Original Article: Pyridazine derivatives act as phosphodiesterase-III, IV, and V Inhibitors

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ABSTRACT

Pyridazine derivatives are significant bioactive molecules having wide range of biological activities. Phosphodiesterase (PDE) enzymes, particularly PDE-III, PDE-IV, and PDE-V are inhibited by some pyridazine compounds. PDEs are cyclic nucleotide-hydrolyzing enzymes that regulate intracellular levels of the secondary messengers (cAMP and cGMP), cell activities and their specific inhibitory effects for the treatment of various disorders. PDE isoenzyme selective inhibitors include PDE-III inhibitors for congestive heart failure (CHF), PDE-IV inhibitors for inflammatory disorders, and PDE-V inhibitors for erectile dysfunction. The PDE-V inhibitor should be utilized in pulmonary hypertension. In this article, the PDE activities of various pyridazine compounds were investigated.

Introduction

Phosphodiesterase (PDE) was firstly isolated from rat brains in 1972, and a series of drugs were quickly recognized to especially inhibit it in the brain and other tissues [1]. Selective PDE inhibitor medicinal potential was first expected in 1977 [2,3]. PDE inhibitor inhibits the PDE enzyme, avoiding the PDE subtype from inactivating the intracellular second messengers, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). PDEs are a group of enzymes that hydrolyze cyclic nucleotides, regulating intracellular levels of the secondary messengers and cell activities. The recognition of eleven (I-XI) isoenzymes, and their function at the cellular and molecular level, has stimulated the development of isoenzyme-specific inhibitors for the treatment of various disorders.

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PDE isoenzyme selective inhibitors include the PDE-III inhibitors for congestive heart failure (CHF) and their use in improving quality of life in patients with intermittent claudication [4], PDE-IV inhibitors for inflammatory diseases, and PDE-V inhibitors for erectile dysfunction [5]. PDE inhibitors are selectively dangerous to cancer cells because distinct PDE isoenzymes are overexpressed in different tumor cells. PDE inhibitors work with already existing anticancer drugs and might be used in the cancer treatment plan.

In recent years, the activities of pyridazine derivatives have grown widely. These derivatives have a wide range of pharmacological properties, such as cardiovascular and cardiotonic agents (zardaverine, imidazole, bemoradan, indolindan, and pimobendan), vasodilator, antiplatelet, antidepressant, antihypertensive, antithrombotic, antifungal, antibacterial, antimicrobial, analgesic, anti-inflammatory, antifeedant, anticancer, diuretics, anti-HIV, and other pharmacological properties [7-18].

Nonselective phosphodiesterase (PDE) inhibitors

Nonselective adenosine receptor antagonists and competitive nonselective PDE inhibitors enhance intracellular cAMP, activate PKA, inhibit TNF- and leukotriene production, and reduce inflammation and innate immunity. In the pursuit of molecules with improved selectivity for PDE enzyme or adenosine receptor subtypes, several synthetic xanthine derivatives have been formed [19-22].

Phosphodiesterase (PDE) Enzyme Inhibitors

The effects of the diuretics 1,4-dimorpholino-7-phenylpyrido[3,4-d]pyridazine (DS-511) (**1**) and its 4'-hydroxy derivative [DS-511(4'-OH)] on the ADH-cyclic AMP system in rat renal medulla slices have been examined. The basal levels of slices cAMP are unaffected by these substances. After preincubation with DS-511 or DS-511-(4'-OH) in the presence of theophylline, the making of cAMP was prevented, but it was restored after washing the slices. Higher levels were required to block etacrynic acid. Hydrochlorothiazide and furosemide had no effect. DS-511(4'-OH) reduced the effect of cAMP-PDE in the medullary homogenate. The diuretic action of DS-511 was mediated in part by its suppression of the ADH-cyclic AMP pathway [23].

In vitro, theophylline and three lipolytic compounds, 2,5-bis(2-chloro ethylsulfonyl)-pyrrole-3,4-dicarbonitrile (substituted pyrrole), 2,4-diamino-6-butoxy-s-triazine (substituted triazine), and 2,3-dihydro-5,6-dimethyl-3-oxo-4-pyridazine carbonitrile (substituted pyridazine) (**2**), stimulated basal lipolysis in adipose tissue. They also promoted an increase in the release of free fatty acids (FFAs), but not glycerol, from adipose tissue when the adrenaline had already driven lipolysis to its highest. The cyclic AMP PDE and the change of [1-(14)C]glucose to (14)CO were likewise inhibited by these four drugs. The accumulation of FFAs as a result of hindered re-esterification was confirmed. After oral or intraperitoneal (i.p.) injection, the substituted pyridazine and triazine, but not the pyrrole, raised plasma FFAs in rats [24].

Phosphodiesterase (PDE)-III selective inhibitors

Clinically, PDE-III antagonists are used to treating heart dysfunction. These drugs enhance cardiac activity by simulating sympathetic stimulation. Intermittent claudication is also treated with this drug. PDE-III is also known as the cGMP-inhibited PDE [25-27].

