PYRIDAZINONE AS VERSATILE SCAFFOLD IN DRUG DISCOVERY: VIEW ON CURRENT DEVELOPMENT

Boryana Borisova[1,2], Marie Laronze-Cochard[1], Stéphane Gérard[1]

[1]*Université de Reims Champagne-Ardenne*
Institut de Chimie Moléculaire de Reims (ICMR) - UMR CNRS 7312
UFR de Pharmacie, 51 rue Cognacq-Jay -51100
Reims, marie.cochard@univ-reims.fr (M.C.); stephane.gerard@univ-reims.fr (S.G.)
[2]*Biotechnology Department, University of Chemical Technology and Metallurgy,*
8 Kliment Ohridski blvd., 1797 Sofia, borisova@uctm.edu (B.B.)

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ABSTRACT

In modern medicinal chemistry, the pyridazinone core has emerged as a „versatile“ and privileged scaffold for the design of new therapeutic agents. Over the past decades, numerous pyridazinone derivatives have exhibited significant biological activities across diverse therapeutic areas including antiviral, antimicrobial, cardiovascular, anti-inflammatory, anticancer, and central nervous system disorders. This review discusses the structural diversity, structure-activity relationships (SAR), and pharmacological relevance of pyridazinone-based molecules. Furthermore, it highlights recent advances in hybrid drug design, where the pyridazinone moiety is combined with another pharmacophore to produce synergistic effect that enhance the biological activities of both components towards more than one target. Such hybridization strategy show the potential of pyridazinone scaffold as valuable templates for the development of multifunctional therapeutic agents.

Keywords: pyridazinone, biological activity, pharmaceutical scaffold, drug discovery.

INTRODUCTION

Pyridazine-based scaffolds have been identified as “versatile” in medicinal chemistry (Fig. 1) due to its highly functionalized structure which possess variety of physiological effects and activities against a range of biological targets [1, 2]. Many drug discovery researches leverage the pyridazine structure **1** due to its effectiveness in developing therapeutics with various activities as antihistamine (azelastine **2**) [3], antihypertensive (hydralazine **3**) [4], anticancer (taladegib **4**) [5], etc.

The resonance structures of pyridazine **5** involve electron delocalization, with alternating positions of double bonds (Fig. 2) [1]. Some of its structural analogs are dihydropyridazinone **6** and pyridazinone **7**. All those scaffolds are characterized by a six-membered ring containing two nitrogen atoms at positions 1 and 2, with a carbonyl group attached to the third position.

Moreover, pyridazin-3-(*2H*)-one **7** has captured researchers’ attention due to its nitrogen-rich heterocyclic core and its easy functionalization at various positions on the ring resulting in adaptable pharmacological activities [1, 2, 6, 7]. Its composition makes pyridazinone a drug-like core, often referred as a “wonder nucleus” because it can be modified to produce a wide array of derivatives with diverse biological activities such as antiviral [8, 9], anticancer [10 - 12], cardiotonic [13], antidepressant [14], diuretic [15] and anti-inflammatory especially [16 - 19].

ANTIVIRAL ACTIVITY

Viral infections are a major cause of serious diseases globally, particularly in lower respiratory track in the past years due to COVID-19 outbreak [20]. Despite the development of various antiviral agents over the years,

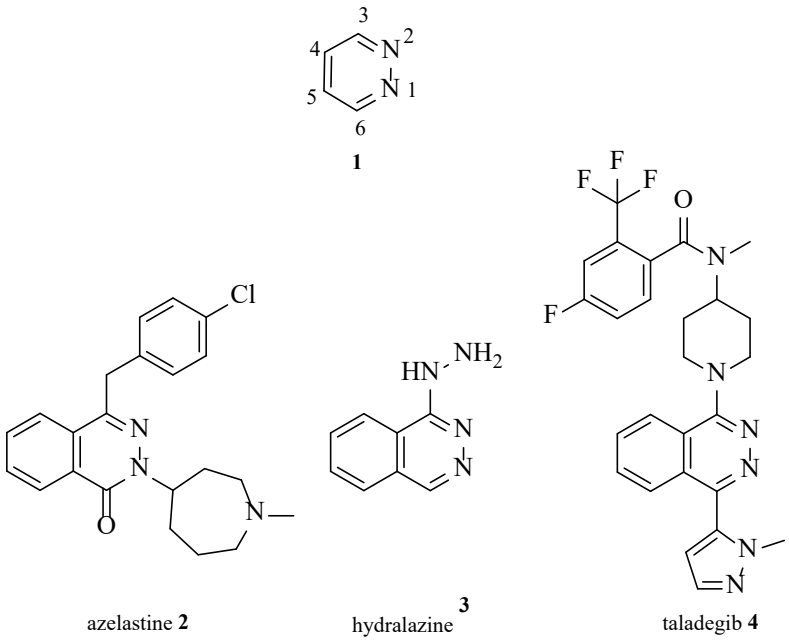


Fig. 1. Pyridazine and common pyridazine-based drugs.

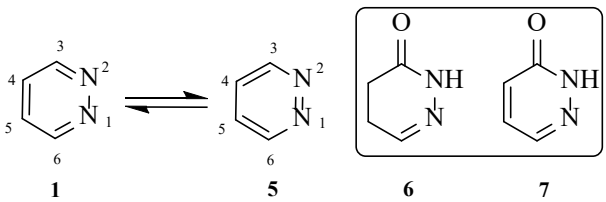


Fig. 2. Pyridazine and its structural analogs.

there remains a significant need for new and safer drugs. Researchers have evaluated such properties of various pyridazinone derivatives using different virus strains, including human Herpes Simplex Virus (HSV-1), Human cytomegalovirus (HCMV), Hepatitis B and C viruses (HBV and HCV), and Human Immunodeficiency Virus (HIV).

