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Synthesis and *in silico* ADMET evaluation of new thiazole and thiazolidine-4-one derivatives as non-ulcerogenic analgesic and anti-inflammatory agents

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Abstract: A series of 1,3-thiazoline-4-one derivatives bearing 2-phenoxyphenyl moiety, were synthesized as potential new analgesic and anti-inflammatory agents. The structures were confirmed by FT-IR, NMR, and Mass spectra. The abdominal constriction (writing) test was selected to evaluate analgesic activity and results showed that nearly all of them were active, and the most potent was **10m** with 96% inhibition when compared to the control. The best compounds were selected to investigate the anti-inflammatory activity by carrageenan induced rat paw edema test. The results showed that compounds **8** and **10h** were active from the 2nd to 5th hours of assessment. The ulcerogenic evaluation of two selected compounds showed that they are comparable with the vehicle control group and without any ulcerogenic effect potential. The target compounds showed an acceptable *in silico* ADME profile.

Keywords: thiazoline; fenamate; writing test; carrageenan induced edema; cyclooxygenase.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are important medications for the treatment of arthritis. NSAIDs alleviate the pain and swelling related to arthritis by prevention of the arachidonic acid metabolism through the

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cyclooxygenase (COX) enzyme pathway and, as a result, thereby, the production of prostaglandins (PGs), which stimulate pain receptors.[1-2]

Additionally, there is a close relationship between some leukotrienes (LTs), as the 5-Lipoxygenase metabolites and the induction of hyperalgesia seen in the inflammation pathway by lowering the sensitivity of C fibers.[3-4]

The LTs and PGs are involved in the acute ulcer caused by NSAIDs. Therefore, compounds that, in turn inhibit both 5-LO and COX alleviate side effects and potentiate the pharmacological activity in the treatment of inflammation. There are some findings about the induction of dual 5-LOX/COX inhibitory activity of known NSAID, mefenamic acid, and its corresponding fenamate-like derivatives by changing their acidic moiety to hydrazone or different heterocyclic rings.[1,5-10] Besides the anti-inflammatory activity of fenamate-like structures, antiepileptic and CCK-B antagonistic effects have been reported in compounds bearing these moieties.[11-12]

However, thiazoline-4-one is another moiety with known biological activities including antimicrobial[13], antiparasitic[14], antidiabetic[15], antiviral[16], anticancer[17], antioxidant[18], antiseizure[19] and anti-inflammatory properties[20] (Figure 1). Amongst different thiazolidinones, the arylydene substituted derivatives are more attractive for medicinal chemists due to their pharmacological potential. The 4-arylidene conjugated with carbonyl moiety of this kind of heterocyclic ring can prepare an electrophilic position to the nucleophilic groups in different proteins and enzymes[21]. On this basis and using molecular hybridization of previously reported active compounds **1-3** (Figure 2)[22], herein the new 5-arylidene thiazoline-4-ones bearing fenamate-like structure **10a-10n** were designed, and synthesized and their biological activities were evaluated.

EXPERIMENTAL

Chemistry

Thin layer chromatography was applied to control the reaction and purity of the products. Melting points were taken on an electrothermal IA 9300 capillary melting-point apparatus (Ontario, Canada) and are uncorrected. FT-IR spectra were recorded on Shimadzu FT-IR-8400 instrument in KBr disk. ^{1}H NMR spectra were recorded on Bruker AC-400 MHz FT NMR (Brucker, Rheinstetten, Germany). 13C-NMR spectra were recorded on a Varian Unity INOVA 500 MHz spectrometer**.** Mass spectra were obtained using a Finnigan Mat TSQ-70 spectrometer at 70 ev (FinniganMat, Bremen, Germany) and a 5973 network mass selective detector (Agilent technology).Elemental analysis was performed with a Perkin-Elmer Model 240-c apparatus (Perkin Elmer, Norwalk, CT, USA). The results of the elemental analyses (C, H, N) were within ± 0.4% of the calculated amount. Compound **6** was synthesized as reported previously.[23]

Synthesis of (2-phenoxybenzylidene)thiosemicarbazide (7).

A suspension of 2-phenoxybenzaldehyde **6** (1g, 5mmol), thiosemicarbazide (0.45g, 5mmol) and ethanol (10 mL) was refluxed for 3 h. After cooling, the resulting thiosemicarbazone was removed by filtration and washed with water to give compound **7**.

