Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.47750/jptcp.2023.30.17.0xyz

ANTI-INFLAMMATORY ACTIVITIES OF SOME NEWER HETEROCYCLIC DERIVATIVES

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Abstract:
Inflammation is a complicated biological reaction to damaging stimuli such as infections, poisons, and physical damage. NSAIDs and corticosteroids are commonly used to manage inflammation. NSAIDs function by reducing the COX enzyme activity, which has the role in the formation of prostaglandins, a kind of pro-inflammatory mediator. Most nonsteroidal anti-inflammatory medicines (NSAIDs) are very acidic in nature and are associated with a variety of adverse effects, the most prevalent of which is gastrointestinal damage. Moreover, recently developed NSAIDS are either non-acidic or weakly acidic drug like Nabumetone, Nemuliside and meloxicam possessed substantially lower incidence of gastric ulcers, hence it is worthwhile to explore synthesis of new non-steroidal anti-inflammatory inhibitors with an attempt that these newly developed. Inflammatory inhibitors will exhibit superiority over the already existing acidic anti-inflammatory,non-steroidal, andnon-acidicdrugs. According to researchers, some newer derivatives of quinazolinone, indole, naphthalene, thiadiazole, thiazolidinone, and azetidinone will be synthesized for effective anti-inflammatory agents than existing drugs. We have chosen four compounds quinazolinone, indole, naphthalene, thiadiazole against inflammation and checked the anti-inflammatory properties of these drug compounds on Albino rodents and its ADMET properties.

Keywords: Anti-inflammatory properties, NSAIDs, ADMET analysis, Albino rats.

Introduction

Inflammation is a complicated biological reaction to damaging stimuli such as infections, poisons, and physical damage. It is a natural defence mechanism of the immune system to protect the body from further damage(Verma et al., 1981). However, when inflammation persists, it can lead to chronic diseases such as arthritis, cancer, and cardiovascular diseases. Traditional approaches to tackling inflammation involve the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and

corticosteroids. Although effective, these drugs have limitations such as adverse side effects and reduced efficacy with prolonged use(RANI et al., 1991). Therefore, researchers have turned their attention to newer heterocyclic derivatives as a promising approach to tackling inflammation(Winter et al., 1962). Inflammation can be activated by various parameters such as infections, tissue injuries, and autoimmune disorders. The immune system responds by releasing an array of cytokines and chemokines, which attract immune cells to the site of inflammation. These immune cells, including neutrophils, macrophages, and lymphocytes, release reactive oxygen species (ROS) and other pro-inflammatory mediators, leading to tissue damage and further inflammation(Rakesh et al., 2015). Chronic inflammation can lead to tissue fibrosis and dysfunction and increase the possibility of developing chronic illnesses such as cancer(Sheehan et al., 1952). Inflammation is typically treated with NSAIDs and corticosteroids. NSAIDs function by reducing the levels of COX enzymes, which are involved in the formation of prostaglandins, a kind of pro-inflammatory transmitter. Corticosteroids act by reducing the production of cytokines and chemokines and inhibiting the activity of immune cells. However, prolonged consumption of these medications might result in negative side effects such as gastrointestinal bleeding, cardiovascular problems, and immunological suppression(Moldovan et al., 2011).

These medications had analgesic, antipyretic, and analgesic properties(Bano et al., 2011). These medications neither depress the CNS nor cause physical dependency. For millennia, salicylic acid was produced by hydrolysis of the bitter glycoside derived from willow bark (salix alba)(El-Hashash et al., 2016). In 1875, sodium salicylate was used to treat fever and discomfort; its success led to the invention of acetyl salicylic acid (aspirin) in 1899. During this time, phenacetin and antipyrine were also synthesised. The discovery of phenylbutazone in 1949 was the next important breakthrough. Indomethacin was first made available in 1963. Propionic acid derivatives (Ibuprofen and Naproxen) are another prominent class of NSAIDS(Alagarsamy et al., 2007)(Sondhi et al., 2007).