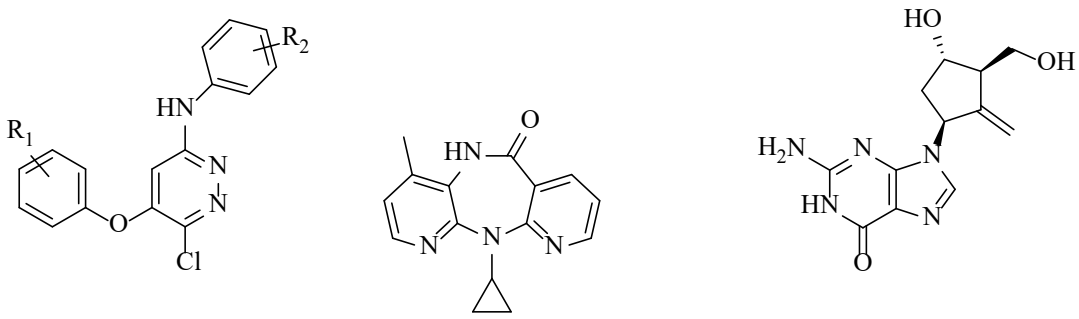
Li et al. synthesized pyridazine-based derivatives **8** to evaluate their antiviral potency against wild-type HIV-1 subtype B (HIV-1B) [9]. Most of compounds **8** inhibits HIV-1 replication at sub-micromolar range (Fig. 3). Among the synthesized analogs, **8a** was identified as the most potent, with an EC_{50} = 0.034 ± 0.012 μM and selectivity index (SI) 563 against HIV-1B. Moreover, **8a** showed higher inhibition activity against HIV-1 reverse transcriptase (RT) IC_{50} = 0.55 μM than the reference drugs nevirapine **9** and entecavir **10** (IC_{50} = 3.18 μM *vs* 1.20 μM respectively).

Another research describe preparation of structural pyridazinone derivatives as HIV-1 inhibitors [21]. The synthetic process is based on a novel rearrangement reaction, involving 4-fluorobenzylamine (Scheme 1). Among all compounds **13a** and **13b** exhibited relatively higher inhibitory effect against HIV-1 at 10 μM with respectively 53.5 % and 41.9 % of inhibition.

The synthesized compounds were also tested *in-vitro* for their anti- Tobacco Mosaic Virus (TMV) activity. Most of the compounds showed good anti-TMV activity. In particular, compound **13c** demonstrated the same inhibitory activity (IC_{50}= 2.8 μM) as the commercial plant virucide Ribavirin, highlighting its potential as an effective agent against plant viruses.

ANTIMICROBIAL ACTIVITY

A relatively new class of systemic antifungal agents works by disrupting the fungal cell wall. Specifically,

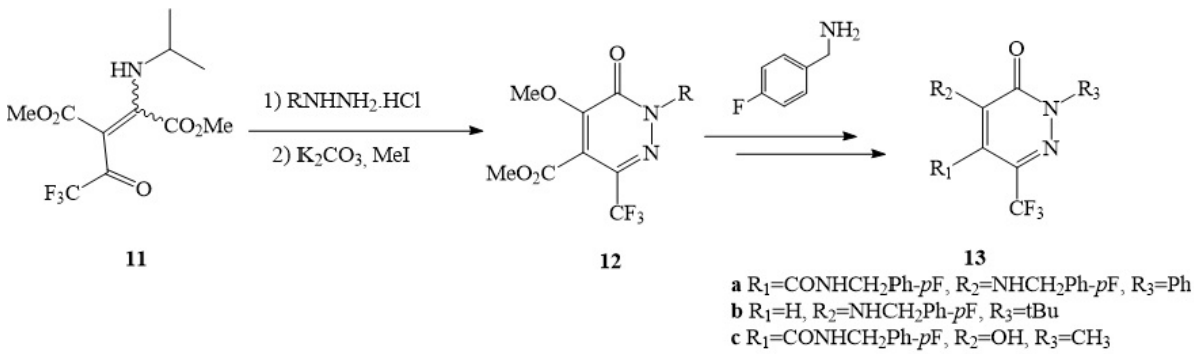


8 **a** R_1=2,6-DiBr-4-Me; R_2=4-CN

nevirapine **9**

entecavir **10**

Fig. 3. Compound **8a** developed by Li et al. and the reference drugs nevirapine **9** and **10** entecavir [9].



11 **12** **13**

a R_1=CONHCH$_2$Ph-*p*F, R_2=NHCH$_2$Ph-*p*F, R_3=Ph
b R_1=H, R_2=NHCH$_2$Ph-*p*F, R_3=tBu
c R_1=CONHCH$_2$Ph-*p*F, R_2=OH, R_3=CH$_3$

Scheme 1. Synthesis approach described by Wang et al. and their most active compounds **13a-c**.

these agents inhibit 1,3-*β*-d-glucan synthase (SG), a crucial component of the fungal cell wall. The research of Zhou et al., focus on synthesis a series of sulfonamide substituted pyridazinones **14** and their evaluation as SG inhibitors (Fig. 4) [22]. They identified compound **14a** possessing activity against *Candida albicans* C697 with MIC value 0.13 mg mL^{-1}. According to their research in **14a** the key modification to the core structure was addition of aniline, so this pharmacophore was selected and several modifications were performed to this scaffold [23]. To decrease the overall lipophilicity of the target molecules, the methylcyclopropylmethyl group was introduced on compounds **15a** and its fluorinated analog **15b**. They were identified as the most potent agents possessing high antifungal activity (IC_{50} = 0.03 μM) while maintaining a compact hydrophobic group. However, further changes of R_2 = Ph with aniline analogs bearing different small substituents on its moiety such as F, Cl, Me, or OMe resulted in decreased potency, despite the promising results observed for compound **14a**.

