*Journal of Medicinal and chemical Sciences*

*Journal homepage: www.jmchemsci.com*

Review Article

# Study of heterocyclic-fused pyridazinone analogues having phosphodiestrase-IV inhibitor activities as anti-inflammatory agents

Mohammad Asif[a], Abid[b], Md. Tauquir Alam[b]

[a]*Department of Pharmacy, Guru Ram Das (PG) Institute of Management and Technology, Dehradun, (Uttarakhand), 248009, India*
[b]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Northern Border University, Rafha 91911, PO Box 840, Saudi Arabia*

**ARTICLE INFORMATION**

Received: 04 January 2019
Received in revised: 17 January 2019
Accepted: 11 June 2019
Available online: 01 April 2020

DOI: 10.26655/jmchemsci.2020.2.3

**KEYWORDS**

Phosphodiesterase - IV inhibitor
Inflammation
Pyridazinone derivatives

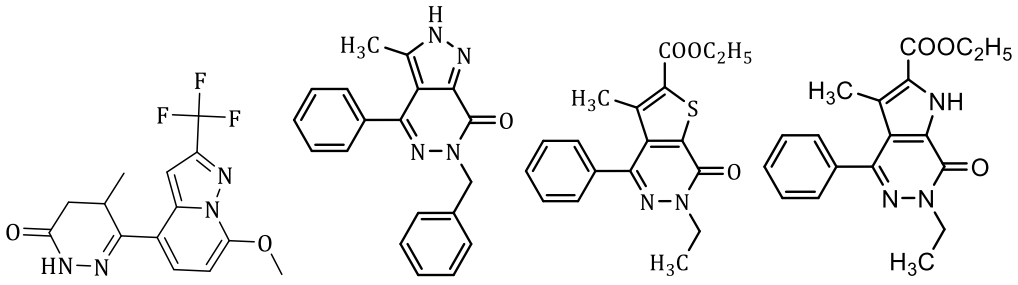
**ABSTRACT**

Phosphodiesterase-IV (PDE- IV) inhibitors which are effective anti-inflammatory agents have forced researchers to find new PDE-IV inhibitors with less adverse effects than conventional anti-inflammatory drugs. Some pyridazinone derivatives reduced inflammation by inhibiting PDE-IV enzyme and acted as anti-inflammatory agents. The new pyridazinone derivatives will be more suitable than the currently developed pyridazinone compounds for future studies and could be developed as more safe anti-inflammatory drugs for humans.



**Journal of Medicinal and Chemical Sciences:** http://www.jmchemsci.com/

## Graphical Abstract




**KCA-1490 (1)** **2** **3** **4**

Corresponding author, email: aasif321@gmail.com (M. Asif).
Tel.: +919897088910

## Introduction

Heteroaromatic scaffolds, such as pyridazine derivatives, have been shown to be 'privileged structures' in medicinal chemistry, and many drug discovery programes utilize a pyridazine as a core scaffold. Examples are far too numerous to give more than a flavor of the reported chemistry, however it should be noted that pyridazine based systems are less common in the literature than those based on pyridine or the other diazines. Various pyridazine-based heterocyclic scaffolds have been utilized in recent medicinal chemistry programs against a range of biological targets and physiological effects [1–5].

Phosphodiesterases (PDEs) enzymes are responsible for the hydrolysis of the intracellular messengers, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) causing their inactivation. The cAMP and cGMP are important signaling molecules regulating inflammatory cell response. The PDEs constitute a class of at least 11 different isozymes characterized by different functional roles [1]. The PDE-III family has dual specificity for both cAMP and cGMP nucleotides. It consists of two members, PDE-IIIA and PDE-IIIB [2]. PDE-IIIA is mainly expressed in the cardiovascular system and platelets where as PDE-IIIB is abundant in adipose tissue, hepatocytes, spermatocytes and in the renal collecting duct epithelium [3]. The PDE-IV family of enzymes is cAMP specific and consists of four subtypes (PDE-IVA to PDE-IVD) particularly abundant in brain and immunocompetent cells as neutrophils, T-lymphocytes, macrophages and eosinophils. In these cells, PDE-IV inhibitors reduce the synthesis and release of proinflammatory mediators, cytokines and active oxygen species [4]. These effects on immunocompetent cells may explain the anti-inflammatory and bronchodilatatory effects induced by PDE-IV inhibitors of inflammatory diseases [1, 5]. The uses of PDE4 inhibitors are used in the treatment of inflammatory-based disease along with asthma, chronic obstructive pulmonary disease and multiple sclerosis [6].