Synthesis of (2-phenoxybenzylidene)-2-(4-phenylthiazol-2-yl)hydrazine (8).

A mixture of thiosemicarbazone **7** (1g, 3.7 mmol), phenacyl chloride (0.57 g , 3.7 mmol) and dry sodium acetate (1.5 g, 18 mmol) was dissolved in 15 mL of dry1,4- Dioxan. The solution was heated under reflux for 12 h. The mixture was cooled and diluted with water to give compound **8**.

Synthesis of 2-(-2(2-phenoxybenzylidene)hydrazinyl)thiazol-4(5H)-one (9).

A mixture of thiosemicarbazone **7** (1g, 3.7 mmol), and ethyl bromoacetate (0.4 mL, 3.7 mmol), dry sodium acetate (1.2 g, 14.7 mmol) was dissolved in 15 mL of dry1,4- Dioxan. The solution was heated under reflux for 15 h. The mixture was cooled and diluted with water to give compound (**9**).

General procedure for the preparation of 1,3-thiazoline-4-ones (10a–10n).

A mixture of thiazolone **9** (1g, 3.2 mmol) in glacial acetic acid (10 mL), corresponding aldehydes 10a-10s (3.4 mmol), and anhydrous sodium acetate (1g, 12.8 mmol) were stirred under reflux for 18 hrs. The end of the reaction was observed by TLC, then cold water was added to the reaction mixture, and the resulting precipitate was filtered, washed water, and crystallized by ethanol. The structural parameters of **10a-10n** were evaluated by FT-IR, N-NMR, Mass spectra and have been reported at supplementary material.

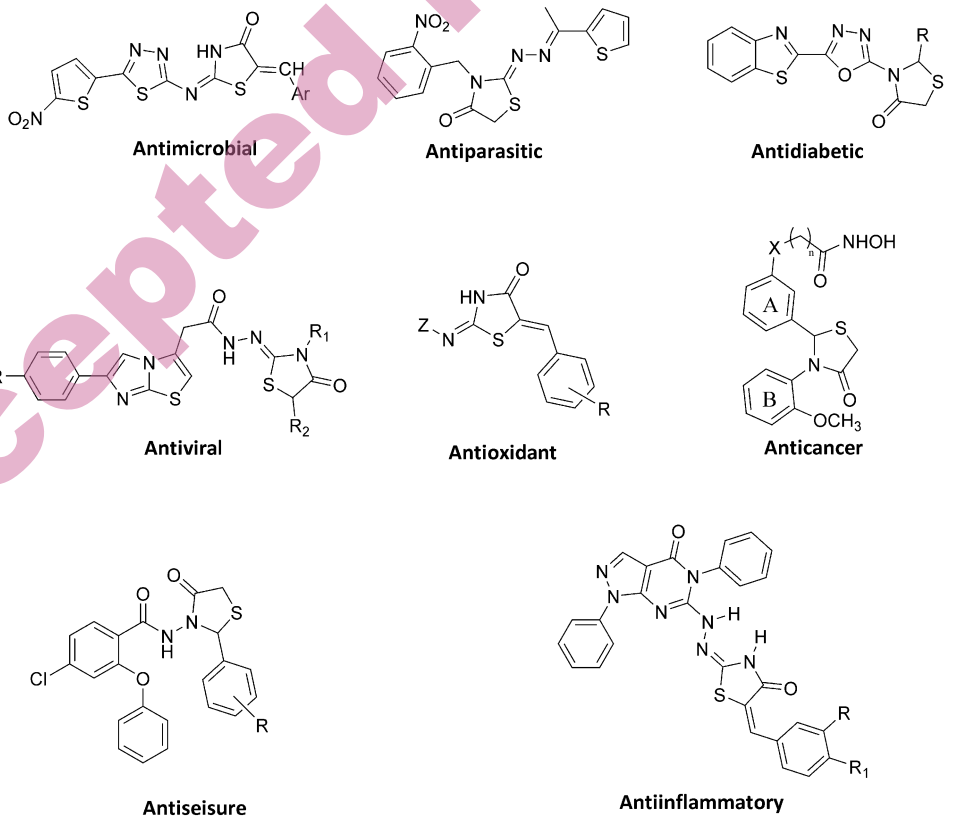


Figure 1. Biologically Active compounds bearing thiazolidinone ring.

