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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Transformations of naproxen into pyrazolecarboxamides: search for potent anti-inflammatory, analgesic and ulcerogenic agents

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Abstract Many derivatives of naproxen containing a variety of pyrazolecarboxamides were synthesized through the reaction of naproxenoyl hydrazide with formylpyrazole, acetylacetone, enaminone, Mannich base, and arylhydrazonomalononitrile derivatives. Also, many derivatives of naproxen were synthesized through the reaction of naprexenoyl chloride with amine derivatives containing pyrazole moiety. The synthesized compounds were screened for anti-inflammatory, analgesic, and ulcerogenic activities. Screening of anti-inflammatory revealed that compound **5** having a 1,3-diphenyl-pyrazol-4-yl moiety had the most promising activity. Compounds **8**, **9**, and **12**, possessing 3,5-dimethyl-pyrazol-1-yl, 3-phenyl-pyrazol-1-yl, and 3,5-diamino-4-(4-methoxyphenylazo)-pyrazol-1-yl groups, respectively, showed moderate activity. Moreover, compounds **8** and **12** showed higher analgesic activity than the reference drug. In ulcerogenic effect, compound **22** which has methoxphenyl pyrazoline moiety devoid of ulcerogenic effect.

Keywords Naproxen · Pyrazoles · Hydrazides · Chalcones · Anti-inflammatory activity

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Introduction

Currently available non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, naproxen, diclofenac, indomethacin, and flurbiprofen exhibit gastric toxicity. Long-term use of these drugs has been associated with gastrointestinal (GI) ulceration, bleeding, and nephrotoxicity (Kimmey, 1992). The GI damage from NSAIDs is generally attributed to two factors, local irritation by the carboxylic acid moiety, common to most NSAIDs (topical effect) and decreased tissue prostaglandin production, which undermines the physiological role of cytoprotective prostaglandins in maintaining the GI health and homeostasis (Smith *et al*., 1998; Hawkey *et al*., 2000). The pharmacological activity of NSAIDs is related to the suppression of prostaglandin biosynthesis from arachidonic acid by inhibiting cyclooxygenases (COXs) (Smith *et al*., 1998; Warner *et al*., 1999). Chronic use of NSAIDs, including ibuprofen, may elicit appreciable GI toxicity (Lanza, 1998). Naproxen was one of the leading NSAIDs used for relieving arthritic pain, but its long-term use invites GI complications ranging from stomach irritation to life threatening GI ulceration and bleeding (Cash and Klippel, 1994; Davies and Wallace, 1997; Wallace, 1997). These clinical shortcomings comprise a major challenge confronting medicinal chemists to develop safer agents that spare COX-1 and subsequently its gastric cytoprotective role. It was discovered that COXs exist in two isoforms, COX-1 and COX-2, which are regulated differently (Marnett and Kalgutkar, 1999; Marnett and Kalgutkar, 1998). COX-1 provides cytoprotection in the gastrointestinal tract whereas inducible COX-2 mediates inflammation (Almansa *et al*., 2003). Therefore, synthetic approaches based upon NSAIDs chemical modification have been undertaken with the aim of improving the NSAID safety profile (Farag *et al*., 2013). Pyrazole derivatives have been

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reported to possess significant anti-inflammatory activity (Sukuroglu *et al*., 2005; Machado *et al*., 2007; Mathew *et al*., 2011; Youssef *et al*., 2010; Froravanti *et al*., 2010). Previous studies described that the derivatization of the carboxylate function of representative NSAIDs, resulted in an increased anti-inflammatory activity with reduced ulcerogenic effect (Kalgutkar *et al*., 2000; Duflos *et al*., 2001).

In an attempt to discover new and useful agents for treating inflammatory diseases, we have replaced the carboxylic acid group of naproxen with additional heterocycles, which have been found to possess an interesting profile of anti-inflammatory activity with significant reduction of their ulcerogenic effect. Structure modifications suggested in the present investigation focused mainly on studying the effect of linking various polysubstituted pyrazoles. The substitution pattern of the target compounds includes various functionalities that would act as hydrogen-bond forming centers, such as the carbonyl, amide, amino, cyano, hydroxy, and carbethoxy groups. In addition, variation in the nature and size of other substituents was also attempted, as it would offer variable electronic, lipophilic, and steric environment that would influence the targeted biological activity.