Most of non-steroidal drug are highly acidic nature and are associated with different side effects; the most common drawback of these drugs is gastrointestinal toxicity. Moreover, recently developed NSAIDS are either non-acidic or weakly acidic drug like Nabumetone, Nemuliside and meloxicam possessed substantially lower incidence of gastric ulcers, hence it is worthwhile to explore synthesis of new non-steroidal anti-inflammatory inhibitors with an attempt that these newly developed. Inflammatory inhibitors will exhibit superiority over the already existing acidic anti-inflammatory, non-steroidal, and non-acidicdrugs(Sondhi et al., 2010).

Literature review

Aspirin (acetyl salicylic acid);Indomethacin[1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-aceticacid]sulindac [5-fluoro-2-methyl-1-[4-(methyl sulfinyl) phenyl methylene]-1H-indene-3-acetic acid] ; Naproxen (6-methoxy-methyl-2-naphthalene-aceticacid) ; Nabumetone [5-methoxy-2-(2-oxabutyl)naphthalene] ; phenylbutazone (4-butyl-1,2-diphenyl-3, 5 pyrazolidine dione) ; Mefenamic acid (2-[(2,3-dimethylphenyl)amino]-benzoic acid) : ibuprofen (methyl-4-(2-methyl propyl) benzene acetic acid, are successfully utilized by clinician for the treatment of inflammatory disorders(*3-Oxo-2,3-Dihydro-1H-Indazole-4-Carboxylic Acid AldrichCPR 7384-17-0*, n.d.; Amir et al., 1999; Amir & Shikha, 2004; Çalişkan et al., 2011). These possess serious inherent side effects like gastric haemorrhage, gastric ulcer, gastric perforation, and bone marrow depression.

Newer heterocyclic derivatives are a class of compounds that contain one or more heterocyclic rings in their structure. These compounds shown anti-inflammatory properties by inhibiting the activity of pro-inflammatory enzymes and cytokines. Moreover, they exhibit minimal side effects and higher efficacy compared to conventional anti-inflammatory drugs. The development of newer heterocyclic derivatives as anti-inflammatory agents is an active area of research(Sharma et al., 2003).One of the major benefits of using newer heterocyclic derivatives for inflammation treatment is their selectivity and potency. These compounds target specific enzymes and cytokines involved in the inflammatory response, leading to reduced side effects and improved efficacy. Additionally, they exhibit wider

range of pharmacological properties such as antitumor,antioxidant, and analgesic effects, making them an attractive therapeutic option for various diseases(Biradar et al., 2010).

Newer heterocyclic derivatives can be classified into various categories based on their chemical structure and mode of action. Some of the commonly studied derivatives include benzimidazole, benzofuran, imidazole, and pyrazole derivatives(Bisht et al., 2020). Benzimidazole derivatives shown anti-inflammatory and antioxidant properties. Benzofuran derivatives inhibit the activity of COX-2 enzymes and shown anti-inflammatory, analgesic, and antipyretic effects. Imidazole derivatives exhibit anti-inflammatory and antimicrobial properties and have potential treatment of periodontitis. Pyrazole derivatives show anti-inflammatory and antitumor properties and have potential role in the therapeutics of cancer(Srivastava· et al., 1999b).

In addition to this chemical literature (1-24) several scientists have reported remarkable anti-inflammatory activity in the congeners of quinazolines, Indole, Naphthalene, Thiadiazole, Thiazolidinone, Azetidinone. In the light of above observation, some newer derivatives of quinazolinone, indole, naphthalene, thiadiazole, thiazolidinone, and azetidinone will be synthesized to get improved anti-inflammatory drugs than the existing drugs(Song et al., 1999).

Objective and scope

To develop newer potent nonsteroidal anti-inflammatory agents which might be useful in different inflammatory disorders.