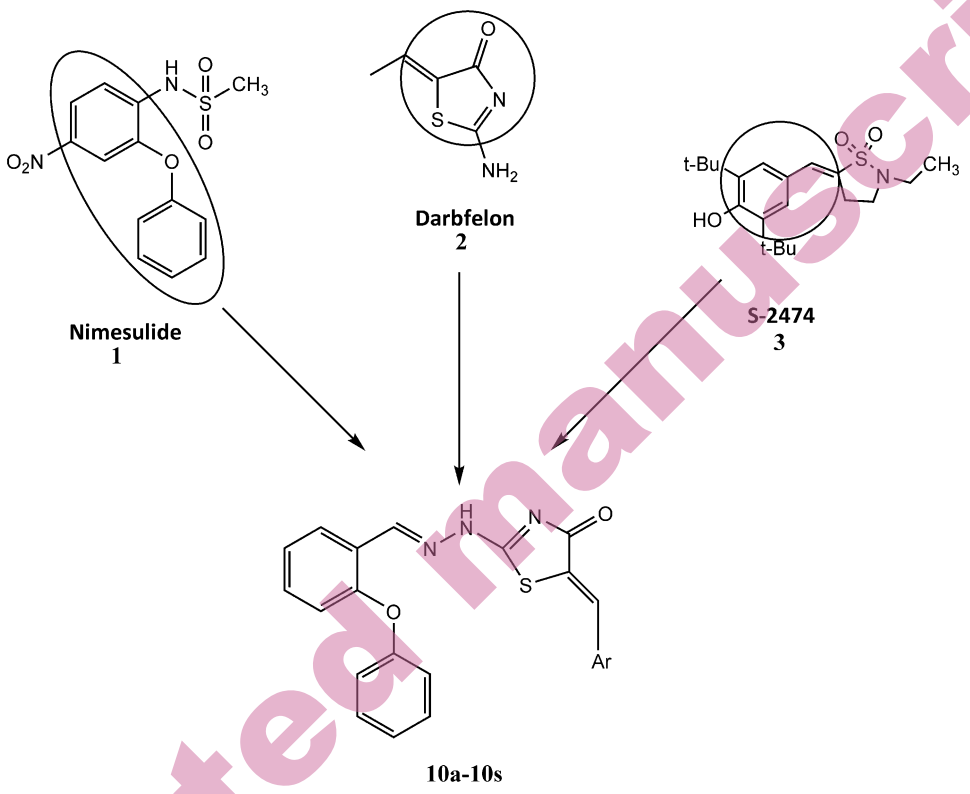


Figure 2.The design of compounds **10a-10n** according to the pharmacophoric pattern of well-known analgesic agents.

RESULTS AND DISCUSSION

Compound **6** was prepared by the reaction of Salicylaldehyde **4** with bromobenzene **5** in dry DMF.[23] The reaction of **6** with thiosemicarbazide gave the thiosemicarbazone **7.** Treatment of **7** with phenacylchloride afforded compound **8.**[25] The thiazolidinone **9** was obtained through the cyclization of **7** by ethyl bromoacetate. The final derivatives (**10a-10**n**)** were prepared via the reaction of **9** with different aldehydes (Figure 3, Table I).[26]