Phosphodiesterase (PDE)-III Inhibitors and Pyridazine Derivatives

A sequence of 6-(4-(substituted-amino)phenyl)-4,5-dihydro-pyridazin-3(*2H*)-ones have antiplatelet action. The tail transaction bleeding test was used to assess the antiplatelet test. The pyridazine derivatives substantially inhibited platelet aggregation when compared with the normal drug aspirin, certain compounds have a greater inhibitory effect on platelet aggregation [28]. Potent PDE-IIIB subtype-selective inhibitors have been identified as aryl dihydro pyridazine and aryl dimethyl pyrazolones with 2-benzyl vinyl amide substituents.

For *in vivo* estimation of lipolysis activation, metabolic rate rise, and cardiovascular results, dihydro pyridazine (PDE-IIIB IC_{50}=0.19 nM, 3A IC_{50}=1.3 nM) were chosen [29]. The cardiovascular actions and mode of action of the cardiotonic drug 6[4-(4'-pyridyl)aminophenyl]-4,5-dihydro-pyridazin-3(*2H*)-one hydrochloride (MCI-154) (**3**) were tested. MCI-154 (0.01-0.3 mumol/kg i.v., bolus injection) resulted in a dose-dependent rise in left ventricular dP/dt and a reduction in mean arterial pressure in anesthetized rats. There was just a slight rise in heart rate. Canine cardiac PDE-III was selectively blocked by the drug (IC_{50} 2.5+/-0.6 mumol/l). MCI-154 increased the Ca^{2+} sensitivity of contractile proteins in skinned porcine trabeculae just slightly. The MCI-154 is a potent cardiotonic agent, with PDE-III inhibition possibly playing a role in this effect [30].

Hydrazinopyridazines have antihypertensive and vasorelaxant effects. Some 6-aryl-5-piperidino-3-hydrazino-pyridazines (**4**) with structurally similar to the well-known antihypertensive drug hydralazine have been found to exhibit vasodilator actions. In rat aortic rings with or without endothelium, hydralazine and the present hydrazino-pyridazines alleviated contractions produced by noradrenaline or a high K^+ concentration in a concentration-dependent and unspecified manner. Considering the IC_{50} (50% inhibitory concentrations) values obtained, the compounds' vasorelaxant efficacy was larger than hydralazine.

In a Ca^{2+}-free media, the hydrazino-pyridazines and hydralazines effectively prevented the contractions caused by noradrenaline or caffeine. These compounds and hydralazine showed no impact on Ca^{2+} uptake triggered by basal, noradrenaline, or K^+. These drugs have stronger endothelium-independent vasorelaxant action than hydralazine in isolated rat aortic rings and that their action is not mediated by blocking of transmembrane Ca^{2+} fluxes through complicated channels [31]. The actions of the 6-(2,3,4,5-tetrahydro-5-methyl-3-oxo-pyridazine-6-yl)-1,2,3,4-tetrahydro-1-methyl quinolin-2-one (Y-590) (**5**) on platelet PDE were tested. Incubation of Y-590 with washed rabbit platelets did not affect the concentration of cAMP. It improved the capacity of prostaglandin I_2 (PGI_2) to increase cAMP when added to washed platelets 1.5 minutes before PGI_2. Y-590 substantially suppressed cAMP-PDE in rabbit platelets, although it exhibited a less inhibitory impact on cGMP-PDE. The IC_{50} for cGMP-PDE/IC_{50} for cAMP-PDE was roughly 60 times that of papaverine (IC_{50} for cGMP-PDE/IC_{50} for cAMP-PDE). The concentration of Y-590 that prohibited platelet aggregation was the same as the one that inhibited cAMP-PDE. The Y-590 is a cAMP-PDE inhibitor that inhibits cAMP breakdown in platelets, so has anti-platelet properties [32].

Phosphodiesterase (PDE)-IV selective inhibitors

PDE-IV inhibitors are used as a pharmacological testing tool as well as a neuroprotective and bronchodilator drug for treating asthma and stroke. It inhibits PDE-IV the most, but it also inhibits other PDE subtypes in substantial amounts, making it either a selective PDE-IV inhibitor or a non-selective PDE inhibitor, depending on the dose. To reduce renal colic discomfort and hasten cervical dilation during labor, this supplement can be used. People who are experiencing severe symptoms, including coughing and excessive mucus, should take this drug to prevent their symptoms from worsening. PDE-IV, the major cAMP-metabolizing enzyme, is found in inflammatory and immunological cells. PDE-IV inhibitors have been proven to have anti-inflammatory actions, particularly in inflammatory pulmonary illnesses including asthma and rhinitis. They decrease the production of cytokines and other inflammatory signals by inhibiting the production of reactive oxygen species. PDE-IV inhibitors have lately been proposed as antipsychotics and may also have antidepressant properties. By boosting inadequate cAMP levels, treatment with a PDE-IV inhibitor restored partial functioning of Hippocampus-based memory processes [33-35].