Materials and methodlogy

Chemical compounds:

1. Quinazolinone (Scheme-I):

The quinazolinone nucleus has recently acquired notoriety because to its significant anti-inflammatory, anti-bacterial, anti-biotic, hypnotic, and anti-convulsant pharmacological effects. Furthermore, its impacts on numerous enzyme systems in the body, particularly those directly involved with regular operation of the (CNS) central nervous system and cardiovascular system. Additionally, this heterosystem has changeable sites (2 and 3 positions) that can be appropriately adjusted by the insertion of alternative pharmacophoric groups to generate a viable anti-inflammatory agent capable of meeting the theoretical criteria of the medicine created. As a result, we believe that inserting a triazole ring at the third position of this nucleus will allow us to synthesise several quinazolinone derivatives(Maarouf et al., 2004).

2. Indole derivatives (Scheme-II):

Indoles as well as indolinones have been found to be medicinally important versatile compounds, which possess antihypertensive, anti-inflammatory, hypnotic, antipsychotic, antifungal and antibacterial activities. Further, indomethacin and sulindac (Goodman and Gilman, 1996) are derivatives of indoles, which have been successfully utilized for the treatment of inflammation(Verma et al., 1994). Several scientists have also reported that modification (at 2/3 position) in indole nucleus by different heterocyclic moieties like thiadiazine, thiadiazole and azetidinone. It is therefore proposed to synthesize the derivatives of indole by incorporating thiadiazine, azetidinone andthiadiazole moieties at 2/3-position of indole nucleus. Further, these compounds will be tested for their anti-inflammatory and ADMET studies(El-Salam et al., 2013).

3. Naphthalene derivatives (Scheme-III):

Nabumetone, a non-acidic metabolite of naphthalene, is being utilised to treat a variety of anti-inflammatory illnesses. Substitution within the naphthalene nucleus stimulates anti-inflammatory activity(Huang et al., 2003). Furthermore, thiazole, azetidinone, and 4-oxo-thiazolidine of various heterocyclic nuclei have been demonstrated to exhibit substantial anti-inflammatory effect. It was therefore believed beneficial to synthesise a novel series of (2-oxo-azetidin-1-yl/thiazolidin-4-thiazolyl) naphthalene by inserting the thiazolyl azetidinone and thiazolyl thiazolidinone moieties at the site of the naphthalene nucleus. These chemicals will be tested for anti-inflammatory properties(Srivastava· et al., 1999a).

4. Thiadiazoles (Scheme-IV):

In recent years, some heterocyclic compounds have gained medical interest. Thiadiazoles have proven the most powerful of them. Furthermore, the substitution pattern in the thiazole nucleus is important in distinguishing biological functions such as anti-inflammatory, anti-convulsant, and cardiovascular. However, replacement by other heterocyclic moieties with azetidinone and thiazolidine rings at positions 2 and 4 were discovered to have substantial anti-inflammatory effect(Vigorita et al., 2001).

METHODOLOGY

(a) Anti-inflammatory activity:

The anti-inflammatory effect of all test compounds was assessed using a carrageenan-induced rear foot edoema evaluate with ibuprofen as a reference medication. In a nutshell, male or female rodents endure starvation overnight. A test chemical was administered to a group of 5 rodents of both sexes (pregnant females were omitted) and conventional Indomethacin (10 mg/kg) was used as relative control. After an hour, the rodents were challenged with a subcutaneous injection of 0.1 ml of 1% carrageenan solution (Sigma-Aldrich) into the plantar region of the left rear foot. The thickness of the dorso-ventral diameter of each rodent was measured using a set of mechanical thickness gauge callipers accurate to 0.001 cm^3 at 1,2,3 and 4 hours after inflammation induction. Edoema is significantly reduced in animals that have been well treated. The proportion of anti-inflammatory activity (% suppression of inflammation) was estimated using the following equation:

$$\%\text{anti-inflammatory effect}=v_c - \frac{v_t}{v_c} \times 100$$

Vt is the mean increase in foot thickness in rodents treated with the tested compounds and Vc is the mean increase in foot thickness in control group(F. Zayed & H. Hassan, 2014).