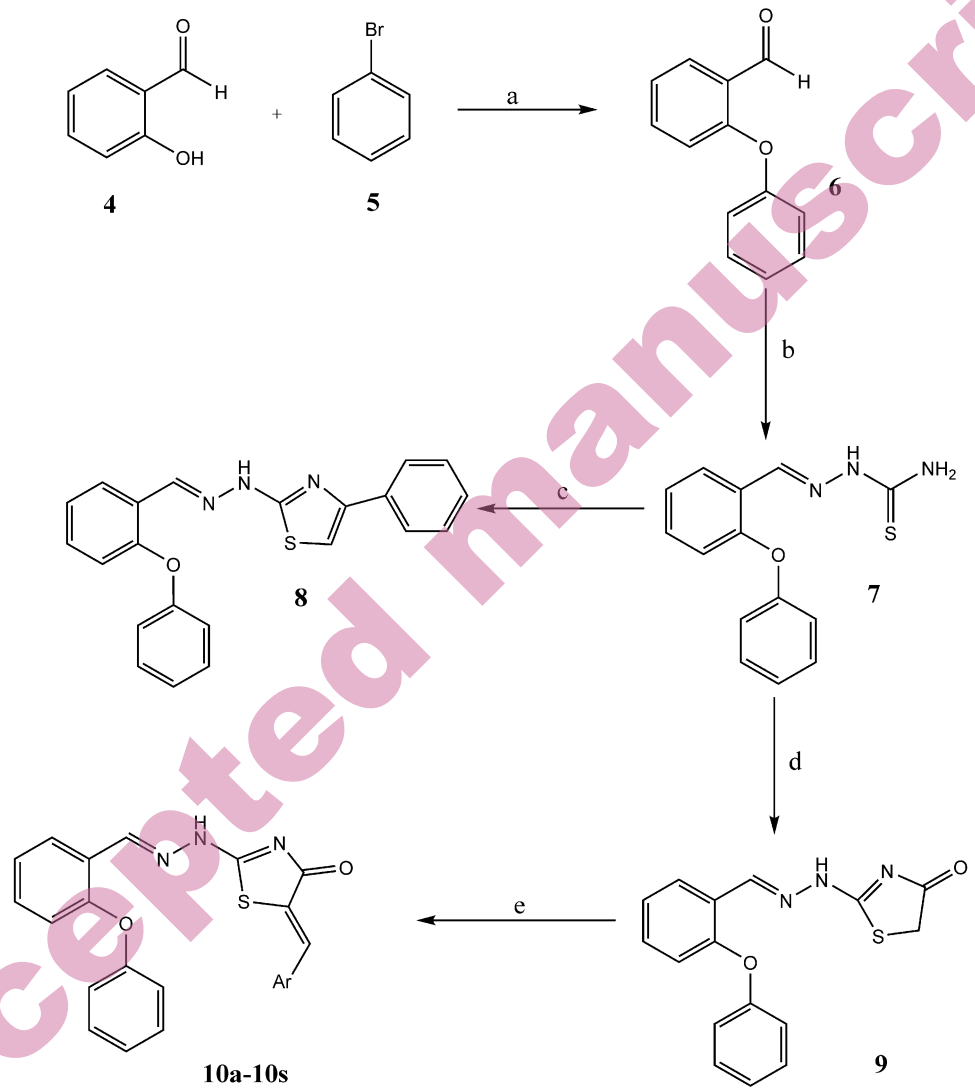
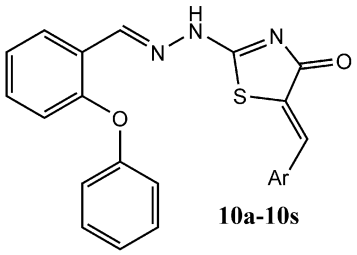
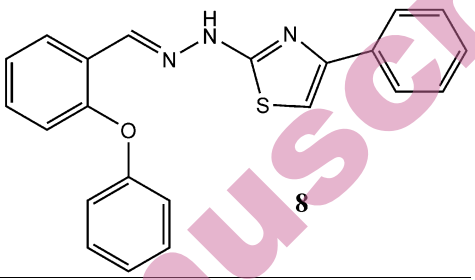


Figure 3. Synthesis of Compounds 10a-10s: a) Cu, CuCl, K_2CO_3, DMF, reflux; b) $NH_2NHCSNH_2$, EtOH, reflux; c) Ph-$COCH_2Cl$, 1,4-Dioxan, reflux; d) $BrCH_2CO_2Et$, 1,4-Dioxan, reflux; e) ArCHO, AcONa, AcOH, reflux.