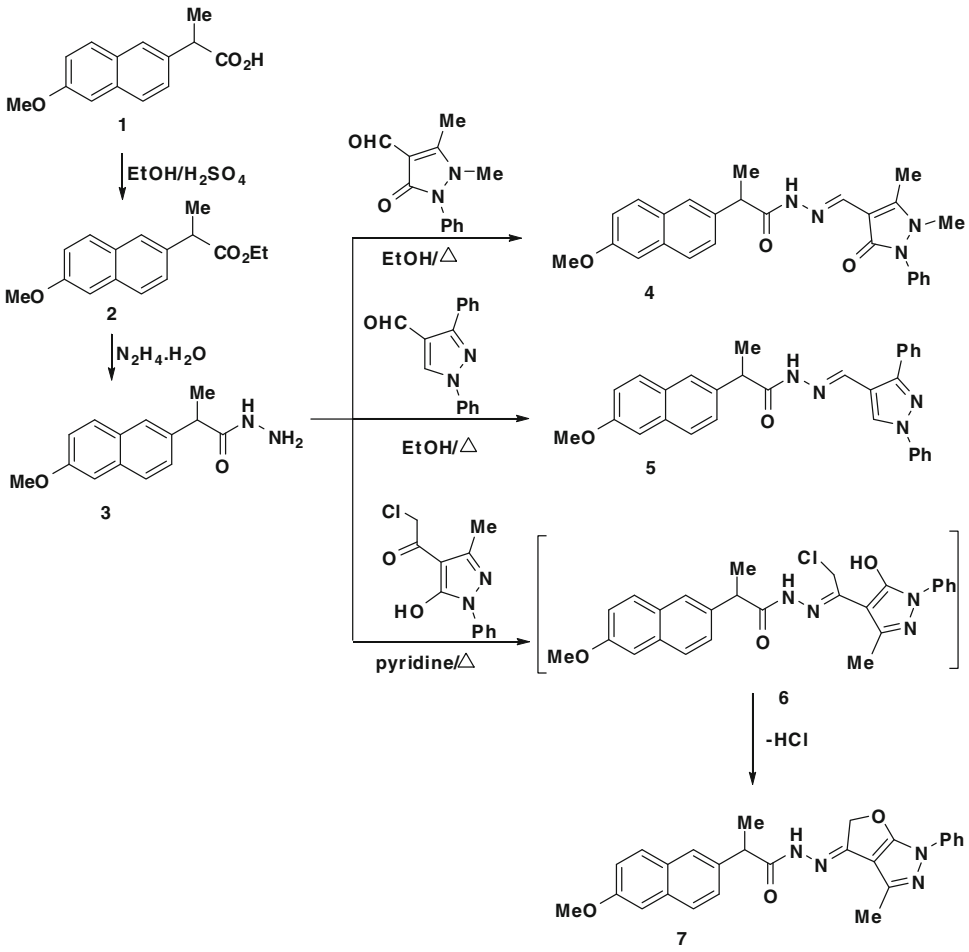
Results and discussion

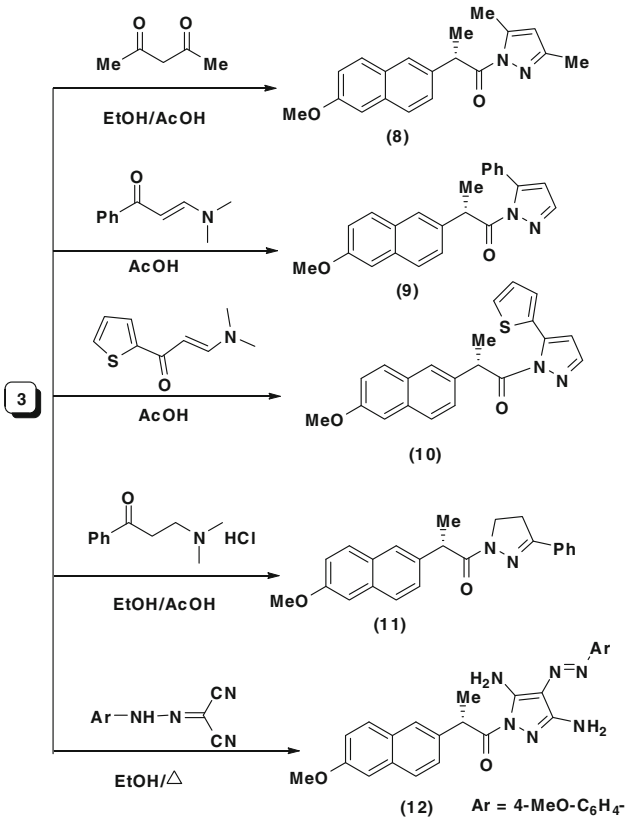
Chemistry

The synthesis of the target compounds is depicted in Schemes 1–3. The starting material 2-(6-methoxy-2-naphthyl)propanoic acid hydrazide **(3)** was prepared in two consequence steps by esterification of racemic naproxen, 2-(6-methoxy-2-naphthyl)propanoic acid **(1)**, with boiling ethanol containing a catalytic amount of concentrated H_2SO_4 followed by treatment of the resulting ester **2** with hydrazine hydrate in refluxing absolute ethanol (Amir *et al*., 2007). The hydrazide derivatives have proved to be a good synthons for construction of many biological active heterocyclic compounds. In fact, some evidences suggest that the hydrazone moiety possess a pharmacophoric character for the inhibition of COX (Reitz *et al*., 1994).

Thus, condensation of the hydrazide **3** with each of 4-formylantipyrine and 1,3-diphenyl-4-formylpyrazole (Kira *et al*., 1969) in refluxing ethanol afforded the respective hydrazone derivatives **4** and **5**. The structures of the latter products were confirmed by spectroscopic studies and elemental analysis. The IR spectrum of compound **4**,

Scheme 1 Synthetic pathways to compounds **2**–**7**





Scheme 2 Synthetic pathways to compounds **8–12**

for example, revealed absorption bands at 3352, 1670, and 1656 cm^{-1} corresponding to an NH and two amidic carbonyl groups. Its ^{1}H-NMR spectrum revealed, besides the expected naproxen signals, four new singlets at δ 2.56, 3.22, 8.01, and 10.99 ppm attributed to CH_3, $-NCH_3$, –N=CH, and –NH protons, respectively. The ^{13}C NMR spectrum revealed 26 carbon types, the most important signals being displayed at 156.7, 171.9, and 176.7 ppm characteristic for the azomethine carbon and two amidic carbonyl carbons.

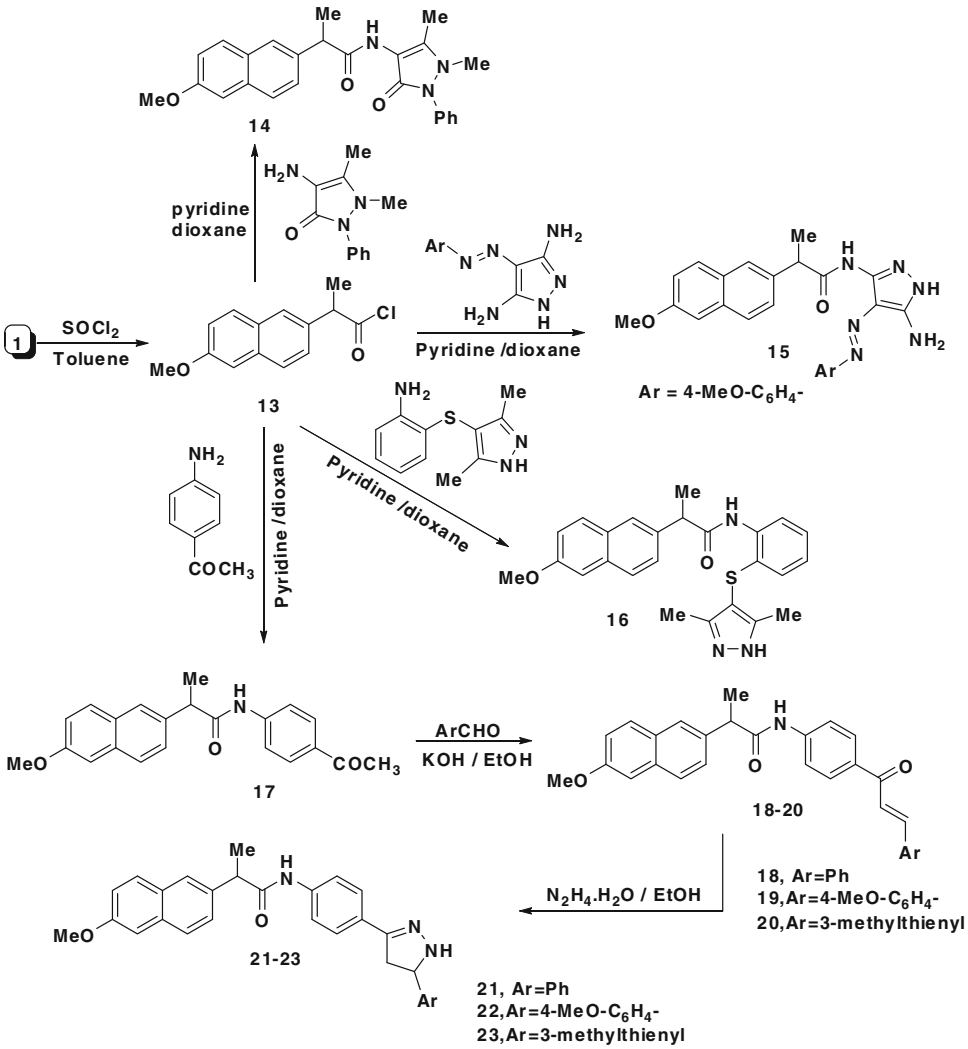
In addition, cyclocondensation of the hydrazide **3** with 2-chloro-1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl) ethanone (Jensen, 1959) in refluxing pyridine gave the non-isolable hydrazone **6** which in situ underwent cyclization through elimination of HCl molecule to give *N*-[1-(3-methyl-1-phenyl-1*H*-furo[2,3-*c*]pyrazol-4-ylidene)-2-(6-methoxynaphthalen-2-yl)propionylhydrazide **(7)**. The IR spectrum of compound **7** showed absorption bands at 3214 and 1659 cm^{-1} due to an NH and amidic carbonyl group. Its ^{1}H-NMR spectrum exhibited four characteristic singlets at δ 2.20, 3.86, 5.94, and 9.29 ppm which were assigned to CH_3, OCH_3, OCH_2 of furan ring, and NH protons, respectively. Moreover, its ^{13}C NMR spectrum showed 26 carbon types, the most important signals appeared at δ 156.9, 156.9, and 172.8 ppm due to C=N, OCH_2 of furan ring, and amidic carbonyl carbon, respectively.

Next, we focussed our attention to use the hydrazide **3** as versatile precursor for construction of pyrazole scaffold via its reaction with acetylacetone, enaminones, Mannich base, and arylhydrazonomalononitrile. Thus, refluxing of hydrazide **3** with acetylacetone in glacial acetic acid afforded 3,5-dimethylpyrazole derivative **8** in good yield. The structure of the latter product was assigned by IR spectrum which lacked absorption bands due to the carbohydrazide moiety CON-HNH_2. Its ^{1}H-NMR spectrum exhibited four characteristic singlets at δ 2.16, 2.46, 3.86, and 6.16 ppm assigned for two CH_3, OCH_3, and pyrazole-H4, respectively. The carbonyl carbon atom showed a signal at 174.0 ppm in ^{13}C NMR spectrum.

Reaction of the hydrazide **3** with enaminones, namely, 3-dimethylamino-1-phenyl-propenone and 3-dimethylamino-1-thiophen-2-ylpropenone (Al-Omran *et al*., 1997) in boiling glacial acetic afforded, in each case, only one isolable product that was identified as pyrazole derivatives **9** and **10** based on their microanalysis and spectral data. The formation of regioisomeric pyrazole products **9** and **10** is in the line with reported results published earlier by Stanovic and Svete (2004) who stated that selectivity of reaction of enaminone with hydrazines is acid catalyzed and controlled by reaction conditions: under mild conditions (20–80 °C), the dimethylamine substitution products are formed, whereas up on heating at (90–120 °C) further cyclization takes place to give pyrazoles. Pyrazole derivatives **9** and **10** based on their microanalysis and spectral data. The structure of **9**, as representative example, was substantiated by the ^{1}H-NMR spectrum which displayed new pair of doublets at δ 7.12 and 7.77 ppm with coupling constant (J = 7.5 Hz) corresponding to pyrazole protons at positions 4 and 5, respectively. The formation of compounds **9** and **10** may be rationalized via initial addition of the amino group in hydrazide **3** to the enaminone double bond, followed by elimination of dimethylamine molecule as depicted in Scheme 2.