(b) ADME analysis:

The findings were validated further by performing in silico ADMET prediction on all four medications to analyse their pharmacokinetics and pharmacodynamic properties. Several clinical investigations have already studied these compounds as potent therapeutic agents. The compounds are regarded to be excellent therapeutic agents for treating inflammatory diseases. The compound SMILE was submitted to the ADMET-SAR server (http://lmmd. ecust.edu.cn:8000) for evaluation of drug likeliness and various pharmacokinetic and pharmacodynamic parameters such ashuman intestinal absorption,blood brain barrier penetration, Caco-2 permeability,cytochrome P (CYP) inhibitory promiscuity, cytochrome P450 solubility,human ether-a-go-go related genes inhibition, renal organic cation transportation, fish toxicity, acute oral toxicity,Ames toxicity, and Tetrahymena pyriformis toxicity(Malik et al., 2017).

RESULT:

The compounds were analysed on Nuclear magnetic resonance spectroscopy (NMR) for evaluation. All compounds found be at different wavelength and picometer.

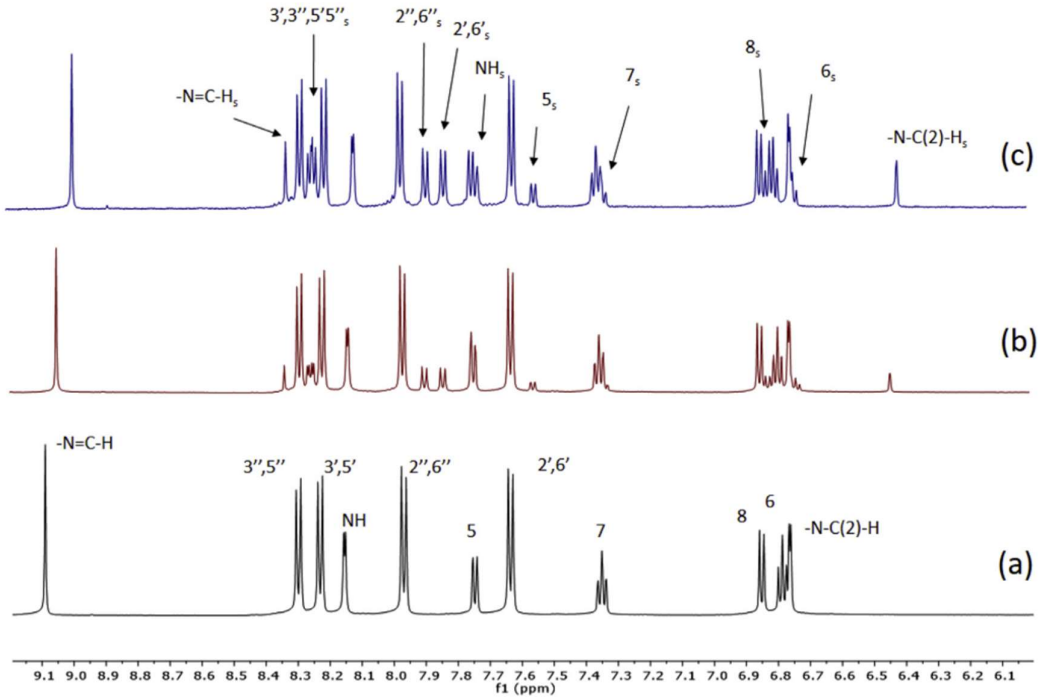


Figure 1: Quinazolinone is shown at 600 MHz frequency. Spectra of 1 H NMR in DMSO at a temperature of 25 degrees C (a) Spectra of 1 H after exposure to ultraviolet (UV) rays (365 nm): Irradiation for 60 minutes (b) Irradiation for 240 minutes (c) Lesser visible signs (described with a subscript) correlate to the irradiated syn-isomer; objectives lacking measurements belong to the primary configuration (anti-isomer). (Hricovíni&Hricovíni, 2017).

