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*RESEARCH ARTICLE*

# Synthesis and Anti-Inflammatory Activity of Some Novel Quinazolinone Derivatives

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***Synthesis and Anti-Inflammatory Activity of Some Novel Quinazolinone Derivatives***

***SUMMARY***

*Novel derivatives of quinazolinone with the help of Vilsmeier reagent linked through aniline derivatives have been synthesized and evaluated for anti-inflammatory activity. The synthesized compounds were characterized by 1H-NMR, FT-IR and mass spectral data and tested for in-vivo anti-inflammatory activity using Carrageenan induced paw inflammatory model. The results of anti-inflammatory activity revealed that compounds QA-2 & QA-6 exhibit good anti-inflammatory activity and compounds QA-1, QA-4 and QA-7 possess average anti-inflammatory activity whereas compounds QA-3, QA-5 and QA-8 show least activity among the synthesized compounds.*

***Key Words:*** *Quinazolinone, Anti-inflammatory activity, Vilsmeier reagent, Aniline derivatives, Carrageenan, Mass*

***Bazı Yeni Kinazolinon Türevlerinin Sentezi ve Anti-enflamatuar Aktivitesi***

***ÖZ***

*Vilsmeier reaktifinin yardımıyla, anilin türevleri aracılığıyla yeni kinazolinon türevleri sentezlendi ve anti-enflamatuar aktivite açısından değerlendirildi. Sentezlenen bileşikler, 1H-NMR, FT-IR ve kütle spektral verileri ile karakterize edildi ve Karragenan kaynaklı pençe enflamatuar modeli kullanılarak in vivo anti-enflamatuar aktivite açısından test edildi. Anti-enflamatuar aktivite sonuçları, QA-2 ve QA-6 bileşiklerinin iyi anti-enflamatuar aktivite sergilediğini ve QA-1, QA-4 ve QA-7 bileşiklerinin ortalama anti-enflamatuar aktiviteye sahip olduğunu gösterirken, QA-3, QA- 5 ve QA-8 bileşiklerinin sentezlenen bileşikler arasında en az aktivite gösterdiğini ortaya koymaktadır.*

***Anahtar Kelimeler:*** *Kinazolinon, Anti-enflamatuar aktivite, Vilsmeier reaktifi, Anilin türevleri, Karragenan, Kütle*

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## INTRODUCTION

Inflammation remains a common and poorly controlled clinical problem which can be life threatening in extreme form of allergy, autoimmune diseases and rejection of transplanted organs ( Huerre & Gounon, 1996). The treatment options which can be used for inflammatory diseases are unsatisfactory and complicated due to their lack of efficacy and adverse effect profile. It seemed worthwhile to look for candidates acting on more than one pathway involved in inflammatory conditions (Bot *et al*., 2011).

Quinazolinone is a fused heterocycles that are of considerable interest because of the diverse range of their biological properties. Compounds containing the quinazolinone ring have been reported to possess different biological activities such as antibacterial, (Gökhan-Kelekçi *et al*., 2009), antitubercular (Kumar *et al*., 1983), antiviral (Corbett *et al*., 2000), anti-convulsant (Usifoh &Scriba, *et al*., 2000) anticancer (Hour *et al*.,2000; Hamel *et al*., 1996) and anti-inflammaotory (Fathalla & Kassem, *et al.* 2008) activity depending on the substituents in the ring system. In view of the medical importance of 4(3H)-quinazolinone, we planned the synthesis of a new class of heterocyclic molecules in which this moiety is present. The present study aimed to synthesize and evaluate the quinazolinone derivatives as potential anti-inflammatory agents(Poojari, *et al*., 2017; Hassanzadeh *et al.,* 2019). The target compounds were designed to have substituted aromatic ring at 3-position and methoxy substitution at position 6,7 and 8.

## MATERIAL AND METHODS

**Analytical methods**- Open capillary tubes method was used to determine the melting point of the synthesized derivatives by Thomas-Hoover melting point apparatus. The purity was checked by TLC (Thin layer chromatography) using Silica gel G coated glass plates taking mobile phase as Ethyl Acetate: N-Hexane (5:5). Spots were visualised by iodine vapours. IR spectras (KBr) were recorded on a Shimadzu FT-IR Spectrophotometer. $^{1}$H-NMR spectras (DMSO) were taken on a 400 MHz spectrometer and LCMS were entrusted on Shimadzu Spectroscope. All the compounds showed satisfactory analytical results.