Moreover, the reaction of hydrazide **3** with Mannich base, namely, 3-dimethylamino-1-phenylpropan-1-one hydrochloride (Blicke and Burckhalter, 1942) in warming ethanol containing a catalytic amount of acetic acid gave only a sole product that was identified as 2-(6-methoxynaphthalen-2-yl)-1-(5-phenyl-2,3-dihydropyrazol-1-yl)propan-1-one **(11)**. The structure of product **11** was deduced from its elemental analysis and spectral data. The ^{1}H-NMR spectrum showed two triplets at δ 1.94 and 4.80 ppm due to H-3 and H-4 of pyrazoline ring. Its ^{13}C NMR spectrum showed the presence of 22 carbon types. Furthermore, 1-[3,5-diamino-4-(4-methoxyphenylazo)-pyrazol-1-yl]-2-(6-methoxynaphthalen-2-yl) propan-1-one **(12)** was obtained through the reaction of the

Scheme 3 Synthesis of pyrazolecarboxamides **14–23**



hydrazide **3** with 2-[(4-methoxyphenyl)hydrazono] malononitrile in ethanol under reflux condition.

Structure modifications of the carboxylic group in naproxen was also extended to attain pyrazolecarboxamides through another synthetic route. Thus, interaction of the naproxenoyl chloride **(13)** (Al-Sehemi *et al*. 2006), obtained by refluxing of **1** with thionyl chloride in toluene, with each of 4-aminoantipyrine, 4-arylazo-3,5-dimethylpyrazole (Tsai and Wang, 2005), and 2-(3,5-dimethyl-1*H*-pyrazol-4-ylthio)aniline (Steiner *et al*., 1993) in refluxing dioxane containing a catalytic amount of pyridine furnished the respective pyrazolecarboxamides **14–16** as outlined in Scheme 3.

The structure of compounds **14–16** were elucidated based on their microanalyses and spectral data. The IR spectrum of compound **14**, for example, showed strong absorption bands at 3218, 1678, and 1660 cm^{-1} due to an NH, amidic C=O, and pyrazole C=O groups, respectively. Its ^{1}H-NMR spectrum revealed three singlets at δ 1.91, 3.34, and 10.00 ppm attributed to CH_3, NCH_3, and amidic NH proton, respectively.

In a similar manner, reaction of **13** with *p*-aminoacetophenone under the same experimental condition afforded *N*-(4-acetylphenyl)-2-(6-methoxynaphthalen-2-yl)propanamide **(17)**. The presence of acetyl group in **17** makes it versatile precursor for the synthesis of pyrazoline derivatives. Thus, the Claisen–Schmidt condensation of **17** with aromatic aldehydes, namely, benzaldehyde, *p*-anisaldehyde, and 3-methylthiophene-2-carboxaldehyde in ethanolic potassium hydroxide furnished the chalcone derivatives **18–20**. The structure of the latter products were confirmed by IR spectra which showed the characteristic band for conjugated C=O at 1639–1654 cm^{-1} and their ^{1}H-NMR spectra displayed a pair of doublets at δ 7.58–7.68 and 7.79–7.89 ppm, with coupling constant value (J = 14.8–15.6 Hz), due to the *trans*-olefinic protons. Cyclocondensation of chalcones **18–20** with hydrazine hydrate in boiling ethanol furnished the respective pyrazolines **21–23**. The structures of the latter

products were established by IR spectra which showed disappearance of C=O band of chalcones. A strong band appeared at 1589–1608 cm^{-1} assigned to C=N of pyrazoline ring. Compounds **21–23** showed an additional sharp band in the region 3325–3395 cm^{-1} due to the NH stretching. Their ^{1}H-NMR spectra revealed, in each case, the signals of CH_2 protons of the pyrazoline ring in the region 3.32–3.39 and 3.60–3.75 ppm as a pair of doublets. The CH proton appeared as double of doublets at 4.80–5.08 ppm. The ^{13}C NMR spectrum of compound **21**, as a representative example, displayed, besides the expected signals, three characteristic signals at δ 38.9, 63.5, and 161.8 ppm due to the carbons of CH_2, CH, and C=N of pyrazoline ring, respectively.

Biological evaluation

Anti-inflammatory activity possessed by NSAIDs is credited to the presence of carboxylic acid moiety which is crucial for binding to COX-1 and COX-2. But this inhibition is associated with GI and renal toxicities which limits the use of NSAIDs. Thus, the biological evaluation is done with the aim of retention in activity and reduction in GI toxicity (Piazza *et al*., 2009).

Anti-inflammatory activity

The anti-inflammatory activity of 12 of the newly synthesized compounds: **4, 5, 7, 8, 9, 12, 14, 15, 19, 21, 22**, and **23** were evaluated by applying carrageenan-induced paw edema bioassay in rats (Winter *et al*., 1962) using naproxen as a reference standard. Results were expressed as mean ± SE. Difference between vehicle control and treatment groups was tested using one way ANOVA followed by the least significant difference (LSD). Methods of statistical analysis were done according to Armitage (1971). According to Table 1, administration of many of tested compounds 60 min prior to carrageenan injection at dose of 10 mg/kg wt caused significant inhibition of paw edema response.

The mean values of the inhibition of paw edema response obtained for these compounds suggest that, compounds **4, 5, 8, 9, 14, 21, 22**, and **23** have good anti-inflammatory activity and compound **5** was the most potent derivative. Using the general structure provided in Fig. 1, certain aspects of the structure activity relationships for these compounds can be more clearly highlighted.

Compounds **4**, **5**, and **7**, X was NH–N side chain ending with substituted pyrazole (**4**; antipyrine, **5**; 1,3-diphenyl-pyrazol-4-yl, **7**; furopyrazol-4-yl): the presence of 1,3-diphenyl-pyrazol-4-yl moiety (**5**) resulted in the highest anti-inflammatory activity among all the compounds investigated in this study. The presence of 1,3-diphenyl-pyrazol-4-yl moiety showed activity near to the references drug. Replacement 1,3-diphenyl-pyrazol-4-yl moiety by

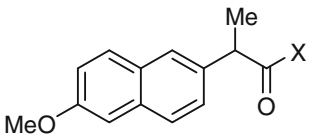


Fig. 1 General formula of the synthesized compounds

Table 1 Anti-inflammatory activity, analgesic activity, and ulcerogenic effect of the tested compounds assessed in comparison to naproxen as reference