Another study aimed to develop antibacterial and antifungal compounds with a broad spectrum of activity, systemic effects, and lower side effects [24]. Specifically, eight new 3(*2H*)-pyridazinone derivatives **16** (Fig. 5) varying in different halogenated atoms on position R_1, were synthesized and evaluated. The study highlights that the new compounds possess broad-spectrum antimicrobial activity, with a particular efficacy against fungal pathogens. The greater effectiveness against fungi suggested potential applications in treating fungal infections, which are often more challenging to manage than bacterial ones. Compound **16a** was shown as the

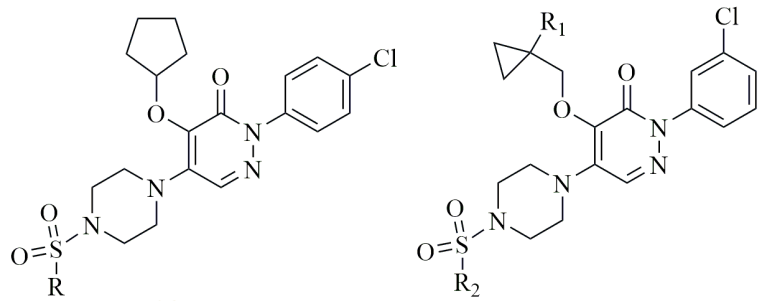
most active, demonstrating lower MIC values against *Candida krusei* than those of the standard antifungal agent fluconazole **17** (MIC=8 μg/mL *vs* 32 μg/mL). Moreover, the molecular docking studies showed higher binding interactions in active site of the enzymes of **16a** *vs* **17** (K_i=18.12 nM *vs* 23.62 μM).

CARDIOVASCULAR ACTIVITY

Sotelo et al. conducted extensive research on 6-phenyl-3(*2H*)-pyridazinones **18** (Fig. 6) with various substituents at position 5 as antiplatelet agents [25]. Their pharmacological studied showed the importance of the substituent on pyridazinone core system influences both the antiplatelet activity and the mechanism of action (MoA), concluded that the substituent plays a crucial role in the inhibitory effect. Many of the studied compounds inhibit platelet aggregation in a dose-dependent manner. No strict correlation was observed on the distance from the pyridazinone core **18a** *vs* **18b** (IC_{50} = 15 μM *vs* inactive) and **18c** *vs* **18d** (IC_{50} = 500 μM *vs* induces platelet aggregation), as well as **18e** (IC_{50}= 190 μM). Most active compounds from that series were tested against Phosphodiesterase 3 (PDE3), an enzyme that break down cyclic adenosine monophosphate (cAMP) and further disrupt the intracellular signaling pathway. Compounds **18 a**,**c**,**e** didn`t show any inhibitory activity, suggested that the anti-platelet activity shown by **18a-e** is not a cAMP-dependent MoA.

ANTIDEPRESSANT PROPERTIES

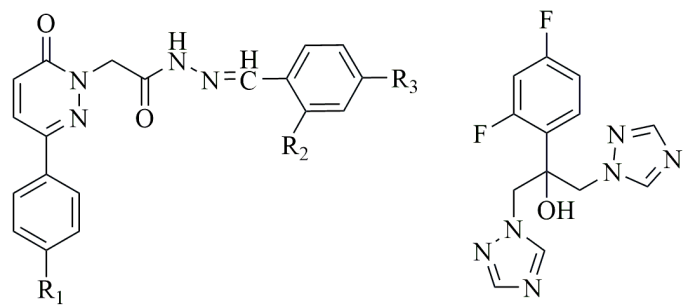
A preclinical *in-vivo* forced swimming test (FST) was conducted on Swiss mice by Boukharsa et al. to evaluate the therapeutic potential of pyridazinones **19** (Fig. 7) for managing mental depression [14]. Several compounds were synthesized to assess the impact of different substituents at the C5 position of the benzofuran moiety from **19** as antidepressant agents. All compounds were tested at a dose of 50 mg kg^{-1} administered orally



14
a R=Ph-*p*NH_2

15
a R_1=H, R_2=Ph
b R_1=F, R_2=Ph

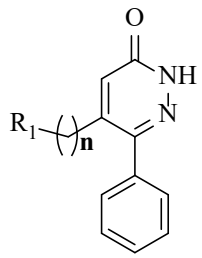
Fig. 4. Pyridazinone derivatives evaluated against *Candida albicans*.



16
a R_1=Br, R_2=H, R_3=CF_3

17

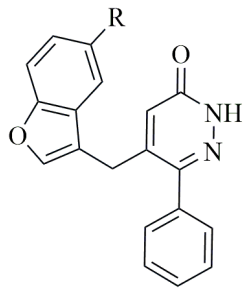
Fig. 5. General structures of the synthesized compound **16a** and fluconazole **17**.

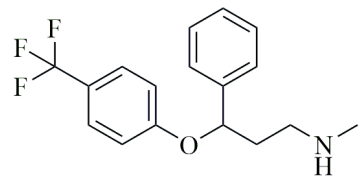


18

a R_1=SPh; n=0
b R_1=SPh; n=1
c R_1=OPh; n=0
d R_1=OPh; n=1
e R_1=$OCOCH_3$; n=1

Fig. 6. Synthesized compounds by Sotelo et al. [25].





