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Original Article

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Synthesis and analgesic activity of new phenoxybenzylidene aroylhydrazine derivatives

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Abstract

A series of phenoxybenzylidene aroylhydrazine derivatives were synthesized and their structures were confirmed using FT-IR and 1H-NMR spectroscopy. Analgesic profiles of all compounds were examined using abdominal constriction test (writhing test). Most of synthesized compounds induced significant reduction in the writhing response as compared with controls. The most active compounds exhibited an analgesic activity comparable with that of mefenamic acid.

Keywords: Hydrazine, Analgesic Activity, Fenamate, NSAIDs.

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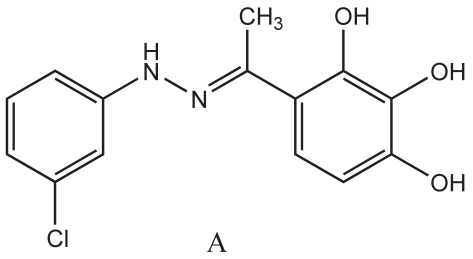
Introduction

Hydrazones are shown to have many biological activities including antiviral (Abdel-Aal et al., 2006), antimicrobial (Rollas et al., 2007), analgesic and antinociceptive (Lima et al., 2000), anti-inflammatory (Todeschini et al., 1998), antitumor (Pandey et al., 2002), and anticonvulsant activities (Ragavendran et al., 2007). Some studies suggest that hydrazone derivatives can function as a dual inhibitor of COX/5-LO (Figure 1) (Leval et al., 2002).

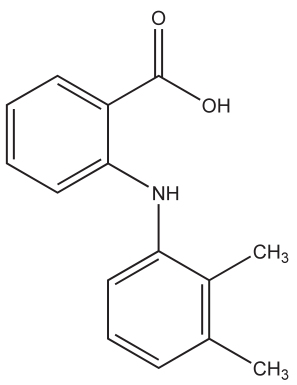
In addition, there are many known non-steroidal anti-inflammatory drugs (NSAIDS) with fenamate structure (compound B). It is shown that fenamate-like derivatives C with hydrazone moiety have analgesic and anti-inflammatory effects (Figure 2) (Almasirad et al., 2006).

In this study we aimed to synthesize new hybrid molecules with both hydrazone and fenamate-like structures to achieve new compounds with improved activity.



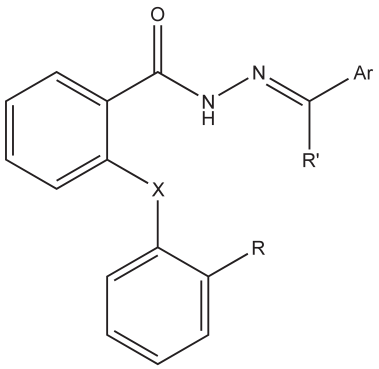
A

Figure 1: Structure of a dual COX/5-LO inhibitor



Mefenamic acid

B



C

Figure 2: Mefenamic acid and hydrazones with fenamate like structure

Material and Methods

Chemistry

Chemicals were purchased from Merck Chemical Company (Darmstadt, Germany) and ACROS. Thin layer chromatography was used to assess end of the reactions and purity of the synthesized compounds. The melting points were determined in open capillary tubes and presented uncorrected. 1H-NMR spectra were obtained using a Bruker FT-400 spectrometer (Bruker, Rheinstetten, Germany). Tetramethylsilane was used as an internal standard. The FT-IR spectra were obtained using a Nicolet FT-IR Magna 550 Spectrographs (KBr disks)

(Nicolet, Madision, WI, USA). Target compounds were synthesized according to the pathways illustrated in figures 3 to 5.
In this research, acids 3, 7 and 8 were prepared according to our previously developed methods (scheme 1) (Almasirad et al., 2011). The hydrazides 14-17 were also prepared by an already described procedures (Almasirad et al., 2006).