**Method of preparation of the compounds (QA-1to QA-8)**

The reaction, reported previously by us (Krishnarth *et al.,* 2019), occured by treating 2-amino-3,4,5-trimethoxybenzoicacid (0.05mmol) with the Vilsmeier reagent. This reaction was carried out at 0°C when two different substituted acids were reacted with a combination of DMF (20ml) and $POCl_3$ (2.5ml). Then, at room temperature, primary amines (0.05 mmol) were made to react with continuous stirring. After amine addition, 90°C temperature was raised, and the reaction was allowed to proceed for 3 hrs on a magnetic stirrer to obtain the different substituted anilines derivatives (QA-1 to QA-8). The purification of the synthesized substituted anilines was performed through recrystallization by using the solvent chloroform.

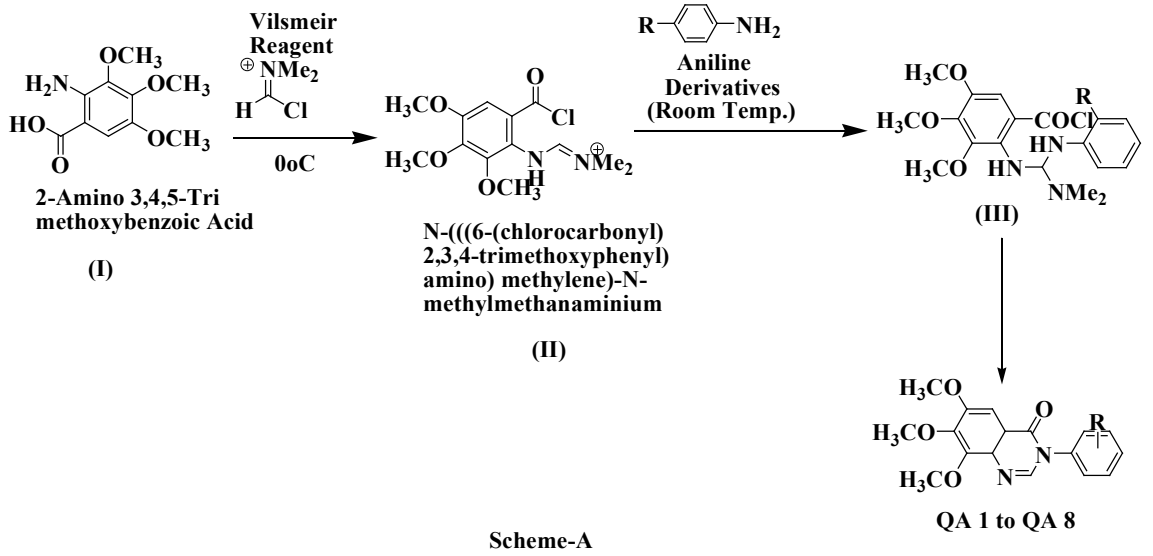


**Figure 1.** Scheme of synthesis of compounds

**Table 1**- Data of the synthesised compounds (QA-1 to QA-8)

| Compounds | R | Molecular Formula | Mol.weight | $R_f$ value[a] |
|---|---|---|---|---|
| **QA-1** | H | $C_{17}H_{16}N_2O_4$ | 312.32 | 0.94 |
| **QA-2** | 2,4-$NO_2$ | $C_{17}H_{15}N_5O_8$ | 417.33 | 0.76 |
| **QA-3** | 4-$NO_2$ | $C_{17}H_{15}N_3O_6$ | 357.32 | 0.93 |
| **QA-4** | 2-Cl | $C_{17}H_{15}ClN_2O_4$ | 346.07 | 0.85 |
| **QA-5** | 4-$NH_2$ | $C_{17}H_{17}N_3O_4$ | 327.33 | 0.84 |
| **QA-6** | 2-$CH_3$ | $C_{18}H_{18}N_2O_4$ | 326.35 | 0.89 |
| **QA-7** | $C_4H_2$ | $C_{19}H_{16}N_2O_4$ | 336.11 | 0.69 |
| **QA-8** | 3-$OC_2H_5$ | $C_{19}H_{20}N_2O_5$ | 356.14 | 0.76 |