19 **20**

a R=CH_3
b R=CH_2CH_3
c R=$CH(CH_3)_2$

Fig. 7. Compounds **19a-c** developed by Boukharsa et al. [14] and fluoxetine **20**.

and compared to fluoxetine **20** at a dose of 32 mg kg^{-1}. A correlation between the length of the aliphatic chain and reduced immobility time was observed, after performed FST with compounds **19a**, **19b** and **19c** (175 ± 20 *vs* 90 ± 25 *vs* 80 ± 24 min). Furthermore, among all tested compounds, **19b** and **19c** displayed the lowest percentage of immobility compared to fluoxetine (respectively 42.82 % and 38.09 % *vs* 45.23 %).

ANTICANCER ACTIVITY

The pyridazinone scaffold is also known for its significant potential in the development of cancer drugs due to its versatility and involvement in inhibiting various cancer pathways dealing with growth, mutation, apoptosis or proliferation. Some pyridazinone derivatives are known to exhibit inhibition activity against C-Met kinase, Tubulin polymerization, Poly(ADP-ribe) polymerase and others [2]. The pyridazinone scaffold's therapeutic potential to interfere with multiple cancer cell mechanisms underscores the importance of further exploration in this area, a focus that has gained significant attention from research teams in the past years.

Potent protein kinase inhibitors

A large number of protein kinases are involved in controlling the phosphorylation of proteins in cells. This process plays an important role in the regulation of various cellular processes. Alterations in kinase signaling are found in numerous human pathologies, such as inflammation, diabetes, Alzheimer`s disease or cancer [26].

Pyridazinones **21** and phthalazinones **22** structures (Fig. 8) were designed by Elagawany et al. and evaluated as protein kinase inhibitors [27]. Among all synthesized compounds **21a-b** and **22a** were found active against tyrosine phosphorylation regulated kinase 1A (DYRK1A) and Glycogen synthase kinase-3 (GSK3) with IC_{50} = 2.2-8.1 µM, on the contrary of casein kinase-1 (CK1) and cyclin-dependent kinases-5 (CDK5), where they were inactive. Substitution of position 6 of pyridazinone scaffold with amino group **21a** showed

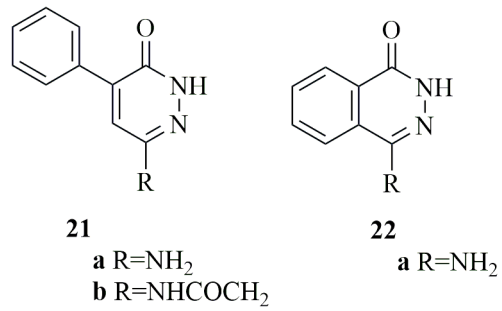


Fig. 8. General scaffolds of pyridazinones **21a-b** and phthalazinone **22a** synthesized by Elagawany et al.[27].

Table 1. Evaluated activity of compound **21a**, **21b** and **22** against four cancer cells.

Compound	Cancer cell (IC_{50}, μM)			
	OVCAR-8	SF-295	HCT-116	HL-60
21a	4.86	5.71	4.40	3.64
21b	14.00	7.66	15.44	11.61
22	11.78	6.06	12.71	8.87

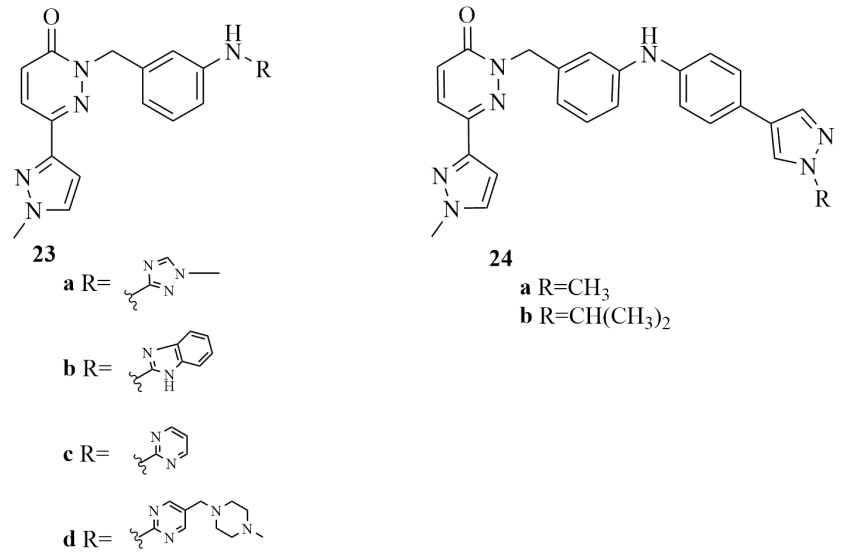


Fig. 9. Tested molecules against c-Met tyrosine kinase.

modest activity against DYRK1A and GSK-3 (6 and 8.1 μM), whereas acylation of this NH_2 group into **21b** lead to selected inhibition only against GSK-3 (IC_{50} = 2.2 μM). The phthalazinones scaffold of **22a** exhibit highest activity and selectivity only toward DYRK1A (IC_{50} = 4.1 μM). Further, during their investigations, Elagawany et al. evaluated their kinase inhibitors against the cancer cells OVCAR-8, SF-295, HCT-116, HL-60 (IC_{50} < 15 μM).

c-Met kinase inhibitors

The mesenchymal epithelial transition factor (c-Met), also known as hepatocyte growth factor receptor (HGFR), is a tyrosine kinase receptor distinct from other members of its subfamily. Overactivation of c-Met is often associated with angiogenesis, cell proliferation, invasive tumor growth, migration, survival and metastasis. Additionally, c-Met/HGF is overexpressed in tumoral processes, such as those affecting the liver, lungs, stomach, kidneys, ovaries and prostate cancers [2].