The prototype inhibitor rolipram is a well known PDE-IV inhibitor; it was used as an antidepressant before the discovery of its PDE-IV inhibitory activity. Rolipram exhibited anti-asthmatic and anti-inflammatory properties, but side-effects such as nausea and emesis have prevented its development as a antidepressant or anti-inflammatory drug [7]. Rolipram induced side-effects such as depression of locomotor activity and markedly enhanced the hypoactivity induced by forskolin. Furthermore, rolipram enhanced the hyperalgesia induced by local administration of several proinflammatory agents [8]. Some new PDE-IV inhibitors such as cilomilast and roflumilast but despite the anti-inflammatory effectiveness, their clinical use appears limited by adverse effects [9]. The PDE-V catalyzes the hydrolysis of cGMP, and the enzyme is abundant in lung, platelets, vascular smooth muscle and kidney. PDE-5 is the primary cGMP-hydrolyzing activity in human corpus-cavernosum tissue and it is potently inhibited by sildenafil [3]. The peripheral inhibition of PDE-V produces analgesia [10, 11] and enhances both morphine [12] and diclofenac [13] analgesia in rats. Some other kinds of drugs, like glucocorticoids, mediate important immunosuppressive and anti-inflammatory effects, but display a wide range of adverse reactions [14]. Alternative strategies should be developed for PDE-IV inhibitors, for instance, local application.

### Pyridazine with phosphodiesterase-4 (pde-4) inhibitor activity:

The pyridazine derivatives, 6-aryl-4, 5-heterocyclic-fused pyridazinones showed good

selectivity for the PDE-IV enzyme, although, to a less extent, they also can inhibited the PDE-III enzyme. Furthermore, some pyridazinones can potently inhibit PDE-V enzyme [15] like pyridazinones derivatives **1**, **2**, **3** and **4** (Figure 1). These were selected on the basis of their ability to inhibit PDE-4 enzyme [16]. The anti-inflammatory activity of **2**, **3** and **4** was compared with rolipram and with indomethacin. Rolipram induces hyperalgesia after local administration [8]. The effects of the pyridazinone derivatives on nociceptive threshold were also investigated. In order to ascertain the mechanism of **2**, **3** and **4** action, and compared to those obtained administering 8-bromo-cAMP, a stable cAMP analogue, 8-bromo-cGMP, a stable cGMP analogue, erythro-9-(2-hydroxy-3-nonyl)adenine hydrochloride (EHNA, a PDE-II inhibitor), cilostamide and cilostazol (PDE-III inhibitors) and sildenafil (PDE-V inhibitor). Rolipram reduces the spontaneous locomotor activity of animals. The (-)-6-(7-Methoxy-2-(trifluoromethyl) pyrazolo[1,5-a]pyridin-4-yl)-5-methyl-4, 5-dihydro pyridazin-3(2H)-one (KCA-1490) (compound **1**) exhibits moderate dual PDE-III/PDE-IV-inhibitory activity and exhibited combined bronchodilatory and anti-inflammatory activity. N-alkylation of the pyridazinone ring enhances potency against PDE-IV but suppresses PDE-III inhibition.