Compound nos.	Edema volume (mL)				Reaction time (sec)			Ulcer index		No. of ulcer rats/5
	1 h	2 h	3 h	4 h	Basal	1 h	2 h	No. of ulcer	Severity	
Control	57.2 ± 6.8	94.3 ± 8.5	100.2 ± 3.3	92.2 ± 3.3	12.1 ± 0.63	12.2 ± 0.83	12.3 ± 1.18	8.3 ± 0.86	19.5 ± 2.2	5
4	49.8 ± 2.5	88.6 ± 6.1	83.6 ± 3.7	73.5 ± 2.3	9.7 ± 1.11	17.2 ± 1.52	17.1 ± 1.25	–	–	–
5	56.1 ± 9.9	65.2 ± 7.5	55.8 ± 10.6	54.6 ± 7.2	12.6 ± 1.13	21.1 ± 2.47	18.4 ± 0.69	0.4 ± 0.4	0.4 ± 0.40	1
7	72.3 ± 4.9	88.1 ± 9.5	88.6 ± 6.5	90.8 ± 5.4	11.9 ± 0.82	13.6 ± 0.75	11.6 ± 0.85	–	–	–
8	60.5 ± 7.1	74.2 ± 5.4	80.2 ± 6.0	77.9 ± 5.5	10.8 ± 1.03	19.7 ± 1.59	21.5 ± 1.54	0.4 ± 0.4	0.6 ± 0.6	1
9	57.8 ± 7.2	65.3 ± 8.8	66.5 ± 6.9	68.7 ± 6.3	13.1 ± 0.85	24.2 ± 1.65	17.9 ± 2.64	7.0 ± 1.64	10.5 ± 2.86	5
12	65.2 ± 7.2	82.2 ± 6.9	83.9 ± 2.3	79.3 ± 7.3	12.8 ± 0.95	15.1 ± 1.02	20.6 ± 1.19	–	–	–
14	85.4 ± 3.1	74.5 ± 7.5	88.1 ± 7.2	89.8 ± 2.1	9.4 ± 0.94	17.2 ± 1.66	18.1 ± 1.23	2.7 ± 1.66	3.2 ± 1.96	2
15	52.1 ± 3.8	79.1 ± 6.9	82.6 ± 8.0	91.5 ± 5.8	10.2 ± 1.03	14.5 ± 0.93	18.5 ± 1.47	–	–	–
19	60.5 ± 6.8	93.7 ± 5.2	94.7 ± 02	78.1 ± 5.5	9.6 ± 0.49	17.1 ± 1.89	9.33 ± 0.89	–	–	–
21	44.3 ± 5.1	59.7 ± 4.7	67.9 ± 3.3	81.8 ± 3.2	9.6 ± 0.68	17.6 ± 1.33	17.3 ± 1.11	–	–	–
22	49.4 ± 7.1	71.9 ± 6.7	76.5 ± 4.8	82.4 ± 5.2	11.1 ± 0.91	19.2 ± 1.46	19.3 ± 1.00	0.0 ± 0.0	0.00 ± 0.00	0
23	61.1 ± 6.6	66.7 ± 5.9	68.6 ± 7.0	72.4 ± 7.4	15.1 ± 1.34	24.8 ± 1.38	19.3 ± 0.61	1.7 ± 1.36	2.0 ± 1.76	2
Naproxen	49.9 ± 5.3	42.8 ± 5.1	45.8 ± 4.6	46.8 ± 5.8	13.2 ± 0.78	17.7 ± 0.32	18.3 ± 0.28	5.9 ± 1.77	9.9 ± 3.23	5

antipyrine moiety do not improve the anti-inflammatory activity; compound **4** showed moderate activity. Further introduction of furopyrazol-4-yl, as in **7** had a detrimental effect on anti-inflammatory activity, compound **7** showed weak anti-inflammatory activity. Compounds **8**, **9**, and **12**, the X was substituted pyrazole moiety; (**8**; 3,5-dimethyl-pyrazol-1-yl, **9**; 3-phenyl-pyrazol-1-yl, **12**; 3,5-diamino-4-(4-methoxyphenylazo)-pyrazol-1-yl): also, the presence of phenyl-pyrazol-4-yl moiety (**9**) resulted in the highest anti-inflammatory activity among this group. While, when methyl moiety (**8**) or arylazo moiety and amino group (**12**) were attached the pyrazole system caused lower potency. Compounds **14** and **15**, X was NH-pyrazole derivatives. In general, treatment of **13** with aminopyrazole derivatives proved to be detrimental to anti-inflammatory activity. Compound **19** with chalcone moiety resulted in the lowest anti-inflammatory activity among all the compounds investigated in this study. Transformation of chalcone **19** to dihydropyrazole **21–23** recorded better anti-inflammatory activity with superior of compound **23** due to the presence of thienyl moiety in position 3.

As brief, compounds **5, 8, 9**, and **23** caused significant decrease in paw oedeama after 2, 3, and 4 h after drug administration, while **21** and **22** gave their response after 2 h of administration and continued to the third hour. Compound **14** showed the effect only after 2 h but compound **4** significantly decreased the paw edema after 4 h post administration. On the other hand, compounds **7, 12, 15**, and **19** were inactive toward carrageenan-induced edema in comparison to the standard reference naproxen which markedly and significantly inhibited the paw edema after 2, 3, and 4 h of carrageenan injection.

Analgesic activity

The analgesic activity of the above mentioned 12 derivatives was also evaluated by applying hot-plate test (Woolfe and MacDonald, 1944) using naproxen as a standard reference. Results were expressed as mean ± SE. Difference between vehicle control and treatment groups was tested using one-way ANOVA followed by the LSD. Methods of statistical analysis were done according to Armitage (1971). The results reported in Table 1 revealed that, compounds **5, 8, 9, 22**, and **23** showed significant analgesic activity higher than that obtained by naproxen 1 and 2 h post administration. While compounds **4, 14**, and **21** exhibited equipotent analgesic effect or slightly less than that of naproxen after 1 and 2 h of their administration. Compounds **15** and **12** exhibited significant analgesic activity higher than or slightly equipotent to naproxen only after 2 h of administration. Compound **19** exhibited the analgesic effect after 1 h of administration only. Compound **7** have no analgesic activity in comparison to the base line of the same group 1 and 2 h post administration. Thus, it can be concluded that, compounds **4, 5, 8, 9, 12, 14, 15, 19, 21, 22**, and **23** have significant analgesic activity and compound **23** is the most potent one. Introduction of dimethylpyrazole and diaminopyrazole moiety to naproxen via carboxamide linkage in compounds **8** and **12** increased the analgesic activity more than naproxen. Compounds **5, 14, 15, 22,** and **23** which have diphenylpyrazole, antipyrine, aminopyrazole, and pyrazoline moieties showed equipotent analgesic effect compared the reference drug naproxen.

Ulcerogenic effect

The ulcerogenic effect of the most active anti-inflammatory and analgesic derivatives: **5, 8, 9, 14, 22**, and **23** was evaluated (Woolfe and MacDonald, 1944). According to Table 1, it has been found that compounds **5, 8, 14,** and **23** have very little ulcerogenic effect with better safety margin in comparison to naproxen. Interestingly, compound **22** exhibited no ulcerogenic effect in all of the experimental animals. On the other hand, compound **9** resulted in ulcer lesions in many of the experimental rats. Therefore, the potential medicinal value of these compounds as anti-inflammatory and analgesic agents that they have better safety margin than naproxen on gastric mucosa. In ulcerogenic effect compound **22** which has methoxphenyl pyrazoline moiety devoid of ulcerogenic effect.

Conclusion

The present work aims to couple naproxen with a series of functionalized pyrazoles through a carboxamide linkage to achieve the synergistic effect and reducing the gastrointestinal toxicity associated with naproxen. It is found to be the appropriate method for increasing therapeutic effectiveness of naproxen with safer pyrazole promoieties. The studies showed that most of the synthesized pyrazolecarboxamides can be successfully applied in attaining the goal of minimized gastrointestinal toxicity with retention of desired anti-inflammatory activity. Coupling of naproxen with pyrazoles through a carboxamide linkage gives an opportunity in medicinal chemistry to improve the clinical and therapeutic effectiveness of a drug that is suffering from some undesirable properties hindering its clinical usefulness.

Experimental

Melting points were determined on a digital Gallen-Kamp MFB-595 instrument and are uncorrected. IR spectra (KBr) were measured on a Shimadzu 440 spectrometer. ^{1}H-NMR

and ^{13}C spectra were recorded in DMSO-d_6 on a Brucker (500 MHz) spectrometer using TMS as an internal standard; chemical shifts are reported as δ_{ppm} units. Mass spectra were performed on a Shimadzu GSMS-QP 1000 Ex mass spectrometer at 70 eV. The elemental analyses were carried out at the Microanalytical Center, Cairo University, Cairo, Egypt.

General procedure for the condensation of the hydrazide 3 with heterocyclic aldehydes

To a solution of the hydrazide **3** (2.44 g, 0.01 mol) in ethanol (30 mL), each of 1,3-dimethyl-1*H*-pyrazole-4-carboxaldehyde (2.48 g, 0.01 mol) and 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-carboxaldehyde (2.16 g, 0.01 mol) was added and the reaction mixture was refluxed for 3 h. The solid obtained upon cooling was collected by filtration, dried, and recrystallized from the ethanol.

