyl- and phenyl hydrazine and in N-alkylation/aralkylation reactions. Reactions with methylhydrazine were performed under the above-mentioned conditions starting from the mixture of **6a** and **6h** [51] by boiling in ethanol. The crude product was purified by preparative thin layer chromatography. The pyridazinones (**13a** and isomeric **13b**) shown in Scheme 6 were isolated and identified.



Scheme 6. Ring closure with methyl hydrazine.

The *N*-phenyl derivatives were prepared first by boiling compounds **6a–c**, **7a,f** with phenylhydrazine in ethanol, but only very low yields were achieved. Changing the solvent to toluene improved the yields and *N*-phenyl derivatives (**14–18**) were isolated (Scheme 7).



Scheme 7. Ring closure with phenyl hydrazine.

N-methyl derivatives were also prepared by *N*-alkylation reactions [52]. By starting from the previously isolated pyridazinone derivatives (**8b**, **8c**, **9**, **10**) and alkylating them with methyl iodide in tetrahydrofuran in the presence of sodium hydride, the *N*-methylated compounds (**19–22**) were isolated in medium yields. In the preparation of *N*-benzylated derivatives we first chose the classical potassium carbonate method, but it did not produce the desired product, so we changed to cesium carbonate, which enabled us to isolate our desired *N*-benzylated pyridazinone derivatives in medium yields (**23–27**) (Scheme 8) (Table 3).

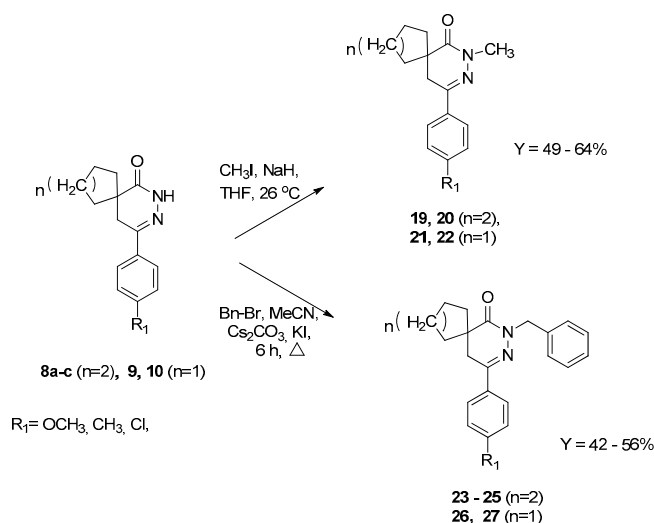
Scheme 8. *N*-methyl- and *N*-benzyl derivatives of pyridazinones.

Table 3. Fsp³ values of substituted pyridazinones.

Starting Material	R ¹	R ³	Product	Fsp ³	LogP	CLogP
6a			13a	0.53	3.14	2.845
6h	OCH ₃	CH ₃	13b ¹	0.53	3.14	2.845
6a	OCH ₃	Ph	14	0.36	4.81	4.744
6b	CH ₃	Ph	15	0.36	5.42	5.324
6c	Cl	Ph	16	0.33	5.49	5.538
7a	CH ₃	Ph	17	0.33	5.00	4.765
7f	Cl	Ph	18	0.30	5.07	4.979
8b	CH ₃	CH ₃	19	0.53	3.76	3.425
8c	Cl	CH ₃	20	0.47	3.83	3.639
9	CH ₃	CH ₃	21	0.50	3.34	2.866
10	Cl	CH ₃	22	0.44	3.41	3.080
8a	OCH ₃	Bn	23	0.39	4.87	5.077
8b	CH ₃	Bn	24	0.39	5.49	5.657
8c	Cl	Bn	25	0.36	5.56	5.871
9	CH ₃	Bn	26	0.36	5.07	5.098
10	Cl	Bn	27	0.33	5.14	5.312

¹ Isomeric structure.

3. Conclusions

In summary, our starting materials 2-oxaspiro[4.5]decane-1,3-dione (**5a**) and 2-oxaspiro[4.4]nonane-1,3-dione (**5b**) were prepared and optimized using methods known in the literature [48,49]. From these 1,3-diones, eleven new isomeric γ -oxocarboxylic acids containing 1,1-disubstituted cycloalkanes were prepared by Friedel–Crafts and Grignard reactions. These were reacted with various hydrazine derivatives, and with further *N*-alkyl/aralkylation reactions we isolated 25 new pyridazinone derivatives. The Fsp³ values of our compounds showed good correlations with logP values; e.g., the logP values of compounds with high Fsp³ character (**8a–d**, **9**, **10**, **11a–b**, **12**) were between 2.36 and 3.59, under 5 (see Table 2). The situation was similar for compounds **13a,b–27** (Table 3). The introduction of a further aromatic ring into compounds **14–18** and **23–27** decreased the Fsp³ character and increased the logP values to over 4.8. A smaller molecule library was created with 36 new compounds with high Fsp³ character, which could be a good starting point for drug research projects [53,54].

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