Addition of a 6-aryl-4, 5-dihydropyridazin-3(2*H*)-one extension to the *N*-alkyl group facilitates both enhancement of PDE-IV-inhibitory activity and restoration of potent PDE-III inhibition [17]. The KCA-1490 is a dual PDE-III/PDE-IV inhibitor that exhibits potent combined broncho-dilatory and anti-inflammatory activity. Potential replacement subunits for the pyrazolo[1, 5-a] pyridine core of KCA-1490 has identified the 4-methoxy-2-(trifluoromethyl)benzo[*d*]thiazol-7-yl and 8-methoxy-2-(trifluoromethyl)quinolin-5-yl derivatives as dual PDE-III/PDE-IV inhibitory agents that potently reduced histamine-induced bronchoconstriction and exhibited anti-inflammatory action [18]. The KCA-1490 is a potent combined bronchodilatory and anti-inflammatory activity and improved therapeutic window over roflumilast [19]. The heterocyclic-fused pyridazinones that inhibit PDE-IV act as anti-inflammatory agents. The 6-Benzyl-3-methyl-4-phenylpyrazolo[3, 4-d]pyridazin-7(6*H*)-one (**2**), ethyl-6, 7-dihydro-6-ethyl-3-methyl-7-oxo-4-phenyl-thieno[2, 3-d]pyridazine-2-carboxylate (**3**) and ethyl 6, 7-dihydro-6-ethyl-3-methyl-4-phenyl-1*H*-pyrrolo[2, 3-*d*] pyridazine-2-carboxylate (**4**) reduced the paw edema induced by zymosan in mice as rolipram and indomethacin. The effect after local administration of **2**, **3** and **4** in the formalin test, compound **3** induced hyperalgesic effects, whereas **2** and **4** did not change the nociceptive threshold. Furthermore, rolipram and compound **3** reduced locomotor activity, whereas **2** and **4** did not change locomotor performance of the mice. Since **2** and **4** neither affected the nociceptive threshold nor changed the locomotor performance, they appear more suitable than **3** and could be developed as an anti-inflammatory drug for humans [6]. The pharmacological effect of a series of phthalazinone/pyridazinone exhibits dual PDE-III/PDE-IV-inhibitory activities, compounds combine the pharmacophores of tetrahydro-2H-phthalazin-1-one-type inhibitors of PDE-IV and 2H-pyridazin-3-one-type PDE-III inhibitors. Most of the compounds are pharmacologically PDE-III/PDE-IV hybrids. All hybrids show potent PDE-IV inhibitory activity, whereas PDE-III values are varied. Analogues with a 5-methyl-4, 5-dihydropyridazinone moiety exhibit the highest PDE-III inhibitory activities. The highest antiinflammatory activity is displayed by phthalazinones, at a dose of 30 μmol/kg po, 46%

inhibition of arachidonic acid (AA) induced mouse ear edema. No correlation was found between PDE-III and/or PDE-IV inhibitory activity and antiinflammatory capacity [20].