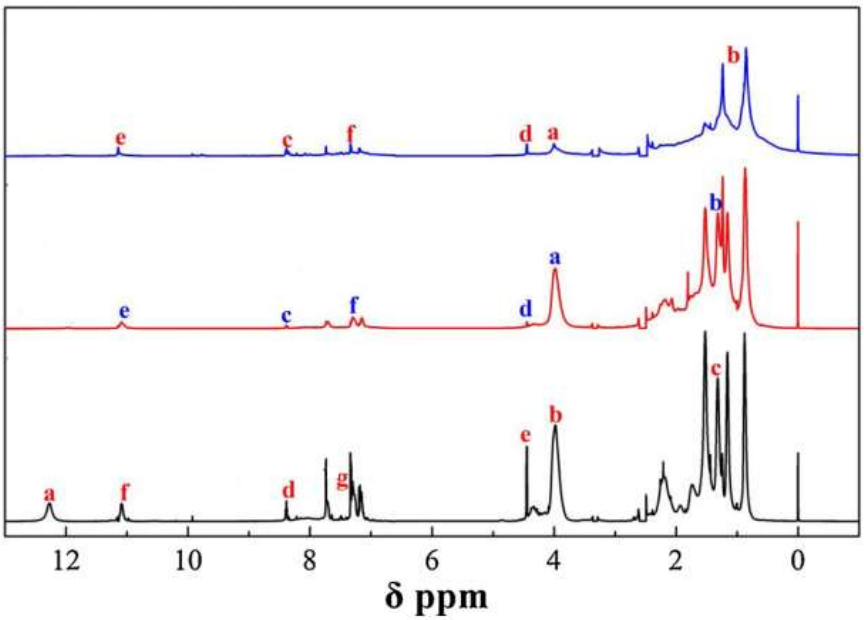


Figure 2: Indole derivatives are displayed at 600 MHz with excellent clarity. Spectra of 1 H NMR in DMSO at a temperature of 25 degrees C (a) 1 H spectrum after UV exposure (8.4ppm): Irradiation for 60 minutes (b) Irradiation for 240 minutes (c) Lesser suggestions (described with a subscript) correlate to the irradiated syn-isomer; objectives without measurements belong to the primary structure (anti-isomer)(Ni et al., 2020).

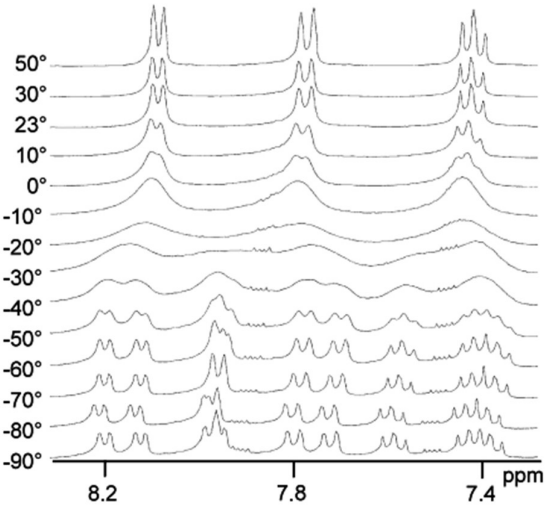


Figure 3: The 600 MHz high-quality 1 H NMR spectra of naphthalene derivatives in DMSO at various temperatures are displayed(Hoefelmeyer et al., 2002).