Following the fact that c-Met tyrosine kinase promotes tumorigenesis and metastasis in cancer patients, Liu et al. conduct a research on pyridazinone-based range of compounds [28]. They screened large number of compounds **23** (Fig. 9) to evaluate their inhibition against c-Met. Methyl-4 substituted pyrazole on position 5 from pyridazinone scaffold remained constant while different nitrogen heterocycles due to their hinge properties were introduced on R. No inhibition was observe with triazole **23a**, benzoimidazole **23b** or pyrimidine **23c**, whereas conformationally more flexible piperazine **23d** display low activity (IC_{50} = 82.1 ± 1.9 nM). On the contrary, addition of another *N*-substituted pyrazole moieties **24a** and **24b** significantly increase the inhibition effect (7.5 ± 0.1 nM and 8.1 ± 1.5 nM). Additionally, when

tested, compound **24a** displayed better anti-proliferation activity against EBC-1 cell line *vs* **24b** (IC_{50} = 31.2 ± 5.1 nM *vs* 94.6 ± 7.6 nM).

Tubulin polymerization inhibitors

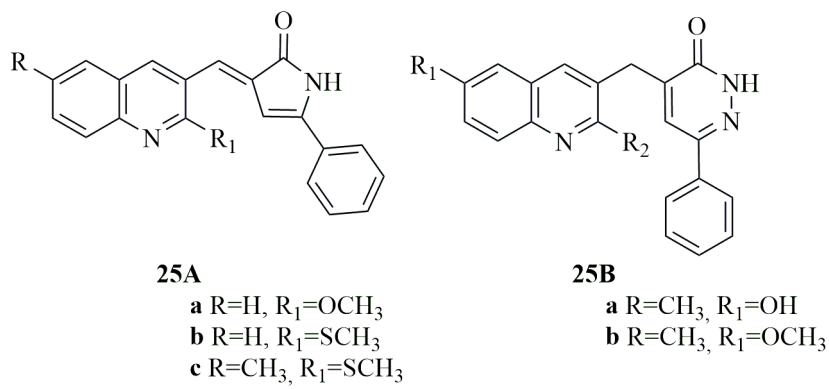
In their research Abdelbaset *et al.* synthesized a series of pyrrol-2(*3H*)-one **25A** and pyridazin-3(*2H*)-one **25B** derivatives (Fig. 10) containing a quinoline moiety and screened them for cytotoxic activity against 60 cell lines [29]. Among the tested compounds, **25Ac** and **25Bb** exhibited remarkable results and were selected for further *in-vitro* testing for antiproliferative activity against several human cancer cell lines. Quinolinyl-pyridazinone **25Bb** demonstrated also higher activity, with IC_{50} values of 2.2 and 2.9 μM against the pancreatic carcinoma cell line PaCa-2 and the human pancreas cancer cell line Panc-1, respectively, compared to its pyrrole analog **25Ac**, which had IC_{50} values of 9.2 and 9.9 μM. Additionally, **25Bb** showed moderate activity against the colon cancer cell line HT-29 and the lung cancer cell line H-460, with IC_{50} values of 4.5 and 5.5 μM. The mechanism of action study for compound **25Bb** revealed weak EGFR inhibition (IC_{50} = 7.8 μM) and good BRAF inhibitory activity (IC_{50} = 2.9 μM).

ANTI-INFLAMMATORY ACTIVITY

Controlling inflammation has become a crucial priority due to its involvement in numerous diseases such as asthma, Chronic obstructive pulmonary disease (COPD), Crohn's and Alzheimer's diseases, multiple sclerosis, rheumatoid arthritis, carcinoma, psoriasis, and various viral and bacterial infections. These pathological conditions are often associated with pain, making it important to seek therapeutic drugs with dual effects. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat inflammation and pain, but their use is restricted due to common side effects such as headache, vertiginous, diarrhea, and skin rash. Encouraging the activity of pyridazinone derivatives, researchers in the field of medicinal chemistry have synthesized several pyridazinone-based compounds that possess high activity as analgesics and anti-inflammatory agents with few associated side effects.

In their study, Abhouzid and Bekhit synthesised a series of 4,5-dihydropyridazinone derivatives **26** (Fig. 11) linked at position C-6 to aryl or biphenyl moieties through carbon spacers for search of Cyclooxygenase-2 (COX-2) inhibitors [30]. All prepared compounds were tested *in-vivo* in carrageenan-induced rat paw edema model for anti-inflammatory activity. Among the synthesized derivatives, **26a** and **b** show the highest activities (ED_{50} = 18.7 and 17.0 μM kg^{-1}). Thus, they were categorized as potential COX-2 inhibitors, which are known to treat inflammatory pain. Further in their research, the authors calculated the activity relative to the know NSAID agent indomethacin **27**, which is to compare the two new molecules. The mentioned relative activity for **26a** was 78.17 % and for **26b** was 82.28 %. Furthermore, compound **26a** was prepared as pyridazinone but did not show any activity.