*N-[(1E)-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)methylene]-2-(6-methoxy)-2-naphthyl)-propionylhydrazide (**4**)*

Colorless powder, Yield (74 %), mp 213–215 °C; IR (KBr) νmax/cm^{-1}: 3352 (NH), 2969, 2935 (CH-sp^3), 1670, 1656 (2C=O), 1604 (C=N); ^{1}H-NMR (DMSO-d_6): $\delta_{ppm} = 1.43$(d, $J = 6.5$ Hz, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.22 (s, 3H, N–CH_3), 3.62 (q, $J = 6.5$ Mz, 1H, CH), 3.86 (s, 3H, OCH_3), 7.12–7.81 (m, 11H, Ar–H), 8.01 (s, 1H, N=CH), 10.99 (bs, 1H, NH); ^{13}C-NMR (DMSO-d_6): $\delta_{ppm} = 12.12$ (CH_3), 18.74 (CH_3), 40.1(CH), 45.9 (N–CH_3), 55.1 (OCH_3), 105.6 (C-5), 118.3 (C-7), 124.1 (C-4), 125.5 (C-8a), 126.31, 127.5, 128.4, 129.3, 130.3, 132.9, 133.9, 135.6, 136.5, 137.4, 137.7, 139.0, 141.9, 145.3, 156.7, 171.9, 176.7. MS (EI, 70 eV): *m/z* (%) = 442 (M^+, 10.2), 285 (44.9), 256 (60.5), 229 (67.5), 228 (35.4), 214 (100), 187 (63.5), 91 (50.6), 77 (55.3). Anal. Calcd for $C_{26}H_{26}N_4O_3$ (442.51): C, 70.57; H, 5.92; N, 12.66. Found: C, 70.43; H, 5.84; N, 12.71 %.

*N-[(1E)-(1,3-diphenyl-1H-pyrazol-4-yl)methylene]-2-(6-methoxy-2-naphthyl)propionyl hydrazide (**5**)*

Colorless powder, Yield (65 %), mp 195–196 °C; IR (KBr) νmax/cm^{-1}: 3191(NH), 3052 (CH–Ar), 2969–2934 (CH-sp3), 1655 (C=O), 1602 (C=N); ^{1}H-NMR (DMSO-d_6): $\delta_{ppm} = 1.48$ (d, $J = 6.5$ Hz, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.1 (q, $J = 6.5$ Hz, 1H, CH), 7.24–8.77 (m, 16H, Ar–H), 8.29 (s, 1H, Pyrazol-H_5), 8.95(s, 1H, CH=N), 11.12 (bs, 1H, NH); ^{13}C-NMR (DMSO-d_6): $\delta_{ppm} = 18.2$ (CH_3), 43.9 (CH), 55.9 (OCH_3), 105.6, 116.6, 116.9, 118.6, 118.7, 125.3, 125.7, 126.2, 126.9, 127.6, 128.3, 128.6, 128.9, 129.5, 131.9, 132.3, 133.2, 135.5, 136.4, 136.9, 138.9, 139.5, 151.7, 151.1, 156.8, 156.9, 169.3, 174.6; Anal. Calcd for $C_{30}H_{26}N_4O_2$ (474.55): C, 75.93; H, 5.52; N, 11.81. Found: C, 75.85; H, 5.64; N, 11.76 %.

*Synthesis of N-[1-(3-methyl-1-phenyl-1H-furo[2,3-c]pyrazol-4-ylidene)-2-(6-methoxynaphthalen-2-yl)propionyl hydrazide (**7**)*

A mixture of the hydrazide **3** (2.44 g, 0.01 mol) and 2-chloro-1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl) ethanone (2.5 g, 0.01 mol) in pyridine (30 mL) was refluxed for 6 h, and then allowed to cool and poured into ice cold water (100 mL) containing few drops of dilute HCl. The precipitated solid was filtered off, dried, and recrystallized from ethanol to give compound **7**.

Pale yellow powder, Yield (70 %), mp 287–288 °C; IR (KBr) νmax/cm^{-1} : 3214 (NH), 3053 (CH–Ar), 2961–2934 (CH-sp^3), 1659 (C=O), 1607 (C=N); ^{1}H-NMR (DMSO-d_6): $\delta_{ppm} = 1.35$ (d, $J = 6.5$ Hz, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.0 (q, $J = 6.5$ Hz, 1H, CH), 5.94 (s, 2H, CH_2), 7.13–7.78 (m, 11H, Ar–H), 9.29 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): $\delta_{ppm} = 13.9$, 18.4 ($2CH_3$), 44.3 (CH), 55.1 (OCH_3), 60.1 (OCH_2 of furan ring), 105.6, 117.2, 118.5, 118.6, 125.2, 125.3, 125.5, 126.1, 126.4, 126.4, 126.9, 126.9, 128.1, 128.2, 128.3, 128.9, 129.1, 133.1, 133.2, 137.0, 156.8, 156.9, 172.8. Anal. Calcd for $C_{26}H_{24}N_4O_3$ (440.49): C, 70.89; H, 5.49; N, 12.72. Found: C, 70.74; H, 5.35; N, 12.81 %.

*Synthesis of 1-(3,5-dimethyl-pyrazol-1-yl)-2-(6-methoxynaphthalen-2-yl)propan-1-one (**8**)*

To a solution of hydrazide **3** (2.44 g, 0.01 mol) in ethanol (30 mL), acetyl acetone (1.3 g, 0.01 mol) and glacial acetic acid (0.5 mL) were added. The reaction mixture was heated under reflux for 8 h, then allowed to cool to room temperature. The solid product thus formed was filtered off, dried, and recrystallized from ethanol to give compound **8**. Colorless powder, Yield (65 %), mp 210–211 °C, IR (KBr) νmax/cm^{-1}: 3045 (CH–Ar), 2976–2948 (CH-sp3), 1669 (C=O), 1599 (C=N); ^{1}H-NMR (DMSO-d_6): $\delta_{ppm} = 1.44$ (d, $J = 6.5$ Hz, 3H, CH_3), 2.16, 2.46 (2s, 6H, $2CH_3$-pyrazole), 3.85 (q, 1H, CH), 3.86 (s, 3H, OCH_3), 6.16 (s, 1H, pyrazole-C_4), 7.13–7.81 (m, 6H, Ar–H); ^{13}C-NMR (DMSO-d_6): $\delta_{ppm} = 13.4$, 13.9, 18.4 ($3CH_3$), 44.3 (CH), 55.1 (OCH_3), 105.6, 111.5, 118.6, 125.5, 126.3, 126.8, 129.0, 133.1, 135.6, 136.2, 143.5, 151.3, 157.0, 174.0. MS (EI, 70 eV): *m/z* (%) = 308 (M^+, 17.2), 214 (86.5), 213 (100), 185 (32.8), 157 (21.8), 128 (37.5), 96 (55.9). Anal. Calcd for $C_{19}H_{20}N_2O_2$ (308.37): C, 74.00; H, 6.54; N, 9.08. Found: C, 74.12; H, 6.68; N, 9.15 %.

General procedure for the reaction of the hydrazide 3 with enaminones

To a solution of the enaminone derivatives (0.001 mol) in glacial acetic acid (10 mL), the hydrazide **3** (0.244 g, 0.001 mol) was added, and the reaction mixture was heated under reflux for 8 h. The reaction mixture was allowed to cool and then treated with ice cold water (30 mL) and the formed product was collected by filtration, dried, and re-crystallized from ethanol.

*2-(6-Methoxynaphthalen-2-yl)-1-(5-phenyl-pyrazol-1-yl)propan-1-one (**9**)*

Colorless powder, Yield (76 %), mp 187–188 °C; IR (KBr) νmax/cm^{-1}: 3065 (CH–Ar), 2978–2942 (CH-sp^3), 1667 (C=O), 1597 (C=N); ^{1}H-NMR (DMSO-d_6): $\delta_{ppm} = 1.43$ (d, $J = 6.5$ Hz, 3H, CH_3), 3.77 (q, $J = 6.5$ Hz, 1H, CH), 3.86 (s, 3H, OCH_3), 7.12–7.77 (2d, $J = 7.5$ Hz, 2H, H_4, H_5-pyrazole),7.14–7.76 (m, 11H, Ar–H); ^{13}C-NMR (DMSO-d_6): $\delta_{ppm} = 18.1$, (CH_3), 42.7 (CH), 55.0 (OCH_3), 105.5, 118.3, 125.0, 125.3, 125.9, 126.4, 126.5, 126.6, 127.3, 127.8, 128.2, 128.6, 128.9, 129.9, 133.1, 136.5, 136.5, 156.9, 172.1, 172.3; Anal. Calcd for $C_{23}H_{20}N_2O_2$ (356.42): C, 77.61; H, 5.66; N, 7.86. Found: C, 77.62; H, 6.58; N, 7.75 %.