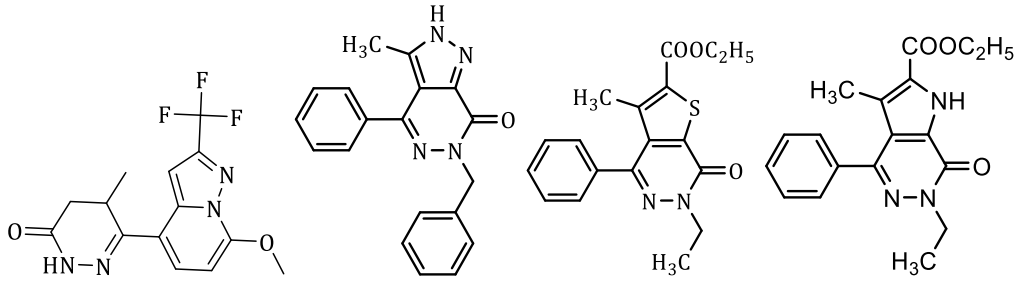



**Figure 1:** Chemical structures of some pyridazinone compounds

Pyridazinone derivatives were able to reduce the increase in paw volume induced by zymosan, although few differences were observed with drug potency between **2**, **3** and **4**. This indicated that their effectiveness followed the magnitude order: **4**>**2**>**3**. A strong dose-dependent reduction in edema development was observed in animals treated with rolipram or indomethacin. The anti-inflammatory effectiveness of the pyridazinone derivatives was confirmed by $ED_{50}$ evaluation. $ED_{50}$ values of pyridazinones in reducing paw edema induced by zymosan. Compounds **2** and **4** were as effective as rolipram and indomethacin in reducing paw edema development. Conversely, **3** was the less effective in reducing paw edema development. The $ED_{50}$ value of **3** was found to be higher. The PDE-II inhibitor EHNA (100 µg/paw) did not change the response to zymosan. The administration of the PDE-III inhibitor cilostamide (100 µg/paw) induced a slight but non significant reduction of the effect of zymosan. The PDE-V inhibitor sildenafil (100 µg/paw) was not able to change the inflammatory effects induced by zymosan. Conversely, rolipram (100 µg/paw) was able to reduce the edema formation induced by zymosan. When cilostamide (100 µg) was administered together with rolipram (100 µg), cilostamide reversed the anti-inflammatory effects induced by rolipram. Concomitant administration of rolipram (100 µg) and sildenafil (100 µg) did not change the effects of rolipram. The PDE-IV inhibitors induced hyperalgesia after local administration. In order to investigate if **2**, **3** and **4** might be able to modify the response to nociceptive stimuli after local administration, some experiments using a 1% solution of formalin as a chemical nociceptive agent. However, effects induced by a local increase of cAMP or cGMP levels. The effects induced by EHNA (PDE-II inhibitor), cilostamide and cilostazol (PDE-III inhibitors), rolipram (PDE-IV inhibitor) and sildenafil (PDE-V inhibitor), since **2**, **3** and **4** inhibit not only the PDE-IV enzyme but also, although to a lesser extent, the PDE-III and probably the PDE-V enzyme. The effects on nociceptive threshold induced by **2**, **3** and **4** are shown. The administration of the stable cAMP analogue 8-Bromo-cAMP at the dose of 10 and 100 µg potentiated the nociceptive response induced by formalin. Conversely, the administration of 8-bromo-cGMP at the dose of 10 µg and 100 µg reduced the response to formalin in the late phase of the test. The effects of EHNA,

cilostamide, cilostazol, and rolipram in formalin test, respectively. EHNA administered at doses of 10, 100 and 200 μg/paw did not change the effect of formalin in the early or in the late phase of the test. Cilostamide and cilostazol at the dose of 100 μg were able to reduce the behavioral response to formalin in the late phase of the test.

The EHNA, cilostamide (CIL), sildenafil (SIL), rolipram (ROL), rolipram and cilostamide (ROL+CIL) and rolipram and sildenafil (ROL+SIL) were administered at the single dose of 100 μg/20 μl/paw 30 min before zymosan. The effects observed after compound **3** administrations were similar to those observed after rolipram administration. Rolipram administered at doses of 10 and 100 μg was able to potentiate the effects of formalin in the late phase of the test. The effect induced by sildenafil (100 μg) is reported. Sildenafil was able to reduce the response to formalin in the late phase of the test. The concomitant administration of rolipram (100 μg) and sildenafil (100 μg) induced a slight but non significant reduction in the early phase of the test. Furthermore, sildenafil administered together with rolipram reduced the hyperalgesic effect of rolipram in the late phase of the test. Different results were obtained when cilostamide was administered together with rolipram. The concomitant management of cilostamide and rolipram induced a strong reduction of both early and late phase of the test. Effects induced by pyridazinones derivatives on locomotor activity, the highest rolipram and **3** doses a reduction in locomotor activity. Drugs administered at the dose of 10 μg/paw or at the dose of 0.1 mg/kg did not change the locomotor performance of mice. The results obtained with the highest doses (100 μg/paw and 1 mg/kg). It has been reported that rolipram reduces locomotor activity. The effects induced by **2**, **3** and **4** on locomotor activity. Compound **2** and **4** induced only a slight but statistically non-significant reduction of the spontaneous locomotor activity. Conversely, **3** reduced locomotor activity in the same way as observed after rolipram administration. Furthermore, effects induced by **2**, **3**, **4** in the formalin test.