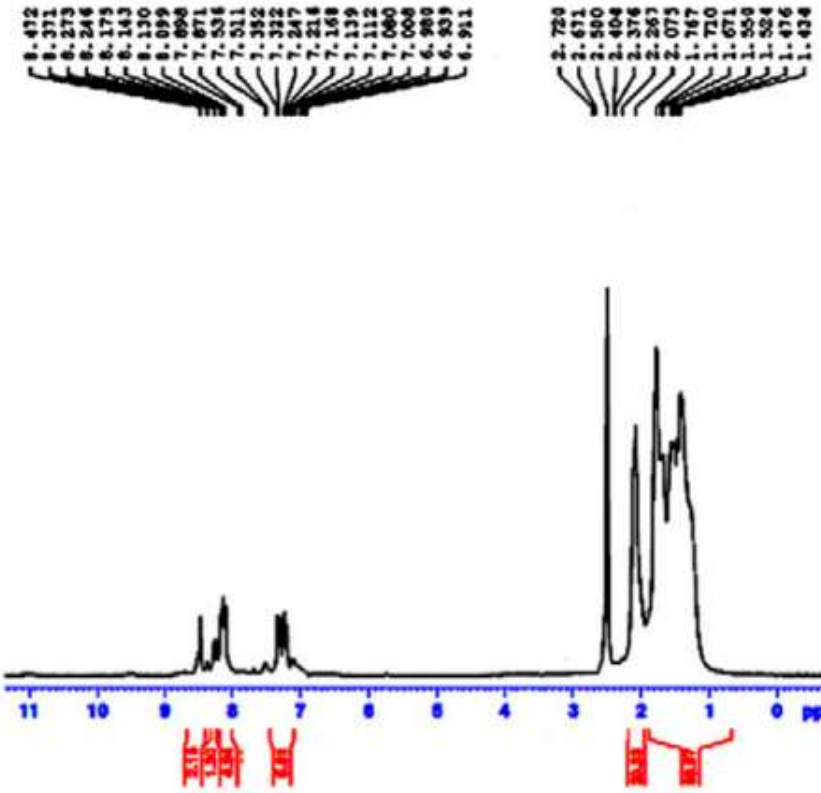


Figure 4: Thiadiazoles compound 1 H NMR spectrum(Tomi et al., 2014).

The four drugs were tested for anti-inflammatory properties against carrageenin-induced rat paw oedema at 10 and 20 mg/kg (p.o), as indicated in table 1.

An insight into the anti-inflammatory activity was measured and change in paw oedema mean was calculated. According to that the from the different four drug compounds the 1,3-thiazolidin-4-one showed the highest change in rat paw oedema and lowest change was observed in 3- [2-(2-Benzimidazolyl ethyl)] indole compound after 4 hours also.The anti-inflammatory activity was calculated the Quinazolinone showed the best anti-inflammatory activity (96.78% and 95.71%) at 10 and 20 mg/kg dosage, respectively.

The ADMET analysis was analysed for four compounds as shown in table 2 and compounds figure and SMILE is shown in Figure 1,2,3 and 4. According to ADMET analysis the all the four compounds obeys the Lipinski rule of five in terms of molecular weight (500KDa), octanol-water partition coefficient (log P 5), molecular refractivity (40 - 130), number of H-bond acceptors (10) and number of H-bond donors (5). Lipinski's rule of five examines different physiochemical characteristics. The Log P an octanol water partition coefficient should be larger than or equal to 5, the number of H-bond donors and acceptors should be 5 and 10, respectively, the molecular weight should be greater than 500, and the molecular refractivity should be between 40 and 130. Lipinski's screening is an important filter that assesses if a chemical is acceptable for drug creation(Guan et al., 2019).

Table 1: Anti-inflammatory activity of the four compounds.