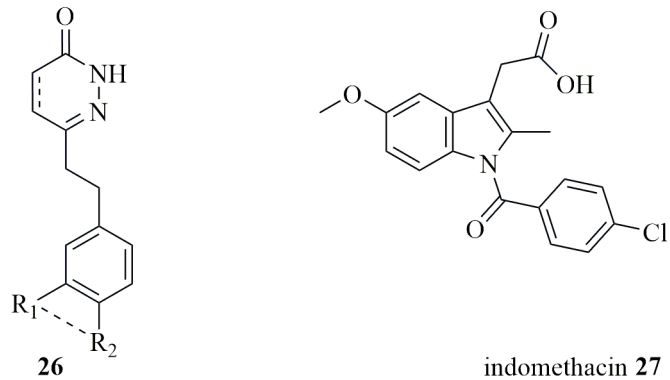
In 2011, the research team of Mogilski et al. performed several basic pharmacological tests on



25A
a R=H, R_1=OCH_3
b R=H, R_1=SCH_3
c R=CH_3, R_1=SCH_3

25B
a R=CH_3, R_1=OH
b R=CH_3, R_1=OCH_3

Fig. 10. Most active compounds from Abdelbaset et al. [29].

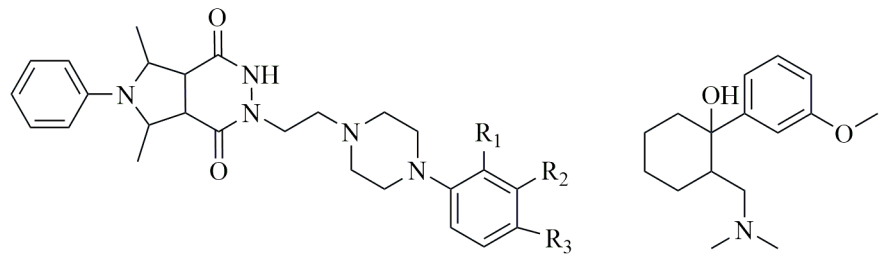


26

a R_1=Ph, R_2=H
b R_1=-OCH_2CH_2O-R_2

indomethacin **27**

Fig. 11. Compounds **26a-b** synthesized by Abhouzid et Bekhit [30] and the reference **27** indomethacin.



28

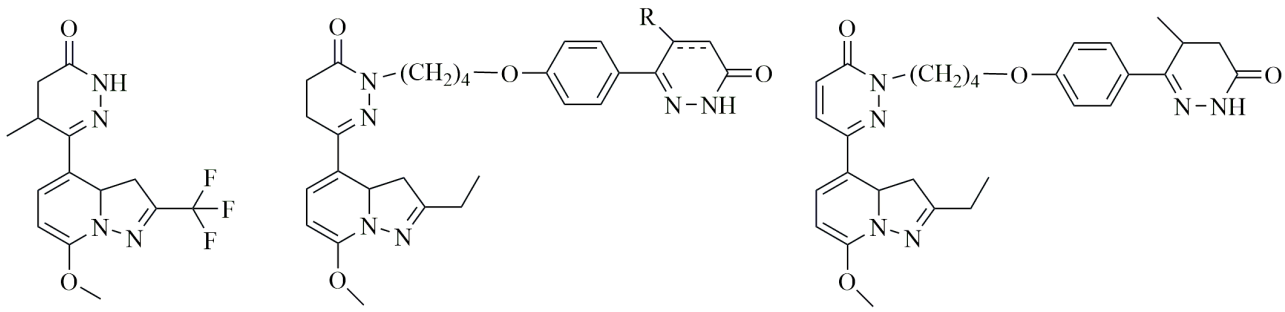
a R_1=F, R_2=H, R_3=H
b R_1=H, R_2=CF_3, R_3=H
c R_1=CH_3, R_2=H, R_3=Cl

tramadol **29**

Fig. 12. Studied compounds by the team of Mogilski et al. [31, 32].

dihydropyridazinone derivatives **28** (Fig. 12) with different substitution on phenyl ring to investigate their analgesic activity [31]. The performed writing plate test showed that all derivatives have better activity (ED_{50} = 0.04 - 11 mg kg^{-1}) than acetylsalicylic acid (ASA) (ED_{50} = 39.15 mg kg^{-1}). Only **28a-c** displayed analgesic activity on hot plate test where they displayed 3 - 5 times higher than that of morphine (ED_{50} = 3.39 mg kg^{-1}). At radioligand binding assay, only **28c** (K_i = 2.6 μM) show affinity for the μ-opioid receptors similar to that of tramadol **29** (K_i = 2.4 μM), which suggested that **28a** and **28b** develop opioid activity in different pathway that doesn`t involve the peripheral μ receptor. Molecules **29a** and **29b** were further investigated.

Extensive study was performed on these two selected compounds and confirmed their analgesic activity in various animal models [32]. Both compounds exhibited significant, dose-dependent antinociceptive effects in animal models induced by formalin, capsaicin, and glutamic acid. Additionally, **28a** and **28c** doesn't damage motor coordination of mice in rotarod test at 25 mg kg^{-1} dose. Both compounds showed high antagonistic potency for H_1 receptors (K_i = 13.56 and 15.84 μM) which was an explanation for their anti-inflammatory and neurogenic pain properties. In addition, compounds **28a** and **28c** also induced greater tracheal smooth muscle relaxation at a 100-μM dose in guinea pig trachea (114.4 % and 123.90 %) compared to the known inhibitor 3-isobutyl-1-methylxanthine (IBMX) (63.02 %). This suggested **28a** and **c** as potential PDE inhibitors because they increase intracellular cAMP levels and reduce the release of pro-inflammatory cytokines. Additional decreased accumulation of Tumor necrosis factor alpha (TNF-α) and Interleukin-1 beta (IL-1b) was observed



KCA-1490 **30** **31** **32**

A. dihydropyridazinone
a R=H
b R=CH_3
B. pyridazinone
a R=H
b R=CH_3

Fig. 13. KCA-1490 **30** and molecules of interest of Ochiai et al. **31** and **32** [33].

with **28a** and **28c**.