TABLE I. The physical data of Compounds **10a-10n**



10a-10s



8

Compounds	Ar	Melting point (°C)	Yield (%)	Mw	Mol. formula
8	-	136-137	51	371	$C_{22}H_{17}N_3OS$
10a	Phenyl	249-251	42	399	$C_{23}H_{17}N_3O_2S$
10b	4-Fluorophenyl	186-188	50	417	$C_{23}H_{16}N_3FO_2S$
10c	4-Chlorophenyl	227-229	51	433.5	$C_{23}H_{16}N_3ClO_2S$
10d	4-Bromophenyl	273-275	67	478	$C_{23}H_{16}N_3BrO_2S$
10e	2-Hydroxyphenyl	169-171	45	415	$C_{23}H_{17}N_3O_3S$
10f	4-Hydroxyphenyl	213-215	50	415	$C_{23}H_{17}N_3O_3S$
10g	4-Methylphenyl	205-207	50	413	$C_{24}H_{19}N_3O_2S$
10h	4-Methoxyphenyl	174-176	71	429	$C_{24}H_{19}N_3O_3S$
10i	4-Thiomethylphenyl	213-215	62	445	$C_{24}H_{19}N_3O_2S_2$
10j	4-Nitrophenyl	251-253	47	444	$C_{23}H_{16}N_4O_4S$
10k	Furyl	186-188	37	389	$C_{21}H_{15}N_3O_3S$
10l	2-Pyridyl	209-211	36	400	$C_{22}H_{16}N_4O_2S$
10m	3-Pyridyl	260-262	42	400	$C_{22}H_{16}N_4O_2S$
10n	2-Phenoxyphenyl	219-221	50	491	$C_{29}H_{21}N_3O_3S$

The thiazolidinone ring formation was confirmed through the FT-IR spectrum by finding of carbonyl in 1712 cm^{-1}, and aliphatic CH2 in 3.85 ppm in ^{1}H-NMR. The structures of target compounds were confirmed by finding carbonyl vibrations over 1700 cm^{-1}, and in ^{1}HNMR, olefinic CH, which was found in some compounds separately from the aromatic protons over 7.50 ppm and the imine proton N=CH that was well defined between 8.50-8.90 ppm. The imine proton has been appeared as two singlet signals in **10a**, **10b**, **10c**, **10e**, **10g**, **10h**, **10i**, **10k**, **10l**, **10m,** and **10n** that proves on the formation of both *Z* & *E* isomers. However, the chemical shift of the olefinic proton in different compounds is an emphasis on the *Z* configuration formation of the target derivatives over this band.[27]

As seen in Table II, nearly all the target compounds showed significant analgesic activity in comparison to control, and amongst them, **10m** were more potent than mefenamic acid.

TABLE II. The Effects of Compounds **10a-10n** and mefenamic acid in the abdominal constrictions induced by acetic acid in mice.

Compound	Constriction No. (mean ± SEM)[1]	Inhibition (%)[2]	P value
Control	63.5±16.77	-	-
mefenamic acid	8.16±3.31	87.13	P < 0.001
8	08.17±02.31	87.13	P < 0.001
10a	83.17±23.57	30.97	P > 0.05
10b	34.00±03.41	46.45	P < 0.001
10c	16.50±06.75	74.01	P < 0.001
10d	26.50±12.69	58.26	P < 0.001
10e	20.00±03.41	68.5	P < 0.001
10f	11.00±02.53	82.67	P < 0.001
10g	20.67±03.88	67.44	P < 0.001
10h	13.17±06.01	79.25	P < 0.001
10i	25.67±14.69	59.57	P < 0.001
10j	25.33±07.39	60.11	P < 0.001
10k	20.00±05.33	68.5	P < 0.001
10l	21.50±03.45	66.14	P < 0.001
10m	02.17±01.72	96.58	P < 0.001
10n	15.00±04.24	76.38	P < 0.001

[1] number of animals in each group n= 6; [2] % inhibition Obtained by comparison with vehicle control group

SAR studies showed that bioisosteric replacement of phenyl with some heterocyclic moieties (compounds **10k-10m**) can lead to more potent compounds. In general, substituted phenyl ring is better than unsubstituted ring. Both electron-donating and withdrawing groups on the para position of the phenyl ring are tolerable. The Comparison of **10e** and **10f** proves that substitution on para position of phenyl ring with electron donating groups is preferable to ortho.

The pharmacological evaluation of the synthesized compounds showed that most of them were active anti-inflammatory agents in comparison to control, and the activity profile of compound **10h** was similar to mefenamic acid (Table III).