Pyridazinone derivatives, **2** and **4**, that inhibit PDE-IV and to a lesser extent PDE-III3, are able to induce the same anti-inflammatory effects as rolipram and indomethacin after local administration. Most importantly, **2** and **4**, unlike rolipram, did not change the nociceptive threshold and did not change the motor activity of mice. The exact mechanism of action of **2**, **3** and **4**, was not known but some hypothesis can be put forward. It is well known that PDE-IV inhibitors have potent anti-inflammatory effects [7]. The anti-inflammatory effects of PDE-IV inhibitors are used in treatment of asthma, shock, autoimmune encephalomyelitis, ischemia–reperfusion injury and rheumatoid arthritis [7]. These effects appear to depend on the PDE-IV effects on cytokine production, since PDE-IV inhibitors inhibit the LPS induced TNF-α production and increase the production of the anti-inflammatory cytokine IL-10 in response to LPS in human monocytes [4]. Furthermore, PDE-IV inhibitors potently block the activation of leukocytes in vitro and modulate the expression of cell adhesion molecules in vitro [21]. However, **2**, **3** and **4** are also PDE-III inhibitors and probably also PDE-V inhibitors. The differences observed in PDE-III inhibition were obtained from guinea pig ventricular tissue. The different anti-inflammatory effectiveness observed after rolipram, **2**, **3** and **4** management is dependent on the difference observed in PDE-III inhibition. PDE-III inhibition, indeed, follows the order of potency **3**>**4**>**2**>rolipram. The cilostamide, a PDE-III inhibitor, reversed the anti-inflammatory effect of rolipram. In contrast, the PDE-V inhibitor sildenafil did not change the anti-inflammatory effect of rolipram. Thus, it is possible that

difference in PDE-III inhibition might explain why **2** and **4** behave like rolipram whereas **3** appears to be less effective in reducing edema formation induced by zymosan. The lack of effects after EHNA administration suggested that PDE-II is probably not involved in the inflammatory response evoked by zymosan.

## Discussion

The effects of treatments that increase cAMP levels on nociception have been studied in the periphery by several investigators. The peripheral injection of forskolin produced a dose-dependent hyperalgesia that was prolonged by rolipram administration. Furthermore, cAMP involvement was also demonstrated in the hyperalgesia that followed peripheral administration of prostaglandins [22]. Stable analogues of cAMP sensitized nociceptors to noxious heat and enhanced interstimulus activity in unmyelinated afferents [23]. Furthermore, animals treated spinally with 8-BromocAMP, a dose-dependent decrease in mechanical nociceptive threshold was observed [24]. The hyperalgesia induced by dopamine, PGE-2, carrageenan, bradykinin, TNFα, IL-1β, IL-6 and IL-8 was potentiated by PDE-IV inhibitors. All the above data and the results obtained in our experiments with the cAMP analogue 8-Bromo-cAMP confirm the association between hyperalgesia and elevated cAMP levels in the periphery and indicated the intracellular levels of cAMP enhancing hyperalgesia being controlled by PDE-IV. However, data from other literature indicated that the effects observed after acute administration are not still present after repetitive rolipram administration [25]. However, since chronic inflammatory diseases decrease per se the nociceptive threshold, it is important to treat these patients with drugs that do not affect nociceptive threshold as **2** and **4** appear to do. Regarding the effects induced by cGMP on nociceptive threshold, several data indicate that an increase of cGMP levels causes antinociception. When examining the role of NO/cGMP pathway in peripheral nerve endings on the modulation of murine mechanical hyperalgesia induced by PGE2, the NO donor SNAP is able to reduce the hyperalgesic effects induced by PGE-II. This anti-hyperalgesic effect is inhibited by ODQ, a soluble guanylate cyclase inhibitor. Furthermore, ODQ potentiates the hyperalgesia induced by bradykin, TNFα, IL-1β, IL-6 and IL-8 [8]. It was also reported that systemically and intrathecally administered NO synthase inhibitors reduce experimentally induced hyperalgesia, [26–28] while NO donors decrease nociceptive thresholds to mechanical and thermal stimulation [29]. The spinal level, a block of cGMP synthesis has an excitatory action on dorsal horn neurons as a block of NO-synthesis [30].