Compound	**Doses (mg/kg) (P.O)**	**Change in paw oedema mean ± SEM in**				**% Activity**			
		1st hr	2nd hr	3rd hr	4th hr	1st hr	2nd hr	3rd hr	4th hr
Quinazolinone	10	3.28 ± 0.28	3.73 ± 0.44	2.33 ± 0.41	1.63 ± 0.48	94.82	96.78	95.71	92.64
	20	1.33 ± 0.25	2.80 ± 0.39	1.73 ± 0.39	0.73 ± 0.39	87.22	95.71	94.22	83.56
3-[2-(2-Benzimidazolylethyl)] indole	10	0.120+ 0.012	0.034+ 0.005	0.017+ 0.003	0.07+ 0.007	89.50	79.01	56.79	54.36
	20	0.139+ 0.013	0.065+ 0.010	0.033+ 0.006	0.139+ 0.010	74.24	64.02	43.70	41.30
2-oxo-azetidin-1-yl	10	0.28±0.02	0.21±0.02	0.18±0.02	0.15±0.02	15.15	32.25	40.00	48.27
	20	0.26±0.02	0.19±0.02	0.15±0.02	0.09±0.02	21.21	38.70	50.00	68.96
1,3-thiazolidin-4-one	10	21.8 ± 5.6	52.0 ± 5.8	45.8 ± 3.5	27.6 ± 2.3	59.67	22.58	25.8	9.67
	20	24.1 ± 2.5	44.0 ± 3.4	56.1 ± 7.1	40.0 ± 3.1	19.35	30.64	11.29	16.11

Table 2: ADMET analysis of the four compounds.

Compound	**ADME Properties**									
	Human Intestinal Absorption	Caco-2	BBB permanent	CYP1A2 inhibitor	CYP inhibitory promiscuity	Ames mutagenesis	Human Ether-a-go-go-Related Gene inhibition	Acute oral Toxicity	Fish aquatic toxicity	Tetrahymena pyriformis pIGC50 (ug/L)
Quinazolinone	1.0000	0.8312	0.9250	0.8491	0.8121	0.8500	0.8096	0.7427	0.7654	0.223
3-[2-(2-Benzimidazolyl ethyl)] indole	0.9974	0.6733	0.8000	0.8303	0.7977	0.5100	0.8107	0.6708	0.6413	1.316
2-oxo-azetidin-1-yl	0.7495	0.7954	0.6500	0.8015	0.9822	0.6354	0.4571	0.5795	0.4152	-0.795
1,3-thiazolidin-4-one	0.9878	0.5000	0.9750	0.6526	0.8541	0.6600	0.7951	0.4489	0.9778	-0.377

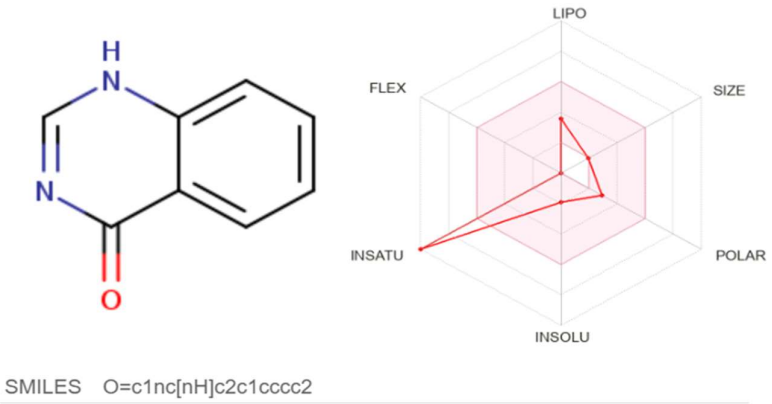
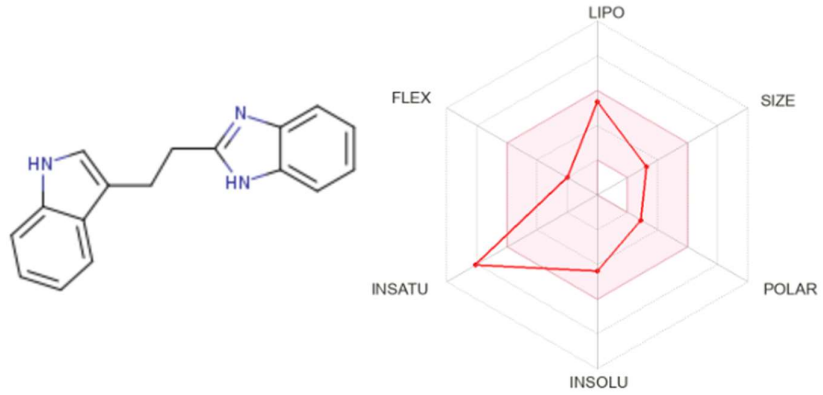
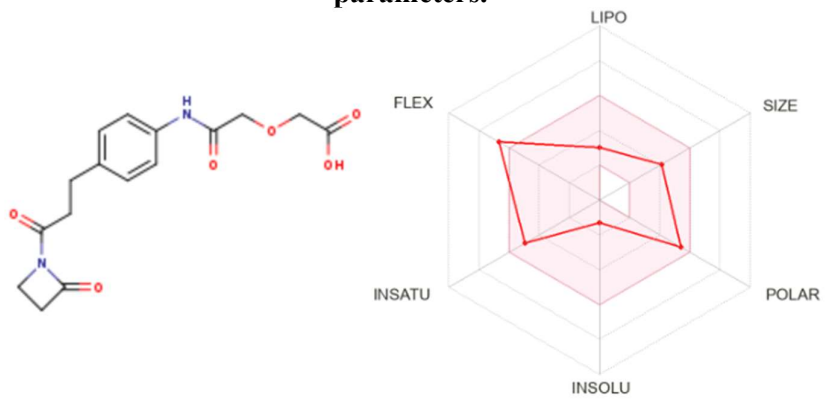