Phosphodiesterase (PDE)-IV inhibitorsand pyridazine derivatives

A scaffold with a bicyclic core and pyridazine ring showed anti-inflammatory action *in vivo.* These compounds inhibited the COX-2 enzyme. The action of a chloro analog was similar to that of diclofenac [36]. The [1,2,4]triazolo[3,4-b][1,3,4]pyridazine-based PDE-IV inhibitor, a series of substituted 7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine act as PDE-IV inhibitors. The (R)-3-(2,5-dimethoxy phenyl)-6-(4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl)-7H-1,2,4] triazolo [3,4-b] [1,3,4]thiadiazine and (R)-3-(2,5-dimethoxy phenyl)-6-(4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl)-[1,2,4]triazolo[4,3-b]pyridazine (**6**) were identified as highly potent PDE-IVA inhibitors. In a panel of 21 PDE family members, both of these analogs were found to be highly selective for PDE-IV isoforms (PDE-IVA, PDE-IVB, PDE-IVC, PDE-IVD). To evaluate if they could be used as PDE-IV activity probes, both compounds were tested in a variety of cell-based assays [37]. Pyrolo [2,3-d]pyridazinones' inhibitory activity on PDE-IV subtypes A, B, and D, as well as selectivity against the Rolipram high-affinity binding site, were examined (HARBS). One drug was 8 times more active (IC_{50}=0.32 M) for PDE-IVB (anti-inflammatory) than for PDE-IVD (IC_{50}=2.5 M), assumed to be responsible for emesis. Certain drugs can decrease TNF production, and the findings reflect their PDE-IV inhibitory activity [38].

PDE-IV inhibitors are powerful anti-inflammatory drugs, although they have certain negative side effects. The researchers have been driven to find new PDE-IV inhibitors with fewer negative effects. The heterocyclic-fused pyridazine inhibited PDE-IV enzymes. The effects of pyridazine derivatives used locally in a mouse model of acute inflammation, 6-Benzyl-3-methyl-4-phenylpyrazolo[3,4-d]pyridazin-7(6H)-one (**7**), ethyl 6,7-dihydro-6-ethyl-3-methyl-7-oxo-4-phenyl-thieno[2,3-d]pyridazine-2-carboxylate (**8**) and ethyl 6,7-dihydro-6-ethyl-3-methyl-4-phenyl-1H-pyrrolo[2,3-d]pyridazine-2-carboxylate (**9**) reduced the paw edema induced by zymosan in mice as rolipram (a PDE-IV inhibitor prototype with anti-inflammatory potential) and indomethacin both decreased zymosan-induced paw edema in mice. Compounds **7** and **9** showed minimal impact on the nociceptive threshold, but compound **8** induced hyperalgesia. Furthermore, rolipram and **8** reduced locomotor activity, but 7 and 9 had no impact on the mice's locomotor activity. Because **7** and **9** had minimal influence on nociceptive thresholds or locomotor output in mice, they appear to be better acceptable for future animal tests and might be developed as an anti-inflammatory drug [39].

Pyridazine is a useful starting point for selective COX-2 inhibitors. In rat paw edema and rat pyresis models, two strong, selective, and orally active COX-2 inhibitors were found, both of which were extremely effective. pyridazine is a useful starting point for selective COX-2 inhibitors. A series of 6-aryl-4,5-heterocyclic-fused pyridazines were produced as selective PDE-IV inhibitors. These compounds showed a strong selectivity profile against the PDEIV family, as well as a decreased affinity for the Rolipram high-affinity binding site, which appears to be the cause of undesired side effects. According to the structure-activity relationships (SARs) study, the presence of an ethyl group at pyridazine N-2 is associated with the greatest potency and selectivity profile [40].

Phosphodiesterase (PDE)-V selective inhibitors

PDE-V inhibitor inhibits PDE5, a cGMP-specific enzyme that is responsible for cGMP degradation in the corpus cavernosum. These PDE inhibitors are mainly used to treat erectile dysfunction, but they also have other medicinal uses, such as treating pulmonary hypertension. It is combined with nitrous oxide (NO) or statins, providing an additional advantage [41].

Phosphodiesterase (PDE)-V inhibitors and Pyridazine Derivatives

A series of isoxazolo- pyridazines and analogs were used to test PDE inhibitors for *Leishmania mexicana*. Some chemicals showed weak PDE inhibitory action at 100 M [42]. PDE-V was isolated from human platelets, and a series of

pyrazolo[3,4-d] pyridazines (**10**) and analogs were tested as inhibitors of PDE-V, which might be beneficial as peripheral vasodilators. The majority of them had IC_{50} values ranging from 0.14 to 1.4 M. 6-benzyl-3-methyl-1-isopropyl-4-phenylpyrazolo[3,4-*d*]pyridazin-7(*6H*)-one inhibited PDE-VI with high activity and selectivity. The benzyl group at position-6 of the pyrazolo-pyridazine system is crucial. Other pyridazines, namely, pyrrole, isoxazole, pyridine, and dihydropyridine, fused with five and six-membered heterocycles, i.e. pyrrole, isoxazole, pyridine, and dihydropyridine, were tested, as well as some open variants. In addition to pyrazole, isoxazole and pyridine were shown to be the best-fused structures [43].