Additionally, it was reported that sildenafil (a PDE-V inhibitor), increases morphine and diclofenac antinociception in the formalin test [12,13] like sildenafil-induced peripheral antinociception via the activation of NO/cGMP pathway [10]. The antinociceptive effect of sildenafil was confirmed also in our experiments. Cilostamide and cilostazol are PDE-III inhibitors, and PDE-III hydrolyzes both cAMP and cGMP although with a 2-10 fold higher Vmax for cAMP. However, cGMP can compete with cAMP hydrolysis and this competition could play an important role in some instances [3]. Thus, depending on the different tissue or metabolic state, PDE-III inhibition might induce an increase of cAMP level or an increase of cGMP level. These hypotheses could explain both the hyperalgesic effects observed after the administration of the PDE-III inhibitor trequinsin [31] and the antinociceptive effects observed after cilostamide or cilostazol administration.

The effects observed after the concomitant administration of PDE-IV and PDE-III or PDE-V inhibitors. Indeed, the coadministration of rolipran and cilostamide induced antinociception in the formalin test. The concomitant management of rolipram and sildenafil reduced the hyperalgesic effect of rolipram. The activity on the PDE-III enzyme, **3** appears to be the most active compound. After **3** administration, reduction in the late phase of the formalin test as observed after cilostamide or cilostazol management. Furthermore, if the contemporaneous inhibition of PDE-III and PDE-IV enzyme is acting after **3** use reduction of the formalin test was observed. Reduction in nociceptive threshold was observed after **3** use and no effects after **2** or **4** uses. Thus, an involvement of PDE-III in the **2**, **3** and **4** effects on nociceptive threshold appears unlikely. Although other piridazynone derivatives are potent PDE-V inhibitors [15], compound **2**, **3** and **4** may be inhibits PDE-V. However, the results obtained from the concomitant administration of rolipram and sildenafil appear useful, since they could explain the results obtained after **2**, **3** and **4** administration. Thus, **2** and **4** might be more effective PDE-V inhibitors than **3** at reversing the hyperalgesic effects induced by PDE-IV inhibition. However, **2** and **4** might also be PDE-II inhibitors, since EHNA administration did not change the nociceptive threshold in the formalin test. It is well known that PDE-IV inhibitors display central effects and exhibit antidepressive effects. Like typical antidepressant drugs, PDE-IV inhibitors reduce the time of immobility in the forced-swim test, reverse the effects of chronic mild stress, normalize the behavioral deficits observed in olfactory-bulbecomized rats, antagonize the effects of reserpine, and potentiate yohimbine-induced toxicity. In humans, the antidepressant efficacy of PDE-IV inhibitors [32], but the therapeutic use of PDE-IV inhibitors was stopped because of several side-effects including sedation, nausea and emesis. This has prompted attempts to dissociate the antidepressant effects of PDE-IV inhibitors from the side-effects [33, 34]. Sedation in animals means a reduction in locomotor activity. A strong reduction in locomotor activity after rolipram and **3** administration. Conversely, **2** and **4** did not reduce locomotor performance of mice, and this result appears of relevance for further development of **2** and **4** as potential anti-inflammatory drugs.