[a]Solvent system was Dichloro methane:Carbon tetrachloride:methane (5:5:0.5)

**Spectral data of the synthesized compounds**

**6,7,8-Trimethoxy-3-phenylquinazolin-4(3*H*)-one (QA-1):**

**Yield** - 42%;Light grey solid**; M.P** - 370-375°C, **IR (KBr): ῡ(cm$^{-1}$);** = 2982 (CH, str, Ali); 1680 (C=O, str, quinazoline); 1623 (C=N, str, quinazoline); 3080 (CH, str, Ar); cm$^{-1}$,**$^1$H-NMR (δ, ppm/ DMSO-*d6*):=** 3.87 (m, 9H, 3*-$OCH_3$), 6.16-7.13 (m, 6H, Ar-H), 8.15-8.52 (m, 1H, $Ar_{Quinazoline}$), **MS:m/e** 312.11. **Anal. Calcd**: C, 65.38; H, 5.16; N, 8.97; O, 20.49. **Found**: C, 65.40; H, 5.14; N, 9.01; O, 20.46.

**3-(2,4-Dinitrophenyl)-6,7,8-trimethoxyquinazolin-4(3*H*)-one (QA-2):**

**Yield –** 45%**,** Cream solid; **M.P** – 426-430**°C**, **IR (KBr): ῡ(cm$^{-1}$);** = 2975 (CH, str, Ali); 1687 (C=O, str, quinazoline); 1626 (C=N, str, quinazoline); 3087 (CH, str, Ar) cm$^{-1}$, **$^1$H-NMR (DMSO-*d6*) δ =** 3.82 (m, 9H, 3*-$OCH_3$), 6.31-7.49 (m, 4H, Ar-H), 8.15-8.25 (m, 1H, $Ar_{Quinazoline}$), **MS: m/e** 417.09. **Anal. Calcd:** C, 50.75; H, 3.51; N, 13.93; O, 31.81. **Found:** C, 50.77; H, 3.46; N, 13.99; O, 31.80.

**6,7,8-Trimethoxy-3-(4-nitrophenyl)quinazolin-4(3*H*)-one (QA-3):**

**Yield**- 52%,Light brown solid**; M.P** – 358-362**°C, IR (KBr): ῡ(cm$^{-1}$);** = 2979 (CH, str, Ali); 1681 (C=O, str, quinazoline); 1625 (C=N, str, quinazoline); 3081 (CH, str, Ar); cm$^{-1}$, **$^1$H-NMR (δ, ppm/ DMSO-*d6*):=** 3.92 (m, 9H, 3*-$OCH_3$), 6.21-7.51 (m, 5H, Ar-H), 8.30-8.45 (m, 1H, $Ar_{Quinazoline}$), **MS:m/e** 357.10. **Anal. Calcd:** C, 57.14; H, 4.23; N, 11.76; O, 26.87. **Found:** C, 57.17; H, 4.25; N, 11.81; O, 26.86.

**3-(2-Chlorophenyl)-6,7,8-trimethoxyquinazolin-4-(3*H*)-one (QA_4):**

**Yield**- 60%, Dark black solid; **M.P**- 359-365**°C**, **IR (KBr): ῡ(cm$^{-1}$);** = 2972 (CH, str, Ali); 1686 (C=O, str, quinazoline); 1624 (C=N, str, quinazoline); 3082 (CH, str, Ar); cm$^{-1}$, **$^1$H-NMR (δ, ppm/ DMSO-*d6*):=** 4.12 (m, 9H, 3*-$OCH_3$), 6.12-7.18 (m, 5H, Ar-H), 8.89-9.12 (m, 1H, $Ar_{Quinazoline}$), **MS: m/e** 346.07, **M+4** (346.06). **Anal. Calcd:** C, 50.75; H, 3.51; N, 13.93; O, 31.81. **Found:** C, 50.73; H, 3.50; N, 13.99; O, 31.83.