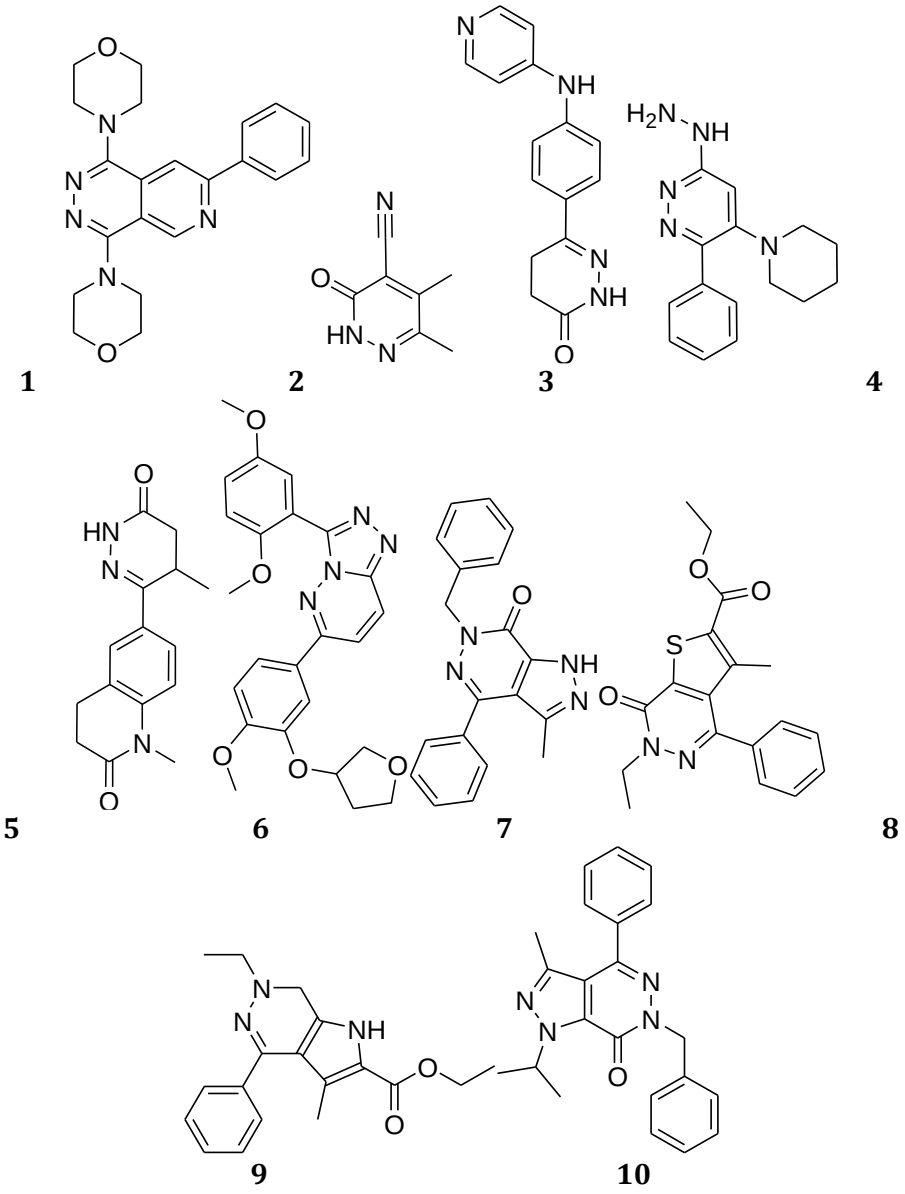


Figure 1. Structure of some pyridazine derivatives with phosphodiesterase (PDE) inhibitor activities

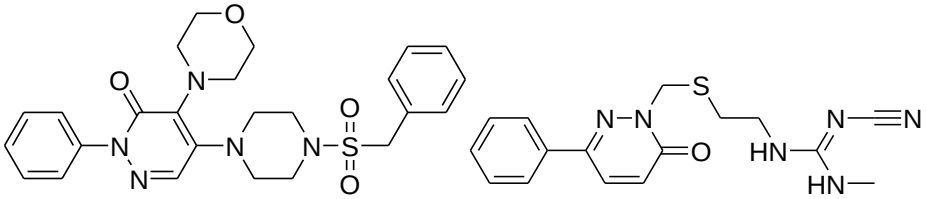
Other Activities

5-[4-(benzyl sulfonyl)piperazin-1-yl]-4-morpholino-2-phenyl-pyridazin-3(2*H*)-one (**11**) showed significant antifungal activity against *Candida glabrata* and *Candida albicans* [44]. A series of 4-(aryl/heteroaryl-2-ylmethyl) aryl/heteroaryl-2-ylmethyl) aryl/heteroaryl-2-y 2-[3-(4-substituted piperazine-1-yl)propyl]-6-phenyl-2-[3-(4-substituted piperazine-1-

yl)propyl] pyridazin-3(2H)-ones at different levels, were tested for cytotoxicity against five human cancer cell lines of different origins, namely HeLa (Cervical), SKBR3 (Breast), HCT116 (colon), A375 (Skin), and H1299 (Lung), and the IC_{50} values were calculated. The chemicals examined are most hazardous to HCT116 and HeLa cells, one of which exhibited modest cytotoxicity when tested against SKBR3. The majority of the compounds were just moderately active [45].