## Conclusion

Recently, large numbers of pyridazinone compounds were tested against various types of diseases and disorders. Previously reported pyridazinone compounds possess almost all type biological activities like antimicrobial, analgesic, anti-inflammatory, selective and nonselective COX inhibitor, anticancer, antipyretics, antisecretory, antiulcer, antidepressants, antipsychotic, sedative-hypnotics, anticonvulsants, GABA antagonists, antihypertensive, antithrombotics, cardiotonics, PDE inhibitors and other anticipated biological and pharmacological properties. The PDE inhibitor activity activities of pyridazine compounds are well known such as PDE-III and PDE-IV were mainly reported. Some pyridazinones act as PDE-IV inhibitors and display the same anti-inflammatory effectiveness of rolipram, but with no effects on nociceptive threshold and no effects on locomotor activity of mice after topically use. The structural feature of pyridazine compounds allowed the design of many biologically active compounds with diverse pharmacological activities. Pyridazines hold considerable interest relative to the physiologically active compounds. Some compounds bearing pyridazinone rings have been reported as PDE-

IV inhibitor. Pyridazinones focused attention because of their easy functionalization and makes attractive compounds for development of new drugs in future, including some with PDE-IV inhibitor activity. However, some pyridazinones act as PDE-IV inhibitor agents and substituted pyridazine compounds has been used for development of new molecule for the effective treatment. The interest in pyridazine derivatives has established considerable attention for researcher to search for new effective drugs.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

## References

1. Asif M., Singh A., Siddiqui A.A. *Med. Chem. Res*., 2012, **21**: 3336
2. Asif M. *Chron. Young Sci*.., 2010, **1**: 3
3. Asif M. *J. Adv. Sci. Res*., 2010, **1**, 35
4. Asif M., Singh A. *Lakshmayya, Chron. Young Sci.,* 2013, 4: 1
5. Asif M. *Mini Rev. Org. Chem.,* 2013, **10**: 113
6. Huang Z., Ducharme Y., Macdonald D., Robichaud A. *Curr. Opin. Chem. Biol*., 2001, **5**: 432
7. Jeon Y.H., Heo Y-S., Kim C.M., Hyun Y-L., Lee T.G., Ro S., Cho J.M. *Cell. Mol Life Sci.*, 2005, **62**: 1198
8. Francis S.H., Turko I.V., Corbin J.D. *Prog Nucleic Acid Res. Mol Biol*., 2001, **65**: 1
9. Jacob C., Martin-Chouly C., Lagente V. *Therapie*. **2002**, 57: 163
10. Souness J.E., Aldous D., Sargent C. *Immunopharmacol.* 2000, **47**:127
11. Pieretti S., Dominici L., Di Giannuario A., Cesari N., Dal Piaz V. *Life Sci.*, 2006, **79**: 791
12. Teixeira M.M., Gristwood R.W., Cooper N., Hellewell P.G. *Trends in Pharmacol Sci.*, 1997, **18**: 164
13. Cunha F.Q., Teixeira M.M., Ferreira S.H. *British J. Pharmacol.*, 1999, **127**: 671
14. Dyke H.J., Montana J.G. *Expert Opin. Investig. Drugs.* 2002, **11**: 1
15. Jain K.N., Patil C.S., Singh A., Kulkarni S.K. *Brain. Res.*, 2001, **909**: 170
16. Ambriz-Tututi M., Velázquez-Zamora D.A., Urquiza-Marín H., Granados-Soto V. *Eur. J. Pharmacol*., 2005, **512**: 121
17. Mixcoatl-Zecuatl T., Aguirre-Bañuelos P., Granados-Soto V. *Eur. J. Pharmacol.* 2000, **400**: 81
18. Asomoza-Espinosa R., Alonso-Lopez R., Mixcoatl-Zecuatl T., Aguirre- Bañuelos P., Torres-Lopez J.E., Granados-Soto V. *Eur J Pharmacol.*, 2001, **418**: 195
19. Hunter J.A., Blyth T.H. *Drug Safety.,* 1999, **21**: 353
20. Feixas J., Giovannoni M.P., Vergelli C., Gavaldà A., Cesari N., Graziano A., Dal Piaz V. *Bioorg. Med. Chem. Lett.*, 2005, **15**: 2381
21. Dal Piaz V., Giovannoni M.P., Castellana C., Palacios J.M., Beleta J., Domenech T., Segarra V. *J. Med. Chem.,* 1997, **40**: 1417
22. Ochiai K., Takita S., Kojima A., Eiraku T., Iwase K., Kishi T., Ohinata A., Yageta Y., Yasue T., Adams D.R., Kohno Y. *Bioorg. Med. Chem. Lett.*, 2013, **23**:375
23. Ochiai K., Takita S., Eiraku T., Kojima A., Iwase K., Kishi T., Fukuchi K., Yasue T., Adams D.R., Allcock R.W., Jiang Z., Kohno Y. *Bioorg. Med. Chem.*, 2012, **20**: 1644
24. Ochiai K., Ando N., Iwase K., Kishi T., Fukuchi K., Ohinata A., Zushi H., Yasue T., Adams D.R., Kohno Y. *Bioorg. Med. Chem. Lett.,* 2011, **21**: 5451
25. Van der Mey M., Bommelé K.M., Boss H., Hatzelmann A., Van Slingerland M., Sterk G.J., Timmerman H.J. *Med. Chem.,* 2003, **46**: 2008
26. Doherty A.M. *Curr. Opin. Chem. Biol.*, 1999, **3**, 466
27. Taiwo Y.O., Levine J.D. *J. Neurosci.,* 1991, **11**: 928