*2-(6-Methoxynaphthalen-2-yl)-1-(5-thiophen-2-ylpyrazol-1-yl)propan-1-one (**10**)*

Pale yellow powder, Yield (73 %), mp 218–219 °C; IR (KBr) νmax/cm^{-1}: 3063 (CH–Ar), 2973–2935 (CH-sp^3), 1674 (C=O), 1612 (C=N); ^{1}H-NMR (DMSO-d_6): $\delta_{ppm} = 1.42$ (d, $J = 6.5$ Hz, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.0 (q, $J = 6.5$ Hz, 1H, CH), 7.12–8.99 (m, 11H, Ar–H); ^{13}C-NMR (DMSO-d_6): $\delta_{ppm} = 18.2$, (CH_3), 42.9 (CH), 55.0 (OCH_3), 105.6, 118.3, 124.1, 125.5, 126.5, 127.2, 128.5, 129.0, 130.4, 133.9, 136.5, 137.71, 139.0, 141.9, 145.3, 156.7, 156.9, 172.2. MS (EI, 70 eV): *m/z* (%) = 362 (M^+, 22.8), 280 (65.2), 279 (60.2), 214 (100), 213 (85.9), 150 (32.8), 128 (26.2), 84 (55.1), 77 (72.2). Anal. Calcd for $C_{21}H_{18}N_2O_2S$ (362.44): C, 69.59; H, 5.01; N, 7.73. Found: C, 69.68; H, 5.28; N, 7.69 %.

*Synthesis of 2-(6-methoxynaphthalen-2-yl)-1-(5-phenyl-2,3-dihydropyrazol-1-yl)propan-1-one (**11**)*

A mixture of the hydrazide **3** (0.244 g, 0.001 mol) and 3-dimethylamino-1-phenylpropan-1-one hydrochloride (0.213 g, 0.001 mol) in ethanol 20 mL containing 5 mL of acetic acid was refluxed for 8 h. The reaction mixture was cooled, treated with ice cooled water (30 mL) and the formed product was filtered off, dried, and recrystallized from ethanol. Colorless powder, Yield (76 %), mp 254–255 °C; IR (KBr) νmax/cm^{-1}: 3035 (CH–Ar), 2974–2946 (CH-sp^3), 1663 (C=O), 1611 (C=N); ^{1}H-NMR (DMSO-d_6): $\delta_{ppm} = 1.44$ (d, $J = 6.5$ Hz, 3H, CH_3), 1.94 (s, 2H, CH_2-pyrazoline), 3.83 (q, $J = 6.5$ Hz, 1H, CH), 3.86 (s, 3H, OCH_3), 4.8 (s, 2H, CH_2-pyrazoline), 7.12–7.79 (m, 11H, Ar–H), 8.9 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): $\delta_{ppm} = 18.0$ (CH_3), 35.8, 42.7 (CH), 55.0 (OCH_3), 60.2, 105.6, 118.5, 125.5, 126.1, 126.6, 127.5, 127.9, 128.1, 128.3, 128.5, 128.6, 128.6, 129.1, 132.9, 136.5, 137.3, 156.8, 172.3; Anal. Calcd for $C_{23}H_{22}N_2O_2$ (358.43): C, 77.07; H, 6.19; N, 7.82. Found: C, 77.11; H, 6.24; N, 7.72 %.

*Synthesis of 1-[3,5-diamino-4-(4-methoxyphenylazo)-pyrazol-1-yl]-2-(6-methoxynaphthalen-2-yl) propan-1-one (**12**)*

To a solution of the hydrazide **3** (0.244 g, 0.001 mol) in ethanol (20 mL), 2-[(4-methoxyphenyl)hydrazono]malononitrile was added. The reaction mixture was refluxed for 6 h. After cooling to room temperature, the formed product was filtered off and recrystallized from ethanol. Greenish powder, Yield (78 %), mp 243–245 °C; IR (KBr) νmax/cm^{-1}: 3342, 3245 (NH_2), 3064 (CH–Ar), 2979–2921 (CH-sp^3), 1685 (C=O), 1609 (C=N); ^{1}H-NMR (DMSO-d_6): $\delta_{ppm} = 1.43$ (d, $J = 6.5$ Hz, 3H, CH_3), 3.75, 3.80 (2s, 6H, 2OCH_3), 3.86 (q, $J = 6.5$ Hz, 1H, CH), 6.31, 8.22 (2s, 4H, 2NH_2), 6.98–7.81 (m, 10H, Ar–H); ^{13}C-NMR (DMSO-d_6): $\delta_{ppm} = 18.2$, (CH_3), 42.2 (CH), 55.0, 55.2 (2OCH_3), 105.5, 114.4, 118.4, 118.6, 122.5, 125.3, 125.7, 126.3, 126.7, 128.2, 128.6, 128.9, 129.1, 132.9, 133.1, 136.7, 156.9, 157.1, 157.2, 172.3; Anal. Calcd for $C_{24}H_{24}N_6O_3$ (444.49): C, 64.85; H, 5.44; N, 18.91. Found: C, 64.73; H, 5.30; N, 18.86 %.

General procedure for the condensation of naproxenoyl chloride with aminopyrazoles

A mixture of naproxenoyl chloride (0.248 g, 0.001 mol) and the requisite aminopyrazoles, namely, 4-amino-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one (0.2 g, 0.001 mol), 3,5-diamino-4-(4-methoxyphenylazo)-1*H*-pyrazole (0.232 g, 0.001 mol), or 2-(3,5-dimethyl-1*H*-pyrazol-4-ylsulfanyl)-phenylamine (0.219 g, 0.001 mol) in dioxane (20 mL) was treated with pyridine (0.5 mL). The reaction mixture was refluxed for 3 h, then allowed to cool. The solid product was collected by filtration and recrystallized from ethanol to give compounds **14–16**.

*N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-(6-methoxynaphthalen-2-yl)propionamide (**14**)*

Colorless powder, Yield (65 %), mp 184–186 °C; IR (KBr) νmax/cm^{-1}: 3218 (NH), 3039 (CH–Ar), 2979,

2932 (CH-sp^3), 1678 (C=O), 1660 (pyrazole C=O), 1601 (C=N); ^{1}H-NMR (DMSO-d_6): $\delta_{ppm} = 1.56$ (d, $J = 6.5$ Hz, 3H, CH_3), 1.91, 3.34 (2s, 6H, $2CH_3$-pyrazole), 3.84 (s, 3H, OCH_3), 3.90 (q, 1H, CH), 7.25–8.89 (m, 11H, Ar–H), 10.0 (s, 1H, NH).^{13}C-NMR (DMSO-d_6): $\delta_{ppm} = 18.5$, 21.0 (2 CH_3), 40.1 (NCH_3), 45.97 (CH), 55.1 (OCH_3), 105.6, 118.5, 124.1, 125.4, 125.5, 126.3, 127.5, 128.5, 129.3, 130.2, 132.9, 133.9, 135.6, 137.7, 139.0, 141.9, 145.7, 156.9, 171.9, 182.1. MS (EI, 70 eV): *m/z* (%) = 415 (M^+, 9.8), 258 (35.4), 230 (38.6), 203 (100), 202 (82.9), 188 (51.7), 157 (66.1), 77 (69.1). Anal. Calcd for $C_{25}H_{25}N_3O_3$ (415.48): C, 72.27; H, 6.06; N, 10.11. Found: C, 72.30; H, 6.19; N, 10.28 %.

*N-[5-amino-4-(4-methoxyphenylazo)-1H-pyrazol-3-yl]-2-(6-methoxynaphthalen-2-yl)-propionamide (**15**)*

Brown powder, Yield (63 %), mp 157–158 °C, IR (KBr) νmax/cm^{-1}: 3324, 3278, 3215 (NH_2,NH), 3073 (CH–Ar), 2985–2919 (CH-sp^3), 1678 (C=O), 1600 (C=N); ^{1}H-NMR (DMSO-d_6): $\delta_{ppm} = 1.53$ (d, $J = 6.5$ Hz, 3H, CH_3), 3.78, 3.80 (2s, 6H, $2OCH_3$), 3.86 (q, 1H, CH), 6.81, 8.06, 10.25 (3s, 4H, NH_2 + 2NH), 7.13–7.88 (m, 10H, Ar–H). ^{13}C-NMR (DMSO-d_6): $\delta_{ppm} = 18.51$ (CH_3), 42.5 (CH), 55.1, 55.9 ($2OCH_3$), 105.6, 113.9, 118.6, 122.6, 125.7, 126.4, 126.6, 126.8, 126.9, 128.3, 128.4, 129.1, 133.3, 133.3, 134.7, 136.5, 146.4, 157.2, 159.8, 174.6. Anal. Calcd for $C_{24}H_{24}N_6O_3$ (444.49): C, 64.85; H, 5.44; N, 18.91. Found: C, 64.79; H, 5.39; N, 18.88 %.