The antisecretory and antiulcer properties of pyridazine derivative containing a 2-cyanoguanidine moiety, as well as sulfur or an oxygen atom in the alkylene side chain, were tested. In the pylorus-ligated rat, the Shay approach was used to test all compounds for stomach antisecretory actions, and the selected compounds were tested in the stress-induced ulcer test. The antisecretory and antiulcer activity of compound 2-[[2-(2-cyano-3-methyl-1-guanidino) ethyl]thio]methyl]-6-phenyl-pyridazin-3(2H)-one (**12**) was the strongest. These chemicals are not anticholinergics or histamine H_2 receptor inhibitors [46].

1,2,3,4-tetrahydro-6-substituted-2,5,7-trimethyl-6H-pyrrolo[3,4-d]N-methylhydrazine Pyridazin-1,4-ones acted as cystostatic agents, and all compounds exhibited a minor anti-*Mycobacteriumtuberculosis* action [47]. The affinity of a sequence of pyridazine derivatives for α_1-α_2-adrenoceptors *in vitro* was assessed using radio ligand-receptor binding assays. When the fragment 4-[2-(2-methoxy phenoxy)-ethyl]-1-piperazinyl is linked in 5 positions of the pyridazine ring, a gradual increase in affinity was observed when the polymethylene chain length of this series increased up to a highest of six and seven carbon atoms, while a slight decrease was observed for the higher affinities. When the 4-[2-(2-methoxyphenoxy)-ethyl]-1-piperazinyl group is connected in 6 locations of the pyridazine ring, increasing the chain length has a distinct effect: the polymethylene chain with four carbon atoms has the strongest affinity [48].



11 **12**

Figure 2. Structure of some pyridazine derivatives

Discussion

Intracellular second messengers' cAMP and cGMP govern a multitude of physiological procedures, including vascular resistance, heart activity, visceral motility, immunological response [49], inflammation [50], neuroplasticity, vision [51], and reproduction [52]. The intracellular levels of these cyclic nucleotide second messengers are regulated by the dynamic superfamily of cyclic nucleotide PDE enzymes. PDEs that cleave the 3′,5′-cyclic phosphate moiety of cAMP and/or cGMP to create the matching 5′-nucleotide belong to the cyclic nucleotide PDEs super family of metallo-phosphohydrolases. PDEs are significant determinants in the control of cellular cAMP and/or cGMP levels by a variety of stimuli [53]. PDEs, which are ever-present, play a key role in regulating cell signaling by breaking down cAMP and cGMP [54]. PDE inhibitors are drugs that target PDE isoenzymes and prevent the metabolism of secondary messengers (cAMP, cGMP), hence enhancing the biological impact of the cell type. Non-selective and selective PDE inhibitors are being studied as possible treatments for various conditions, including sexual dysfunction, Alzheimer's disease, and other ailments [55,56]. By blocking the up-regulated PDE isozyme (s) using newly formed powerful and isozyme specific PDE inhibitors, it may be feasible to restore normal intracellular signaling selectively, resulting in treatment with fewer adverse effects [57,58]. In vitro

cardiotonic activity was linked to the 1,2-diazine mechanism in a series of novel pyridazine derivatives structurally similar to bipyridine cardiotonic, starting with 4-methyl pyridazine or 4-acetyl pyridazine, respectively [59]. pyridazine derivatives have a wide range of pharmacological properties. The basic pyridazine ring is found in compounds that are being evaluated for new drugs that have anti-inflammatory, cardiotonic, antihypertensive, analgesic, anti-platelet accumulation, vasodilatory, antidiabetic, and anticonvulsant properties, etc. [60-62].

Conclusion

This review focused on pyridazine derivatives, which have biological potential that is still being investigated in terms of creating strong active leads in medicinal chemistry. PDE inhibitors that are non-selective are used to treat some illnesses. Potent PDE selective drugs have begun to show promise in the treatment of various illnesses such as pulmonary hypertension, asthma, allergic rhinitis, psoriasis, multiple sclerosis, epilepsy, Alzheimer's disease, and schizophrenia. Cardiovascular disease is being treated with PDE-III inhibitors; inflammation is being treated with PDE-IV inhibitors, and sexual dysfunction is being treated with PDE-V inhibitors [63,54]. The development of a specific inhibitor for each type of PDE might open the way for basic research into PDE treatment and, eventually, therapeutic application to regulate unusual function. To learn more about the drug's pharmacological action, further research seems essential. These novel pyridazine compounds have far superior biological characteristics than prior generations.