28. Kress M., Rodl J., Reeh P.W. *Neurosci*, 1996, **74**:609
29. Sluka K.A. *British J. Pharmacol*., 1997, **122**: 1165
30. Francischi J.N., Yokoro C.M., Poole S., Tafuri W.L., Cunha F.Q., Teixeira M.M. *Eur. J. Pharmacol*., 2000, **399**: 243
31. Duarte I.D., Ferreira S.H. *Mediators of Inflammation*., 2000, **9**: 25
32. Meller S.T., Cummings C.P., Traub R.J., Gebhart G.F. *Neurosci.,* 1994, **60**: 347
33. Sakurada C., Sugiyama A., Nakayama M., Yonezawa A., Sakurada S., TanNo K., Kisara K., Sacurada T. *Neurochem Inter.*, 2001, **38**: 417
34. Machelska H., Przewlocki R., Radomski M.W., Przewlocka B. *Polish J. Pharmacol.*, 1998, **50**: 407
35. Hoheisel U., Unger T., Mense S. *Pain*., 2005, **117**: 358
36. Torres-López J.E., Granados-Soto V. *Eur. J. Pharmacol.,* 2005, 519: 75
37. Fleischhacker W.W., Hinterhuber H., Bauer H., Pflug B., Berner P., Simhandl C., Wolf R., Gerlach W., Jaklitsch H., Sastre-y-Hernandez M., Schmeding-Wiegel H.,*Neuropsychobiol*., 1992, **26**: 59
38. Robichaud A., Tattersall F.D., Choudhury I., Rodger I.W. *Neuropharmacol*., 1999, **38**: 289
39. Silvestre J.S., Fernandez A.G., Palacios J.M. *Pharmacol. Biochem. Behav.,* 1999, **64**: 1
40. Asif M. *Curr. Med. Chem.*, 2012, **19**: 2984

**How to cite this manuscript:** Mohammad Asif[a], Abid [b], Mohd Imran[b]. Study of heterocyclic-fused pyridazinone analogues having phosphodiestrase-IV inhibitor activities as anti-inflammatory agents. *Journal of Medicinal and Chemical Sciences*, 2020, 3(2), 109-117. DOI: 10.26655/jmchemsci.2020.2.3