TABLE III. The anti-inflammatory activity of the selected compounds in the carrageenan-induced paw edema model in rat

Compound	Increase in paw volume[1] (%)±SEM				
	1 h	2 h	3 h	4 h	5 h
Control	30.29±3.146	49.87±2.10	52.67±2.61	50.87±2.33	46.37±1.85
Mefenamic Acid	21.18±1.34	27.37±1.64***	25.7±1.88***	22.66±1.43***	19.69±0.70***
8	14.72±0.87***	21.81±1.09***	32.71±1.60***	37.83±0.80**	33.12±1.27**
10c	23.37±1.86	30.46±1.54***	36.15±0.82***	41.25±0.65	35.21±0.44*
10f	20.54±1.52	32.63±2.76**	41.74±3.49	49.38±4.51	46.07±4.15
10h	22.14±1.94	26.00±2.43***	29.98±3.75***	30.85±5.27**	27.44±5.27**
10m	23.32±1.39	32.56±4.43**	34.12±5.22*	33.06±6.59*	29.08±6.53**
10n	30.53±1.79	34.34±3.15**	39.13±1.21*	44.98±2.97	42.47±2.58

[1] number of animals in each group n= 6
***p<0.001 **p<0.01 *p<0.05 Compared to Control Group

However, only compound **8** was effective from 1st to 5th hours. It could be deduced by comparison of results that both electron-withdrawing and donating groups on the benzylidene moiety are tolerable. The effectiveness of **10m** emphasizes the possibility of the replacement of phenyl with other heteroaromatic ring systems. Compounds **10c** and **10k** were evaluated for their acute ulcerogenic activity. A significant reduction in ulcerogenic activity without any stomach ulceration was observed the standard drug in both compounds compared to indomethacin (Table IV). However, indomethacin as the standard drug displayed a high score of 4 as shown in Table IV. In contrast, neither 10c nor 10k induced significant ulceration in comparison to control. The anti-oxidative activity of thiazolidinone and thiazoline rings could be the reason of their low ulcerogenic properties.[28]

TABLE IV. The ulcerogenic activity observed on gastric mucosa of rats

Compound	UlcerogenicActivity[1,2] (Mean±SEM)
Control	0.00±0.00
Indomethacin	3.67±0.21
10c	0.00±0.00***
10k	0.00±0.00***

[1] Number of animals in each group n= 6
[2]Ulcerogenic Activity=The mean score of control and each treated group-
*** p<0.001as Compared to indomethacin Group.

Insilico ADMET Evaluation

Eight pharmacokinetic parameters for forecasting oral bioavailability were calculated by the Swiss ADME online program (www.swissadme.ch).[29] As shown in Table SI (supplementary files), all compounds except **10i**, **10j,** and **10n** have high GI absorptions.

One of several tools for evaluating properties such as toxicity risk, log p, log s, fragment-based drug-likeness, and overall drug score is Osiris Property Explorer (OPE) (https://www.organic-chemistry.org/prog/peo/), which is a web-based program. The OPE study demonstrated that except for compound **8,** which showed high risks of tumorigenic effects, compound **10f,** which showed high risk of reproductive effects, and compound **10k** which showed the high risk of mutagenic effects, all compounds are supposed to be non-mutagenic, non-tumorigenic, non-irritant with no reproductive effects. The potential drug-likeness values of all compounds were positive (3.04-5.67) except for **10j** which was negative; hence, their similarity to traded drugs was more than commercial chemicals Table SII (supplementary files). Another tool for assessing the ADMET properties of compounds is a comprehensive platform called admetSAR3.0, which is utilized for search, prediction, and optimization purposes.[30] Due to the admetSAR3.0, all compounds except for **8**, **10g**, **10h**, **10m**, **10n**, **10o**, and **10s** which display low oral bioavailability, are expected to exhibit high oral absorption. Comparing the SwissADME online program with admetSAR3.0, both tools are an indicator of a poor oral bioavailability of derivative **10m**. Furthermore, admetSAR3.0, providing a more comprehensive and precise assessment, reveals poor oral absorption for compounds **8**, **10g**, **10h**, **10n**, **10o**, and **10s**. Regarding the toxicity risks predicting by admetSAR3.0, all compounds, excluding **8**, are anticipated to be non-carcinogenic, non-irritant with no respiratory toxicity. Compound 8 stands out as carcinogenic. Additionally, a comparison between Osiris Property Explorer (OPE) and admetSAR3.0 tools, reveals the mutual carcinogenicity of compound **8.** OPE also highlights compound **10c** for tumorigenicity. According to admetSAR3.0, compounds **8**, **10a**, **10g**, **10h**, **10k**, and **10m** are supposed to have no reproductive toxicity. Conversely, other compounds are anticipated to exhibit harmful reproductive effects. Notably, while OPE identifies compound **10h** with high risks for reproductive effects, admetSAR3.0 categorizes this derivate as posing low risk Table SIII (supplementary files).