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Conflict of interest

The authors declare no conflicts of interest.

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References

1. P. Uzunov, B. Weiss., *Biochim. Biophys. Acta*, 1972, *284*, 220-226. **[Crossref], [Google Scholar], [Publisher]**
2. B. Weiss., *Adv. Cycl. Nucleotide Res.*, 1975, *5*, 195-211**. [PMID: 165666], [Google Scholar], [Publisher]**
3. D.M. Essayan., *J. Allergy. Clin. Immunol.,* **2001**, *108*, 671–680. **[Crossref], [Google Scholar], [Publisher]**
4. M.P. Reilly, E.R. Mohler., *Ann. Pharmacother.*, 2001, *35*, 48-56. **[Crossref], [Google Scholar], [Publisher]**
5. B. Victoria, S. Domenico, P. Clive., *Br. J. Pharmacol.,* 2006, *147*, S252–S257.**[Crossref], [Google Scholar], [Publisher]**
6. M.R. Wilkins, J. Wharton, F. Grimminger, H.A. Ghofrani., *Eur. Respir. J.,* 2008, *32*, 198-209. **[Crossref], [Google Scholar], [Publisher]**
7. M. Asif., *Mini Rev. Med. Chem.,* 2014, *14*, 1093-1103. **[Crossref], [Google Scholar], [Publisher]**
8. M. Asif*., Curr. Med. Chem.*, 2012, *19*, 2984-2991. **[Crossref], [Google Scholar], [Publisher]**
9. M. Asif., *Central Eur. J. Exp. Biol.*, 2017, *5*, 1-19. **[PDF], [Google Scholar], [Publisher]**
10. V. Gupta, V. Kant, *Sci. Int.*, 2013, *7*, 253-260. **[Crossref], [Google Scholar], [Publisher]**
11. F. Yang, N.G. Nickols, B.C. Li, G.K. Marinov, J.W. Said, P.B. Dervan, *Proc. Natl. Acad. Sci. U. S. A.*, 2013, *5*, 1863-1868. **[Crossref], [Google Scholar], [Publisher]**
12. L. Almirante, L. Polo, A. Mugnaini, E. rovinciali, P. Rugarli, A. Biancotti, A. Gamba, W. urmann, *J. Med. Chem*., 1965, *8*, 305-312. [Crossref], [Google Scholar], [Publisher]
13. L.G. Copping, R.J. Birchmore, K. Wright, D.H. Godson, *Pest. Sci*., 1984, *15*, 280-284. [Crossref], [Google Scholar], [Publisher]
14. M. Imran, A. Asif, *Russ. J. Bioorg. Chem.,* 2020, *46*, 745-767. **[Crossref], [Google Scholar], [Publisher]**