The SAR research by Ochiai et al. focused on synthesizing a series of (dihydro)pyridazinone analogs of the dual PDE3/PDE4 inhibitor KCA-1490 **30** (Fig. 13), aiming to enhance its bronchodilatory and anti-inflammatory effects [33]. They found that *N*-alkylation of the pyridazinone ring increased potency of PDE4 but decreased PDE3 one. Previous work indicated that the -NH group of pyridazine in KCA-1490 is crucial for binding to PDE3. Alkylation extended surface contact but reduced substrate binding [34]. Substitution on the *N*-alkyl group was performed to enhance PDE4 and maintain PDE3 inhibition. The addition of another dihydropyridazinone structure **31a** and one more alkyl group (n = 4) showed better activity against PDE3 and PDE4 compared to its shorter analog **31Ab** (n = 3) (IC_{50} = 11 and 5.2 nM *vs* 12 and 1.7 nM, respectively). Further pharmacomodulation of the more active compound **31b** involved oxidizing the dihydropyridazinone core to its saturated pyridazinone analog **32** were tested in order to study the role of the two states. Although the performed changes **31b** showed better activity against PDE3 and PDE4 (IC_{50} = 1.2 and 1.7 nM) compared to **32** (IC_{50} = 2.7 and 20 nM), and remain more active at its inhibitory effect on bronchoconstriction at a 0.1 mg/kg dose (96 % for **31b** *vs* 71 % for **32**). Overall, the authors manage to synthesis series of potent dual PDE3/PDE4 inhibitors with better activity than KCA-1490 **30** (IC_{50} = 360 / 42 nM). The conclusion of Ochiai et al. was that pyridazinone scaffold does not increase inhibition against PDE3 nor PDE4, but remain with a good results [33].

Other pyridazinone scaffolds that have passed the clinical trials and are available, as the ones described in Fig 14, mostly dealing with heart failure. Bemoradan **33**, discovered in 1990s, showed competitive inhibition potency to the rolipam-insessitive cAMP PDE4 in Canine cardiac muscle, with a K_i of 0.09 nM compared to the known agent rolipram (K_i = 0.023 μM) [35]. Indolidane **34** has been described as long-lasting inotropic PDE4 inhibitor in canine cardiac membranes (K_i = 80 nM) with low toxicity at dose as high as 70 mg kg^{-1} [36]. However, its further modifications were discontinued due to low effect compared with the placebo in different *in-vivo* animal models. Another inotropic drug that has been registered is pimobendan **35**, which showed combined activity in veterinary cardiology as both a PDE3 inhibition and calcium sensitization of myocardial proteins in animals, specifically in dogs at dose 0.15 mg kg^{-1} ($p < 0.05$) [37]. Its structural analog levosimedan **36**, leveraged the effects of pimobedan **35** and has been developed as drug-candidate for acute and advanced heart failure [38]. Furthermore, **36** was found to inhibit PDE3 in a dose-dependent manner at low therapeutic concentration IC_{50} = 0.4 ± 3 μM, postulating an inotropic effect in human myocardium [39].

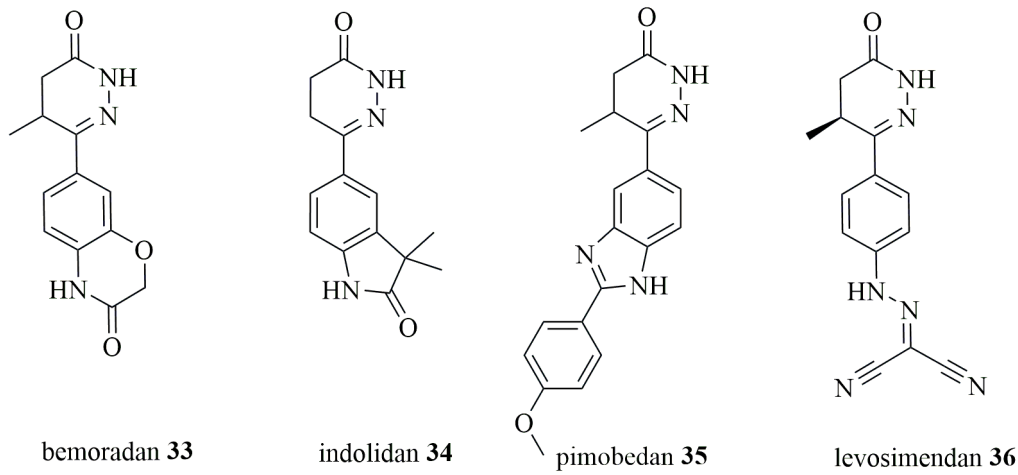


Fig. 14. Structure of pyridazinone-based drugs on the market.