Figure 1: Quinazolinone compound, its SMILE and other ADMET parameters.



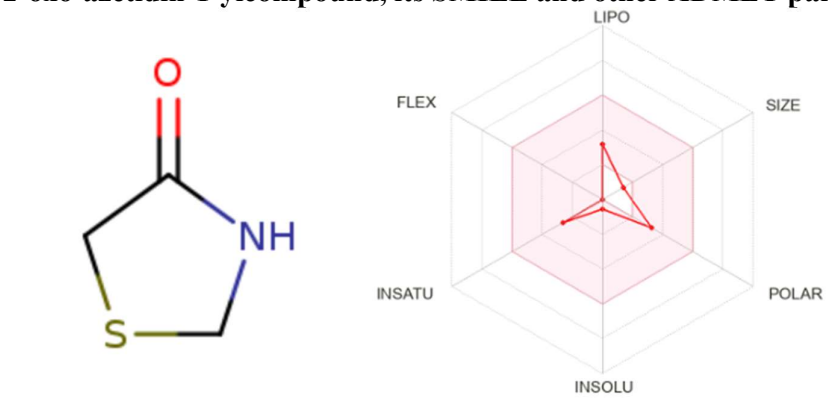
SMILES c1ccc2c(c1)c(CCc1nc3c([nH]1)cccc3)c[nH]2

Figure 2: 3-[2-(2-Benzimidazolylethyl)] indole compound, its SMILE and other ADMET parameters.



SMILES O=C(Nc1ccc(cc1)CCC(=O)N1CCC1=O)COCC(=O)O

Figure 3: 2-oxo-azetidin-1-ylcompound, its SMILE and other ADMET parameters.



SMILES C1SCNC1=O

Figure 4: 1,3-thiazolidin-4-onecompound, its SMILE and other ADMET parameters.

Conclusion and discussion

From our study we conclude that the Quinazolinone compound shown the best anti-inflammatory properties and shows ADMET properties. We can use this drug further as anti-inflammatory drug. In further discussion, inflammation is a complex biological response that can lead to chronic diseases if left untreated. Traditional approaches to tackling inflammation, such as NSAIDs and corticosteroids, have limitations such as adverse side effects and reduced efficacy with prolonged use. Newer heterocyclic derivatives are a promising approach to tackling inflammation, owing to

their selectivity, potency, and minimal side effects. Clinical studies have shown that these compounds exhibit potent anti-inflammatory, antioxidant, and antitumor activities, with potential in the treatment of various diseases. However, further research is required to fully understand the safety and efficacy of these compounds.

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