15. M. Imran, A. Asif, *Russ. J. Bioorg. Chem.,* 2020, *46*, 726-744. **[Crossref], [Google Scholar], [Publisher]**
16. M. Asif, M. Imran, *Anal. Chem. Lett.*, 2020, *10*, 414-427. **[Crossref], [Google Scholar], [Publisher]**
17. M.T. Alam, M. Asif, *Prog. Chem. Biochem. Res.*, 2020, 3, 81-92. **[Crossref], [Google Scholar], [Publisher].**
18. M. Asif, M.T. Alam, *J. Med. Chem. Sci.*, 2020, *3*, 109-117. **[Crossref], [Google Scholar], [Publisher].**
19. J. Deree, J.O. Martins, H. Melbostad, W.H. Loomis, R. Coimbra, *Clinics (Sao Paulo),* 2008*, 63*, 321-328. **[Crossref], [Google Scholar], [Publisher]**
20. L.J. Marques, L. Zheng, N. Poulakis, J. Guzman, U. Costabel, Am. *J. Respir. Crit. Care Med.,* 1999*, 159*, 508-511. **[Crossref], [Google Scholar], [Publisher]**
21. M. Peters-Golden, C. Canetti, P. Mancuso, M.J. Coffey, *J. Immunol.,* 2005, *174*, 589-594.**[Crossref], [Google Scholar], [Publisher]**
22. D. Ukena, C. Schudt, G.W. Sybrecht, *Biochem. Pharmacol.,* 1993, *45*, 847–851. **[Crossref], [Google Scholar], [Publisher]**
23. Y. Shibouta, K. Nishikawa, S. Kikuchi. *Arzneimittelforschung*, 1978, *28*, 1112-1115. [PMID: 226101]**, [Google Scholar], [Publisher]**
24. F.P. Kupiecki, *J. Lipid Res.,* 1973, *14*, 250-254. **[Crossref], [Google Scholar], [Publisher]**
25. P.G. Baraldi, M.A. Tabrizi, S. Gessi, P.A. Borea, *Chem. Rev.,* 2008, *108*, 238–263. **[Crossref], [Google Scholar], [Publisher]**
26. M.P. González, C. Terán, M. Teijeira, *Med. Res. Rev.,* 2008, *28*, 329–371. **[Crossref], [Google Scholar], [Publisher]**
27. Y.P. de Visser, F.J. Walther, E.H. Laghmani, S. van Wijngaarden, K. Nieuwland, G.T. Wagenaar, *Eur. Respir. J.*, 2008, *31*, 633–644.**[Crossref], [Google Scholar], [Publisher]**
28. S. Thota, R. Bansal, *Med. Chem. Res.,* 2010, *19*, 808-816. **[Crossref], [Google Scholar], [Publisher]**
29. S.D. Edmondson, A.Mastracchio, J. He, C.C. Chung, M.J. Forrest, S. Hofsess, E. MacIntyre, J. Metzger, N. O'Connor, K. Patel, X. Tong, M.R. Tota, L.H. Van der Ploeg, J.P. Varnerin, M.H. Fisher, M.J. Wyvratt, A.E. Weber, E.R. Parmee, *Bioorg. Med. Chem. Lett.*, 2003, 13, 3983-3987. **[Crossref], [Google Scholar], [Publisher]**
30. L.C. Sellin, A. Alajoutsijärvi, K. Törnquist, M. Fraser, A. Pippuri, I. Ojala, *Arzneimittelforschung*, 1988, *38*, 1787-1789. **[PMID: 2854467] [Google Scholar], [Publisher]**
31. M. Campos-Toimil, I. Estévez, E. Raviña, F. Orallo, *Gen. Pharmacol.*, 1998, *30*, 201-207. **[Crossref], [Google Scholar], [Publisher]**
32. H. Mikashima, T. Nakao, K. Goto, H. Ochi, H. Yasuda, T. Tsumagari, *Thromb. Res.,* 1984, *35*, 589-594. **[Crossref], [Google Scholar], [Publisher]**
33. S.J. Kanes, J. Tokarczyk, S.J. Siegel, W. Bilker, T. Abel, M.P. Kelly, *Neuroscience,* 2007, *144*, 239-246. **[Crossref], [Google Scholar], [Publisher]**
34. C.R. Maxwell, S.J. Kanes, T. Abel, S.J. Siegel, *Neuroscience,* 2004, *129*, 101–107. **[Crossref], [Google Scholar], [Publisher]**
35. M.C. Yu, J.H. Chen, C.Y. Lai, C.Y., Han, W.C. Ko, *Eur J Pharmacol,* 2010*, 627*, 269–75 **[Crossref], [Google Scholar], [Publisher]**
36. K.A.M. Abouzid, N.A. Khalil, E.M. Ahmed, H.A.E. Abd El-Latif, M. El-Araby, *Med. Chem. Res.*, **2010**, *19*, 629-642. **[Crossref], [Google Scholar], [Publisher]**
37. A.P. Skoumbourdis, C.A.Leclair, E.Stefan, A.G. Turjanski, W.Maguire, S.A. Titus, R. Huang, D.S. Auld, J. Inglese, C.P. Austin, S.W. Michnick, M.Xia, C.J. Thomas,*Bioorg. Med. Chem. Lett.*, 2009, *19*, 3686-3692. **[Crossref], [Google Scholar], [Publisher]**
38. M.P. Giovannoni, N. Cesari, A. Graziano, C. Vergelli, C. Biancalani, P. Biagini, V. Dal Piaz. *J. Enzyme Inhib. Med. Chem.,* 2007, *22*, 309-218. **[Crossref], [Google Scholar], [Publisher]**
39. S. Pieretti, L. Dominici, A. Di Giannuario, N. Cesari, V. Dal Piaz, *Life Sci.,*2006, *79*, 791-800. **[Crossref], [Google Scholar], [Publisher]**
40. V. Dal Piaz, M.P. Giovannoni, C. Castellana, J.M. Palacios, J. Beleta, T. Doménech, V. Segarra, *J. Med. Chem.,* 1997, *40*, 1417-1421. **[Crossref], [Google Scholar], [Publisher]**
41. C.G. Vecsey, G.S. Baillie, D. Jaganath, R. Havekes, A. Daniels, M. Wimmer, T. Huang, K.M. Brown, X.Y. Li, G. Descalzi, S.S. Kim, T. Chen, Y.Z. Shang, M. Zhuo, M.D. Houslay, T. Abel, *Nature,* 2009*, 461*, 1122–1125. **[Crossref], [Google Scholar], [Publisher]**
42. V. Dal Piaz, M.C. Castellana, C., Vergelli, M.P. Giovannoni, A. Gavaldà, V. Segarra, J. Beleta,