*N-[2-(3,5-dimethyl-1H-pyrazol-4-ylsulfanyl)-phenyl]-2-(6-methoxynaphthalen-2-yl)-propionamide (**16**)*

Reddish brown powder, Yield (66 %), mp 205–207 °C, IR (KBr) νmax/cm^{-1}: 3258, 3223 (2NH), 3062 (CH–Ar), 2975–2924 (CH-sp^3), 1665 (C=O), 1610 (C=N); ^{1}H-NMR (DMSO-d_6): $\delta_{ppm} = 1.45$ (d, $J = 6.5$ Hz, 3H, CH_3), 2.09, 2.59 (2s, 6H, $2CH_3$-pyrazole), 3.85 (q, 1H, CH), 3.86 (s, 3H, OCH_3), 7.13–7.87 (m, 11H, Ar–H + NH), 9.65 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): $\delta_{ppm} = 12.3$, 13.2, 18.5 ($3CH_3$), 44.6 (CH), 55.1 (OCH_3), 105.6, 118.5, 118.7, 125.5, 125.6, 126.3, 126.6, 126.8, 127.0, 128.1, 128.4, 129.1, 129.2, 130.7, 133.2, 136.3, 145.6, 157.0, 157.1, 174.5. Anal. Calcd for $C_{25}H_{25}N_3O_2S$ (431.55): C, 69.58; H, 5.84; N, 9.74. Found: C, 69.62; H, 5.76; N, 9.65 %.

*Synthesis of N-(4-acetylphenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (**17**)*

A mixture of naproxenoyl chloride (2.48 g, 0.01 mol) and *p*-aminoacetophenone (1.35 g, 0.01 mol) in dioxane (30 mL) containing 0.5 mL of pyridine was refluxed for 3 h, then allowed to cool. The solid product that obtained was collected by filtration, dried, and recrystallized from ethanol to give compound **17**. Pale yellow powder, Yield (70 %), mp 168–170 °C, IR(KBr) νmax/cm^{-1}: 3332 (NH), 2928 (CH-sp^3), 1672 (C=O). ^{1}H-NMR (DMSO-d_6): $\delta_{ppm} = 1.52$ (d, $J = 6.5$ Hz, 3H, CH_3), 2.51 (s, 3H, $COCH_3$), 3.86 (s, 3H, OCH_3), 4.00 (q, $J = 6.5$ Hz, 1H, CH), 7.14–7.92 (m, 10H, Ar–H), 10.47 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): $\delta_{ppm} = 18.3$ (CH_3), 26.3 (CH_3), 44.5 (CH), 55.1 (OCH_3), 105.6, 118.3, 119.0, 125.4, 126.1, 126.3, 126.8, 128.3, 129.1, 129.3, 131.5, 133.2, 132.1, 136.5, 143.5, 157.9, 172.8, 196.3 (2C=O). Anal. Calcd for $C_{22}H_{21}NO_3$ (347.41): C, 76.06; H, 6.09; N, 4.03. Found: C, 76.10; H, 6.19; N, 4.18 %.

General procedure for the synthesis of chalcones **18–20**

A mixture of *N*-(4-acetylphenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (**17**) (0.694 g, 0.002 mol), appropriate aromatic aldehyde (0.002 mol), and 10 % aqueous potassium hydroxide (10 mL) in ethanol (25 mL) was stirred at room temperature for about 3 h. The resulting solid was filtered off, rinsed with water, dried, and crystallized from ethanol.

*2-(6-Methoxynaphthalen-2-yl)-N-[4-(3-phenylacryloyl)-phenyl]propionamide (**18**)*

Yellow crystals, yield (74 %), mp 217–218 °C, IR (KBr) νmax/cm^{-1}: 3245 (NH), 2984, 2845 (CH-sp^3), 1678 (C=O), 1654 (C=O, chalcone); ^{1}H-NMR (DMSO-d_6): $\delta_{ppm} = 1.52$ (d, $J = 6.5$ Hz, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.03 (q, $J = 6.5$ Hz, 1H, CH), 7.15–8.17 (m, 15H, Ar–H), 7.58 (d, $J = 14.8$ Hz, 1H, CH=), 7.79 (d, $J = 14.8$ Hz, 1H, CH=), 10.03 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): $\delta_{ppm} = 18.6$ (CH_3), 46.0 (CH), 55.1 (OCH_3), 105.6, 118.5, 121.9, 125.5, 126.2, 126.8, 128.2, 128.3, 128.7, 128.7, 128.8, 128.9, 129.1, 129.4, 130.4, 132.2, 133.2, 134.2, 134.5, 134.7, 136.6, 143.3, 143.7, 157.1, 172.9, 186.5 (2C=O); Anal. Calcd for $C_{29}H_{25}NO_3$ (435.51): C, 79.98; H, 5.79; N, 3.22. Found: C, 79.90; H, 5.74; N, 3.29 %.

*2-(6-Methoxynaphthalen-2-yl)-N-{4-[3-(4-methoxyphenyl)-acryloyl)]-phenyl}-propionamide (**19**)*

Yellow crystals, Yield (77 %), mp 229–231 °C, IR(KBr) νmax/cm^{-1}: 3244 (NH), 2975, 2839 (CH-sp^3), 1659 (C=O), 1639 (C=O, chalcone); ^{1}H-NMR (DMSO-d_6): $\delta_{ppm} = 1.52$ (d, $J = 6.5$ Hz, 3H, CH_3), 3.82, 3.86 (2s, 6H, $2OCH_3$), 3.87 (q, 1H, CH), 7.29–8.14 (m, 14H, Ar–H), 7.61 (d, $J = 15.2$ Hz, 1H, CH=), 7.91 (d, $J = 15.2$ Hz, 1H, CH =), 10.53 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6):

δ_{ppm} = 18.4 (CH_3), 44.4 (CH), 55.1, 55.6 ($2OCH_3$), 105.6, 114.3, 118.4, 118.6, 119.3, 125.1, 126.2, 126.8, 127.3, 128.3, 128.6, 129.1, 129.6, 130.6, 131.2, 131.7, 132.4, 133.2, 136.6, 143.3, 143.4, 157.0, 161.2, 164.1, 172.8, 187.3 (2C=O). MS (EI, 70 eV): *m/z* (%) = 465 (M^+, 18.2), 358 (64.2), 332 (31.2), 304 (12.6), 280 (54.9), 253 (100), 237 (64.4), 213 (75.4), 107 (66.8), 77 (65.3). Anal. Calcd for $C_{30}H_{27}NO_4$ (465.54): C, 77.40; H, 5.85; N, 3.01. Found: C, 77.55; H, 5.78; N, 3.17.

*2-(6-Methoxynaphthalen-2-yl)-N-{4-[3-(3-methylthiophen-2-yl)-acryloyl)]phenyl}-propionamide (**20**)*

Brown powder, Yield (72 %), mp 186–187 °C, IR(Br) *v*max/cm^{-1}: 3312 (NH), 2965, 2829 (CH-sp^3), 1686 (C=O), 1645 (C=O, chalcone); ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 1.43 (d, *J* = 6.5 Hz, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.02 (q, 1H, CH), 7.32–8.07 (m, 12H, Ar–H), 7.68 (d, *J* = 15.6 Hz, 1H, CH=), 7.89 (d, *J* = 15.6 Hz, 1H, CH=), 10.5 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): δ_{ppm} = 12.9 (CH_3), 18.5 (CH_3), 46.0 (CH), 55.1 (OCH_3), 105.6, 118.5, 118.6, 119.2, 125.4, 126.2, 126.8, 128.3, 128.6, 129.1, 129.7, 131.6, 132.0, 132.1, 133.2, 133.7, 134.2, 134.3, 136.5, 142.6, 143.5, 157.0, 172.9, 184.5 (2C=O). Anal. Calcd for $C_{28}H_{25}NO_3S$ (455.57): C, 73.82; H, 5.53; N, 3.07. Found: C, 73. 79; H, 5.43; N, 3.18 %.