**3-(4-Aminophenyl)-6,7,8-trimethoxyquinazolin-4(3*H*)-one (QA-5):**

**Yield** = 48%, Light black solid; **M.P**- 468-475**°C**, **IR (KBr): ῡ(cm$^{-1}$);** = 2985 (CH, str, Ali); 1686 (C=O, str, quinazoline); 1627 (C=N, str, quinazoline); 3086 (CH, str, Ar); 3445 (N-H, Str) cm$^{-1}$, **$^1$H-NMR (δ, ppm/ DMSO-*d6*):** = 3.89 (m, 9H, 3*-$OCH_3$), 5.1 (brs, 2H, -$NH_2$-Ar), 6.03-7.09 (m, 4H, Ar-H), 8.25-8.35 (m, 1H, $Ar_{Quinazoline}$), **MS: m/e** 327.12. **Anal. Calcd:** C, 62.38; H, 5.23; N, 12.84; O, 19.55. **Found:** C, 62.34; H, 5.25; N, 12.85; O, 19.57.

**3-(o-Tolyl)-6,7,8-trimethoxyquinazolin-4(3*H*)-one (QA-6):**

**Yield** - 62%; Creamy solid; **M.P.** - 394-398**°C**, **IR (KBr): ῡ(cm$^{-1}$);** = 2982 (CH, str, Ali); 1685 (C=O, str, quinazoline);1624(C=N,str,quinazoline);3082 (CH, str, Ar); cm$^{-1}$, **$^1$ H-NMR(δ, ppm/DMSO-*d6*)**: = 1.88 (t,3H,-CH3), 3.88(m,9H,3*-OCH3), 6.357.50 (m, 5H, Ar-H), 8.84-9.14(m,1H,$Ar_{Quinazoline}$), **MS:m/e** 326.13. **Anal. Calcd**: C, 66.25; H, 5.56; N, 8.58; O, 19.61. **Found**: C, 66.28; H, 5.54; N, 8.60; O, 19.60.

**6,7,8-Trimethoxy-3-(naphthalene-2-yl) quinazolin-4(3*H*)-one(QA-7)** (Krishnarth *et al.,* 2019)**:**

**Yield**-62%,Fluffywhitesolid; **M.P**.- 326-329**°C**,**IR (KBr): ῡ(cm$^{-1}$);** = 2960 (CH, str, Ali); 1686 (C=O, str,quinazoline);1623 (C=N,str,quinazoline);3087 (CH, str, Ar); cm$^{-1}$, **$^1$H-NMR (δ,ppm/DMSO-*d6*)**:=4.09(m,9H,3*-OCH3),6.08-7.11(m,8H,Ar-H),8.25-8.60(m,$^1$H,$Ar_{Quinazoline}$), **MS:m/e** 362.13. **Anal. Calcd**: C, 67.85; H, 4.79; N, 8.33; O, 19.03. **Found**: C, 67.82; H, 4.77; N, 8.29; O, 18.99.

**3-(3-Ethoxyphenyl)-6,7,8-trimethoxyquinazolin-4(3*H*)-one(QA-8)** (Krishnarth *et al.,* 2019)**:**

**Yield** = 58%, Violet solid; **M.P.** - 424-427**°C**, **IR (KBr): ῡ(cm−1);** = 2968 (CH, str, Ali); 1687 (C=O, str,quinazoline);1623(C=N,str,quinazoline);3089 (CH, str, Ar); 1230 (C-O, str); $cm^{-1}$, **$^1$H-NMR (δ, ppm/DMSO-*d6*)**:= 1.68(t,3H,-CH3),1.95-2.05(m, 2H, -CH2), 3.86 (m, 9H, 3*-OCH3), 6.21-7.64 (m, 5H, Ar-H), 8.30-8.60 (m, 1H, $Ar_{Quinazoline}$), **MS: m/e** 356.14. **Anal. Calcd**: C, 64.04; H, 5.66; N, 7.86; O, 22.45. **Found**: C, 64.06; H, 5.65; N, 7.89; O, 22.46.

**PHARMACOLOGICAL ACTIVITY**

**Method for determination of acute toxicity (LD 50)**

The synthesized compounds were tested for acute toxicity test as per CPCSEA guidelines (OECD guidelines No. 425) by albino mice of either sex (20-30g), animals were fasted overnight before the experiment (Veeraraghavan *et al.*, OECD guidelines 420). Effective dose ED50 (Sakr *et al.,* 2013) was calculated as reported. Therapeutic dose was taken as $1/5^{th}$ of lethal dose.