H. Ryder, J.M. Palacios, *J. Enzyme Inhib. Med. Chem.,* 2002, *17*, 227-233. **[Crossref], [Google Scholar], [Publisher]**
43. V. Dal Piaz, A. Rascón, M.E. Dubra, M.P. Giovannoni, C. Vergelli, M.C. Castellana. *Farmaco*, 2002, *57*, 89–96. **[Crossref], [Google Scholar], [Publisher]**
44. G. Zhou, P.C. Ting, R. Aslanian, J. Cao, D.W. Kim, R. Kuang, J.F. Lee, J. Schwerdt, H. Wu, R.J. Herr, A.J. Zych, J. Yang, S. Lam, S., Wainhaus, T.A. Black, P.M. McNicholas, Y. Xu, S.S. Walker. *Bioorg. Med. Chem. Lett.*, 2011, *21*, 2890–2893. **[Crossref], [Google Scholar], [Publisher]**
45. M.S.R. Murty, B.R. Rao, K.R. Ram, J.S. Yadav, J. Antony, R.J. Anto, *Med. Chem. Res.*, 2012, *21*, 3161-3169. **[Crossref], [Google Scholar], [Publisher]**
46. T. Yamada, H. Shimamura, Y. Tsukamoto, A. Yamaguchi, M. Ohki, *J. Med. Chem*., 1983, *26*, 1144-1149. **[Crossref], [Google Scholar], [Publisher]**
47. W. Malinka. *Pharmazie*, 2001, *56*, 384-389. **[Crossref], [Google Scholar], [Publisher]**
48. S. Corsano, G. Strappaghetti, R. Barbaro, G. Giannaccini, L. Betti, A. Lucacchini, *Bioorg. Med. Chem*., 1999, *7*, 933-941. **[Crossref], [Google Scholar], [Publisher]**
49. L. Li, C. Yee, J.A. Beavo. *Science,* 1999, *283*, 848–851. **[Crossref], [Google Scholar], [Publisher]**
50. T.P. Dousa, *Kidney Int.*, 1999, *55*, 29–62. **[Crossref], [Google Scholar], [Publisher]**
51. C. Pfister, N. Bennett, F. Bruckert, P. Catty, A. Clerc, F. Pages, P. Deterre, *Cell. Signal.,* 1993, *5*, 235–241. **[Crossref], [Google Scholar], [Publisher]**
52. S.L. Jin, F.J. Richard, W.P. Kuo, A.J. D'Ercole, M. Conti, *Proc. Natl. Acad. Sci. U.S.A.,*1999, *96*, 11998-12003. **[Crossref], [Google Scholar], [Publisher]**
53. S.H., Francis, I.V. Turko, J.D. Corbin,*Prog. Nucleic Acid Res. Mol. Biol.*, 2000, *65*, 1-52. **[Crossref], [Google Scholar], [Publisher]**
54. J.M. Hetman, N. Robas, R. Baxendale, M. Fidock, S.C. Phillips, S.H. Soderling, J.A. Beavo, *Proc. Natl. Acad. Sci. U.S.A.*, 2000, *97*, 12891-12895. **[Crossref], [Google Scholar], [Publisher]**
55. M.D. Houslay, M. Sullivan, G.B. Bolger, *Adv. Pharmacol.*, 1998, *44*, 225–342. **[Crossref], [Google Scholar], [Publisher]**
56. C.S. Li, C. Brideau, C.C. Chan, C. Savoie, D. Claveau, S. Charleson, R. Gordon, G. Greig, J.Y. Gauthier, C.K. Lau, D. Riendeau, M. Thérien, E. Wong, P. Prasit, *Bioorg. Med. Chem. Lett*., 2003, *13*, 597–600. **[Crossref], [Google Scholar], [Publisher]**
57. C. Lugnier, *Pharmacol. Ther*., 2006, *109*, 366-398. **[Crossref], [Google Scholar], [Publisher]**
58. J. Cheng, J.P. Grande, *Exp. Biol. Med.*, 2007, *232*, 38-51. **[Crossref], [Google Scholar], [Publisher]**
59. N. Haider, G. Heinisch, S. Offenberger, *Pharmazie,* 1989, *44*, 598-601. **[Google Scholar], [Publisher]**
60. V.K. Chintakunta, V. Akella, M.S. Vedula, P.K. Mamnoor, P. Mishra, S.R. Casturi, A. Vangoori, R. Rajagopalan, *Eur. J. Med. Chem*., 2002, *37*, 339–347. **[Crossref], [Google Scholar], [Publisher]**
61. I. Estevez, E. Raviña, E. Sotelo, *J. Heterocyclic Chem*, 1998, *35*, 1421–1428. **[Crossref], [Google Scholar], [Publisher]**
62. M.P. Giovannoni, N. Cesari, A. Graziano, C. Vergelli, C. Biancalani, P. Biagini, V. Dal Piaz, *J. Enzyme Inhib. Med. Chem.,* 2007, *22*, 309-318. **[Crossref], [Google Scholar], [Publisher]**
63. B. Okcelik, S. Unlu, E. Banoglu, E. Küpeli, E. Yesilada, M.F. Şahin, *Int. J. Pharm. Med. Res.,* 2003, *336*, 406–412. **[Crossref], [Google Scholar], [Publisher]**
64. M.C. Toimil, I. Estevez, E. Ravina, F. Orallo, *General Pharmacol*, 1998, *30*, 201-207. **[Crossref], [Google Scholar], [Publisher]**