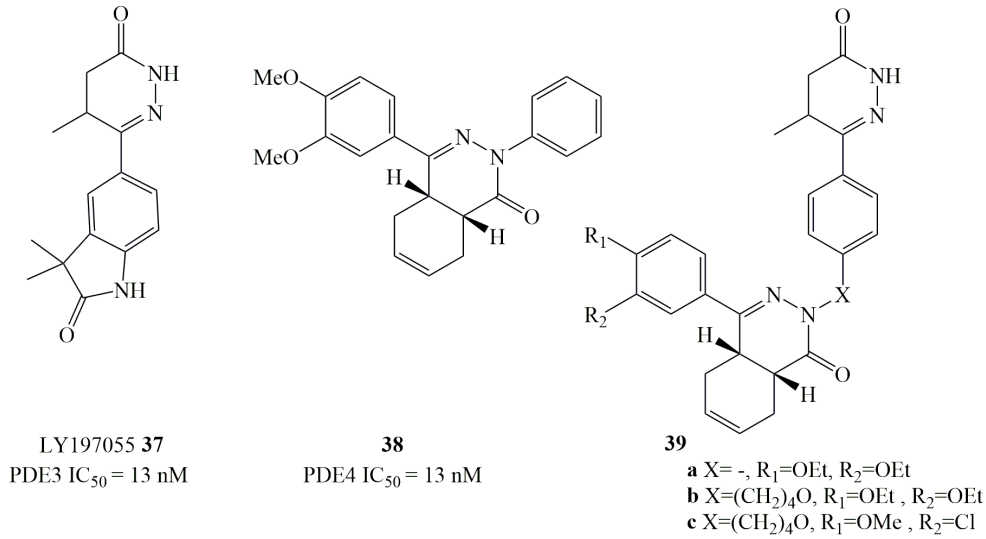


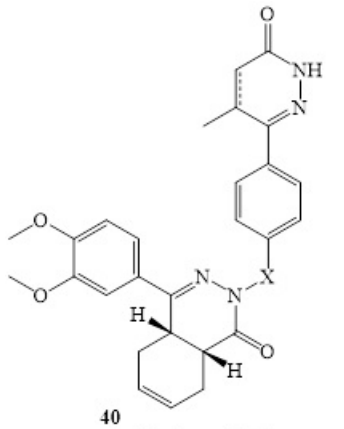
Fig. 15. Structure of dual PDE 3/4 inhibitors synthesized by Mey et al. [40].

Based on the multiple effects of the previously mentioned drugs, dual activity seemed interesting perspective. The team of Van der Mey et al. reported dual PDE3/PDE4 inhibitors, by combining the pharmacophores of dihydropyridazinone-based LY197055 **37** selective against PDE3 and phthalazinone **38** against PDE4 (Fig 15) [40]. Several substitution were performed to increase activity, as they were variations of heterocycle of **37** and different substitution on *m*- and *p*- position of phthalazinone **38**, as well as possible linker group between the two subunits. All of the synthesized derivatives showed moderate anti-inflammatory activity *in-vitro* with advantage against PDE3, proving previously stated potential of dihyropyridazinone scaffold. Further analysed, only **39a-c** displayed the most effective *in-vivo* inhibitory activity in a mouse ear edema assay at 30 μmol kg^{-1}, with inhibition rates of 42 %, 46 % and 47 %, respectively. Moreover, **39a-c** possess higher potency than zardaverine (22 % at the same dosage), proving their dual PDE3/PDE4 inhibitory effect. The SAR data indicated that the linker had no significant impact on activity.

Another comparision were performed by Mey et al. where they replace dihydropyridazinone core **40Aa-c**

with pyridazinone analogs **40Ba-c** (Fig 16) [40]. The *in-vitro* PDE3 / PDE4 inhibitory activity were performed. For PDE3 **40Aa-c** (pIC_{50} = 6.7, 6.7 and 7.0, respectively) were evaluated in comparison of **41Ba-c** (pIC_{50} = 5.4, 5.9 and 6.0). Similar results were demonstrated for PDE4 of **40Aa-c** (pIC_{50} = 8.4, 8.4 and 8.2, respectively) and **41Ba-c** (pIC_{50} = 8.1, 8.2 and 8.2). The obtained results indicated no PDE3 / PDE4 selectivity between the two series. In contrast, there were difference observed in the % of *in-vivo* inhibitory activity in the mouse ear edema assay at 30 μmol kg^{-1}, where no strict correlation could be established between the two core structures **40Aa-c** (34, 13 and 26, respectively) *vs* **41Ba-c** (8, 31, 27, respectively).

As stated in the review of Banner and Press PDE4 inhibitors are highly effective at suppressing release of pro-inflammatory mediators from neutrophils, eosinophils and macrophages [41]. Further evidences in their research suggested that dual PDE3 / PDE4 inhibition can have synergetic effect on functions of other cell types implicated in COPD such as dendritic and epithelial cells, as well as lymphocytes and airway smooth muscle cells. Such example is their synergetic act on spasmogen-induced contraction of human airways.



40

A dihydropyridazinone
- **a** X=$(CH_2)_4CONH$
- **b** X=CH_2CONH
- **c** X= direct bonding to N

B pyridazinone
- **a** X=$(CH_2)_4CONH$
- **b** X=CH_2CONH
- **c** X= direct bonding to N

Fig. 16. Structures of interest **40A** and **B** by Mey et al. possesing dual PDE3/PDE4 inhibition [40].

Another dual effect was suggested on stimulating mucociliary clearance in patients with cystic fibrosis by PDE4D while PDE3 was responsible for suppressing cough [42]. These varieties of biological effects implicated PDE4 and combined PDE3 / PDE4 inhibitors could be promising therapeutic agents for a range of diseases, including asthma and COPD. Additionally, the existing PDE4 inhibitors on the market and the one mentioned in this review make the pyridazinone scaffold a promising entity developing a hybrid molecule against lung inflammatory diseases. Targeting multiple pathways involved in these diseases might yield better clinical outcomes.

CONCLUSIONS

Several literature reports, mentioned in this review, highlighted the diverse range of biological activities exhibited by the "drug-like" pyridazinone scaffold, demonstrating remarkable IC_{50} values. This establishes pyridazinone as a promising scaffold in drug development. Additionally, it is postulated that novel pyridazinone derivatives may possess multi-target actions, making them valuable for targeting diseases through multiple pathways, or to incorporate this heterocyclic system in hybrid molecule to obtain synergistic effects, opening new perspectives in the development of drug candidates.

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Authors' contributions

S.G., M.L.-C.: conceptualization; B.B.: original draft preparation; S.G.: review and editing of the manuscript; S.G., M.L.-C.: supervision.

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