**Method for determination of anti-inflammatory activity**

**By carrageenan induced rat aw oedema model** (Chatterjee & Das *et al*., 1996)

Six groups of albino rats of either sex (each comprising of six animals) weighing between 80-200g were deprived of food and water for 18 hours prior to the experiment.

**Treatment Protocol was done as follows-**

Group I- Control (5% tween 80)

Group II- Standard drug (Diclofenac sodium 20mg/kg in distilled water)

Group III- QA-1 (100 mg/kg) 5% tween 80 suspension

Group IV- QA-2 (100 mg/kg) 5% tween 80 suspension

Group V- QA-3 (100 mg/kg) 5% tween 80 suspension

Group VI- QA-4 (100 mg/kg) 5% tween 80 suspension

Group VII- QA-5 (100 mg/kg) 5% tween 80 suspension

Group VIII- QA-6 (100 mg/kg) 5% tween 80 suspension

Group IX- QA-7 (100 mg/kg) 5% tween 80 suspension

Group X- QA-8 (100 mg/kg) 5% tween 80 suspension

The standard diclofenac sodium and synthesized compounds under study i.e. QA-1 to QA-8 were administered orally to all rats. After 30 minutes 0.1 ml of 1% carrageenan suspension in normal saline was injected in to the sub plantar region of the hind paw of each rat. The oedema volumes ofthe injected paws were measured at 1/2, 1st, 2nd and 4th hour. The difference between the paw volumes of treated animals were compared with that of the control group and the mean oedema volume was calculated. From the data obtained mean volume of oedema, and percentage reduction in oedema were calculated. Percentage reduction or inhibition in oedema volume was calculated by using the formula. Percentage reduction in oedema volume was calculated by using the formula,

**Percentage of oedema inhibition=$(V_o - V_1)/V_o * 100$**

Where, $V_o$=Volume of the paw of control at time 't'

$V_1$=Volume of the paw of drug treated at time 't'

**RESULT AND DISCUSSION**

The chemical reaction between 2-amino-3,4,5-trimethoxybenzoic acid and Vilsmeier reagent has been exploited to produce different derivatives of quinazolinone. This reaction occurred at 0**°C** when two different substituted acids reacted with a combination of DMF and $POCl_3$ followed by the addition of substituted anilines to give the end products. The analytical data of the synthesised compounds are shown in Table 1. The 2-Amino-3,4,5-trimethoxybenzoic acid (I) reacted with Vilsmeier reagent at 0°C yielded N-(((6-(chlorocarbonyl)-2,3,4-trimethoxyphenyl)amino) methylene)-N-methylmethanaminium (II). After that, compound (II) reacted with different primary anilines at room temperature in the presence of DMF to form different substituted quinazolinones (QA-1 to QA-8). The steps involved in the synthesis are shown in scheme (Figure 1).

Various spectral analytical techniques such as FTIR, $^1$H-NMRand mass spectra were employed to elucidate the chemical structure of quinazolinone derivatives. IR spectrum showed absorption band at 2950-2983 $cm^{-1}$ (CH, Ali.), 3090-3080 $cm^{-1}$ (CH, Ar), 1690-1680 $cm^{-1}$ (C=O) and 1630-1620$cm^{-1}$ (C=N). Further, $^1$H-NMR showed a multiplet of nine protons at δ (ppm) 3.87-4.50, multiplet for six protons at δ (ppm) 6.16-7.13 and multiplet of one proton of Aryl-quinazoline at δ (ppm) 8.15-8.52 respectively. Mass spectra revealed molecular ion peak in satisfactory intensity.

Results of anti-inflammatory activity showed that none of the synthesized compound was more active

than standard drug. Compounds QA-2 and QA-6 showed significant anti-inflammatory activity with a %ROV (after 4 hours) of 82.75 and 81.03 respectively. Compounds QA-1, QA-4 and QA-7 showed %ROV of 65.51, 62.06 and 63.79 respectively. Compounds QA-3, QA-5 and QA-8 were least active in the synthesized series with %ROV of less than 50. Results revealed that 2-methyl and 2,4-dinitro substitution at the aromatic ring on 3-position are favourable for anti-inflammatory activity.