Pharmacological Evaluations

All ethical manners for the use of laboratory animals were considered carefully, and the study protocol was approved by the IAU-TMS ethical committee. The Analgesic activity was determined *in vivo* by the acetic acid induced abdominal constriction (writing) test on mice, and all the procedures, statistical analysis, and calculation of inhibition percent were performed conforming to our previously expressed research.[5] In Writing test significant reduction in constrictions when compated to control is an accepted parameter, showing the analgesic potency of a compound and the procedure was explained in supplementary material.

The most potent compounds in the previous test were selected for further evaluation. Anti-inflammatory activity was assessed by carrageenan-induced rat

paw edema test.[6,23] In mentioned test the ability of compound to significantly inhibit the paw edema induced by carrageenan could be considered as an important parameter of anti-inflammatory activity and the procedure was described in supplementary material. Ulcerogenic potential of the two selected target compounds **10c** and **10k** were evaluated and scored by the method of Cioli on Wistar rats.[31] The method of performance and other situations and scoring system (no lesion: 0 to more than one large ulcer: 4), were chosen as the previously described procedures.[27, 32-33] In this experiment the mucosal damage induced by high dose orally administered reference drug and **10c** and **10k** were evaluated according to the mentioned scoring order and the method was illustrated in supplementary material.

CONCLUSION

New 1,3-thiazoline-4-one derivatives with 2-phenoxyphenyl and different aryliden moieties were synthesized, and their analgesic and anti-inflammatory activities were screened *in vivo*. The results revealed that most of them (**10b**-**10n**) were effective analgesic agents in comparison to control, and their activities were comparable or more than mefenamic acid. Most of the evaluated compounds and mefenamic acid were inactive at the 1st hour of evaluation, but compound **8** was active at this hour. Some of the final products (**8**, **10h,** and **10m**) were efficient anti-inflammatory agents when compared to the control, and they were active at the 2nd to 5th hours of assessment, similar to mefenamic acid. The acute gastric ulcerogenic activity of the selected derivatives (**10c** and **10k**) was evaluated, and unlike indomethacin, their severity index was same as the control group.

SUPPLEMENTARY MATERIAL

Additional data are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12641, or from the corresponding author on request.

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И З В О Д

СИНТЕЗА И *IN SILICO* ИСПИТИВАЊЕ ADMET ОСОБИНА СЕРИЈЕ НОВИХ ДЕРИВАТА ТИАЗОЛА И ТИАЗОЛИДИН-4-ОНА КАО НЕ-УЛЦЕРОГЕНСКИХ АНАЛГЕТИКА И АНТИ-ИНФЛАМАТОРНИХ АГЕНАСА

MANSUR NASSIRI KOOPAEI[1], MAHSHID MONAVARI[2], NASIM VOUSOOGHI[3,4], SADAF MOSHIRABADI[5], MOHAMMAD JAVAD ASSARZADEH[5], MOHSEN AMINI[1,6], ALI ALMASIRAD[5]

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Синтетисана је нова серија деривата 1,3-тиазолин-4-она која садржи 2-феноксифенилу групу као потенцијално нови аналгетички и анти-инфламанторни агенси. Структуре једињења су потврђене ФТ-ИЦ, НМР и масеним спектрима. Тест абдоналне пункције је одабран за испитивање аналгетичке активности. Добијени резултати показују да су скоро сва једињења активна, и да је дериват **10m** најактивнији са 96% инхибиције у поређењу са контролним једињењем. Најактивнија једињења су одабрана да им се испита анти-инфламаторна активност у тесте едема изазваног карагенаном на шапи пацова. Резултати показују да су једињења **8** и **10h** активна у 2 и 5 сату тестирања. Испитивање улцерогене активности два одабрана једињења су упоредива са контролном групом и не показују потенцијал за улцерогенску активност. Циљана једињења показују прихватљиве *in silico* ADME профиле.

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