General procedure for the synthesis of 5-aryl-4,5-dihydro-1*H*-pyrazoles **21–23**

A solution of the appropriate chalcone **18–20** (0.01 mol) and hydrazine hydrate (0.02 mol) in ethanol (30 mL) was refluxed for 3 h. The reaction mixture was cooled and kept at 0 °C overnight. The resulting solid was collected by filtration and recrystallized from ethanol to give compounds **21–23**.

*2-(6-Methoxynaphthalen-2-yl)-N-[4-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)-phenyl]propion-amide (**21**)*

Colorless crystals, Yield (74 %), mp 265–266 °C, IR(KBr) *v*max/cm^{-1}: 3325, 3215 (NH), 2975, 2856 (CH-sp^3), 1674 (C=O), 1608 (C=N); ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 1.49 (d, *J* = 6.65 Hz, 3H, CH_3), 3.39 (dd, *J* = 11.6, 5.6 Hz, 1H, pyrazoline H_A-4), 3.65 (dd, *J* = 7.2, 5.6 Hz, 1H, pyrazoline H_B-4), 3.86 (s, 3H, OCH_3), 4.00 (q, 1H, CH), 4.80 (dd, *J* = 11.6, 5.6 Hz, 1H, pyrazoline H-5), 7.14–7.81 (m, 16H, Ar–H + NH), 10.27 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): δ_{ppm} = 18.5 (CH_3), 38.9 (CH_2 pyrazoline), 45.9 (CH), 55.1 (OCH_3), 63.6 (pyrazole-C_5), 105.6, 118.6, 119.0, 125.1, 125.4, 125.9, 126.3, 126.6, 126.8, 127.1, 127.3, 128.0, 128.3, 128.4, 128.9, 129.1, 133.2, 136.9, 138.2, 139.2, 143.0, 148.5, 157.1, 157.1, 161.8, 172.5 (C=O). MS (EI, 70 eV): *m/z* (%) = 449 (M^+, 15.6), 418 (24.7), 372 (25.6), 304 (10.5), 292 (42.6), 264 (31.2), 236 (16.4), 213 (100), 145 (12.6), 77 (68.9). Anal. Calcd for $C_{29}H_{27}N_3O_2$ (449.54): C, 77.48; H, 6.05; N, 9.35. Found: C, 77.55; H, 6.16; N, 9.40 %.

*2-(6-Methoxynaphthalen-2-yl)-N-{4-[5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl]-pheny}-propionamide (**22**)*

Colorless crystals, Yield (72 %), 254–256 °C, IR (KBr) *v*max/cm^{-1}: 3337, 3215 (2NH), 2938, 2839 (CH-sp^3), 1679 (C=O). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 1.49 (d, *J* = 6.5 Hz, 3H, CH_3), 3.32 (dd, *J* = 12.0, 5.4 Hz, 1H, pyrazoline H_A-4), 3.60 (dd, *J* = 7.8, 5 Hz, 1H, Pyrazoline H_B-4), 3.72, 3.86 (2s, 6H, $2OCH_3$), 3.90 (q, 1H, CH), 4.8 (dd, *J* = 12.0, 5 Hz, 1H, pyrazoline H-5), 6.88–7.82 (m, 15H, ArH + NH), 10.26 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): δ_{ppm} = 18.6 (CH_3), 40.5 (CH_2 pyrazoline), 45.8 (CH), 54.9, 55.0 ($2OCH_3$), 63.1 (CH pyrazoline), 105.6, 113.6, 113.9, 118.6, 118.9, 125.3, 125.8, 126.2, 126.4, 126.7, 127.6, 128.2, 128.3, 129.0, 133.1, 134.8, 136.8, 138.6, 139.0, 148.4, 156.9, 158.3, 172.3 (C=O). Anal. Calcd for $C_{30}H_{29}N_3O_3$ (479.22): C, 75.13; H, 6.10; N, 8.76. Found: C, 75.25; H, 6.18; N, 8.69 %.

*2-(6-Methoxynaphthalen-2-yl)-N-{4-[5-(3-methylthiophen-2-yl)-4,5-dihydro-1H-pyrazol-3-yl]-pheny}-propionamide (**23**)*

Pale yellow powder, Yield (70 %), 237–238 °C, IR (KBr) *v*max/cm^{-1}: 3310, 3270 (2NH), 2969, 2932 (CH-sp^3), 1669 (C=O). ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 1.49 (d, *J* = 6.5 Hz, 3H, CH_3), 2.18 (s, 3H, CH_3), 3.35 (dd, *J* = 11.9, 4.8 Hz, 1H, pyrazoline H_A-4), 3.75 (dd, *J* = 7.5, 4.8 Hz, 1H, Pyrazoline H_B-4), 3.86 (s, 3H, OCH_3), 3.90 (q, 1H, CH), 5.08 (dd, *J* = 11.9, 4.8 Hz, 1H, pyrazoline H-5), 6.80–7.80 (m, 13H, Ar–H + NH), 10.20 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): δ_{ppm} = 13.5 (CH_3), 18.6 (CH_3), 38.9 (CH_2 pyrazoline), 45.9 (CH), 55.1 (OCH_3), 59.3 (CH pyrazoline), 105.8, 118.4, 118.6, 119.0, 122.7, 125.3, 126.2, 126.7, 127.9, 128.3, 129.3, 130.1, 132.9, 133.8, 134.2, 136.8, 139.2, 139.8, 149.4, 157.1, 157.9 and 172.35 (C=O). Anal. Calcd for $C_{28}H_{27}N_3O_2S$ (469.60): C, 71.61; H, 5.80; N, 8.95. Found: C, 71.53; H, 5.76; N, 8.87 %.

Biological screening

Materials and methods

Animals-adult rats of both sexes weighing 150–200 g and adult mice weighing 20–25 g were used in the experiments. Animals were housed under standardized conditions for

light and temperature and received standard rat chow and tap water and libitum. Animals were randomly assigned to different experimental groups, each kept in a separate cage. All animal procedures were performed after approval from the Ethics committee of the National Research Center.

Drugs and chemicals

Carrageenan Iambda Sigma–Aldrich chemical company (USA), naproxen Khahira Pharmaceutical and Chemical Company, Cairo, Egypt.

Anti-inflammatory testing

The carrageenan rat paw edema model of inflammation was used to evaluate the anti-inflammatory properties of the tested compounds. Rats were randomly assigned to treatment groups and sterile carrageenan lambda (100 µl of a 1 % solution in saline) was injected sub-planter into right hind paw of the rat. Carrageenan caused visible redness and pronounced swelling that was well developed by 4 h and persisted for more than 48 h. Right hind paw was measured with a planimeter (Obukowics *et al*., 1998; Meng *et al*., 1999) before, and at 1, 2, 3, and 4 h after carrageenan injection. Due to water insolubility of the tested compounds, they were dissolved in DMSO then injected i.p (10 mg/kg b wt). The control animals were injected (i.p) with appropriate volume of DMSO. The standard drug was naproxen (10 mg/kg wt). Different compounds or naproxen were given 1 h before carrageenan injection.

Analgesic testing

The hot-plate test was performed on mice by using an electronically controlled hot-plate (ugo Basile, Italy) heated to 52 °C (0.1 C), for possible centrally mediated analgesic effect of the drugs. Twelve groups of rats each were given vehicle and/or the different compounds and the last group received naproxen (20 mg/kg wt) 60 min prior to testing. Latency to lick a hind paw or jumping (Winter *et al*., 1962) was recorded sequentially before and at 1 and 2 h post treatment.

Ulcerogenic effects

Groups of 5 male Wistar rats with a weight between 150 and 175 g are used. They are starved 48 h prior to drug administration. The test compounds are administered orally in 10 mL/kg as aqueous suspension. Doses are chosen which are highly active in the activity (10 mg/kg) and used. The animals are sacrificed after 7 h. Stomachs are removed and placed on saline soaked filter paper until inspection. A longitudinal incision along the greater curvature is made with fine scissor. The stomach is inverted over the index finger and the presence or the absence of gastric irritation is determined. The presence of a single or multiple lesions (erosion, ulcer, or perforation) is considered to be positive (Amr and Abdulla, 2006). The number of ulcers and the occurrence of hyperemia is noted (determine ulcer index).

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