**Table 2**- Data showing anti-inflammatory activity of quinazolinone derivatives in carrageenan induced acute rat paw oedema model.

| Gp | Treatment | Dose mg/kg | PAW OEDEMA VOLUME | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | After 1/2 hour | | After 1 hour | | After 2 hour | | After 4 hour | |
| | | | Change in Paw oedema ± SEM | % ROV | Change in Paw oedema ± SEM | % ROV | Change in Paw oedema ± SEM | % ROV | Change in Paw oedema ± SEM | % ROV |
| 1 | Control | 0.5 | 0.20±0.02 | ----- | 0.53±0.09 | ------ | 0.62±0.07 | ------- | 0.58±0.12 | ------- |
| 2 | Standard | 20 | 0.11±0.05 | 45 | 0.18±0.07 | 66.03 | 0.13±0.05 | 79.03 | 0.03±0.04 | 94.83 |
| 3 | QA-1 | 100 | 0.12±0.03 | 40 | 0.25±0.06 | 52.83 | 0.23±0.03 | 62.90 | 0.20±0.07 | 65.51 |
| 4 | QA-2 | 100 | 0.08±0.02 | 60 | 0.16±0.05 | 69.81 | 0.13±0.10 | 79.03 | 0.10±0.05 | 82.75 |
| 5 | QA-3 | 100 | 0.25±0.03 | 25 | 0.28±0.04 | 47.16 | 0.31±0.08 | 50 | 0.30±0.12 | 48.27 |
| 6 | QA-4 | 100 | 0.115±0.03 | 42.5 | 0.24±0.03 | 54.71 | 0.25±0.09 | 59.67 | 0.22±0.08 | 62.06 |
| 7 | QA-5 | 100 | 0.26±0.06 | 30 | 0.26±0.09 | 49.05 | 0.32±0.11 | 48.38 | 0.32±0.13 | 44.82 |
| 8 | QA-6 | 100 | 0.07±0.04 | 65 | 0.17±0.06 | 67.92 | 0.14±0.10 | 77.41 | 0.11±0.06 | 81.03 |
| 9 | QA-7 | 100 | 0.117±0.03 | 41.5 | 0.255±0.11 | 51.88 | 0.26±0.08 | 58.06 | 0.21±0.09 | 63.79 |
| 10 | QA-8 | 100 | 0.252±0.04 | 26 | 0.31±0.08 | 41.50 | 0.38±0.12 | 38.70 | 0.35±0.13 | 36.36 |

**ROV- Reduction in paw oedema volume**

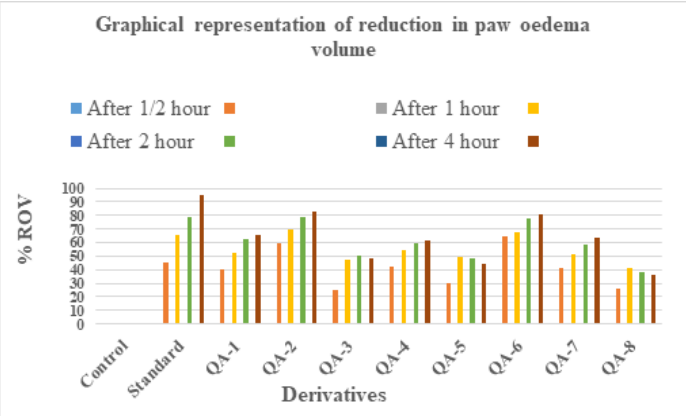


**Figure 2**- Graphical representation of Reduction in Paw Oedema Volume

## CONCLUSION

Some novel (QA-1 to QA-8) quinazolinone derivatives have been synthesized from 2-amino-3,4,5-trimethoxybenzoic acid with Vilsmeier reagent. The spectral analytical methods were employed to characterize and established the structural features of all synthesised compounds. All the synthesised compounds were biologically screened by using*in vivo* carrageenan induced rat paw oedema anti-inflammatory model. The results have indicated that compounds QA-2 & QA-6 exhibit good anti-inflammatory activity and compounds QA-1, QA-4 and QA-7 possess average anti-inflammatory activity whereas compounds QA-3, QA-5 and QA-8 show least anti-inflammatory activity among the synthesized compounds.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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