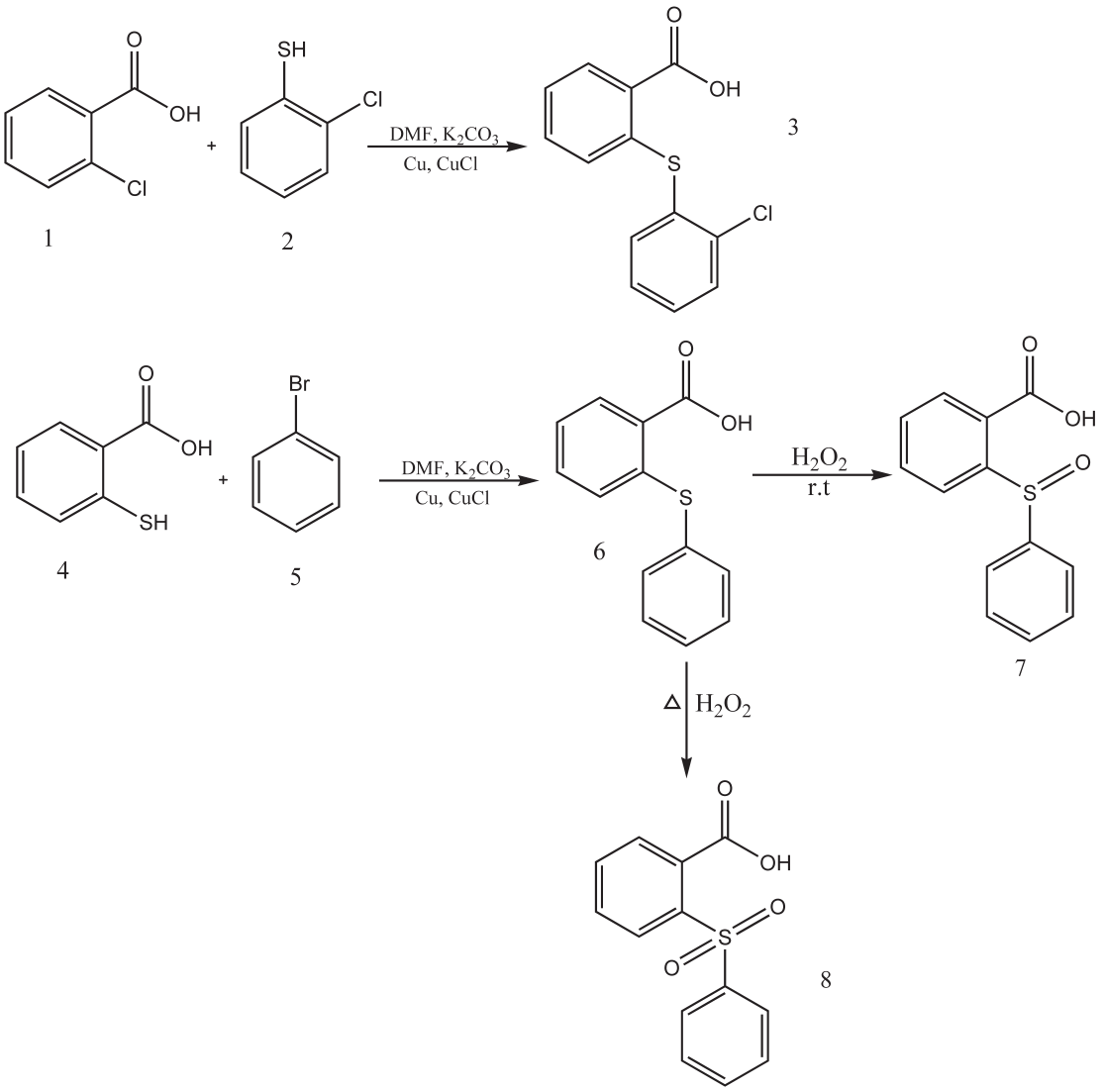
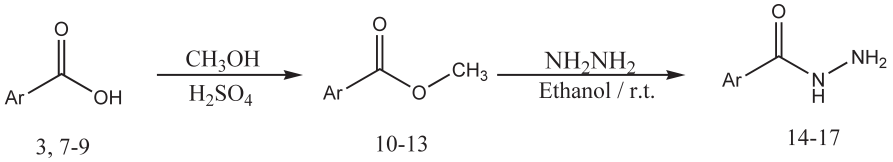


Figure 3: Synthesis pathway of intermediates 3,6,10 and 11



Ar:
3:2-(2-chlorophenylthio)phenyl
7:2-(phenylsulfinyl)phenyl
8:2-(phenylsulfonyl)phenyl
9:2-hydroxyphenyl

Figure 4: Synthesis pathway of hydrazides 14-17

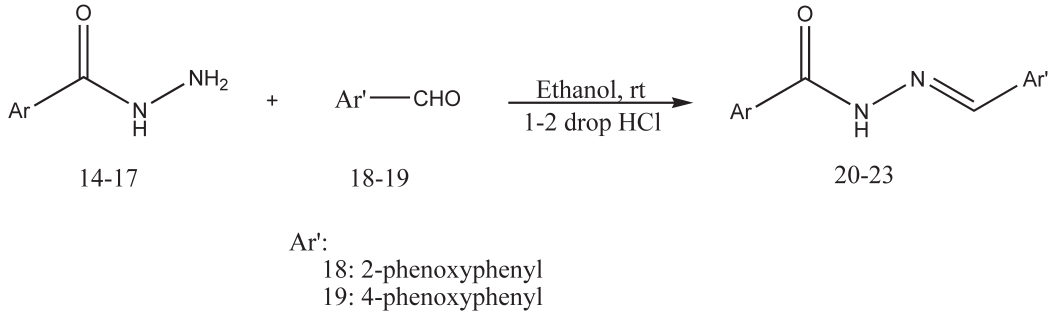


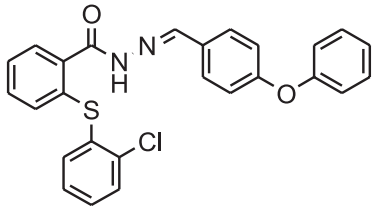
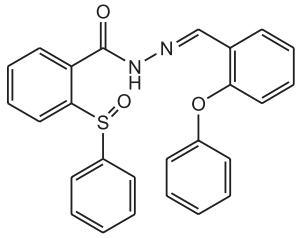
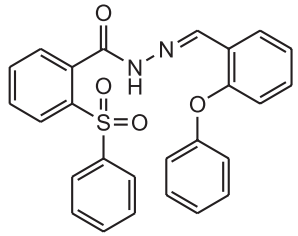
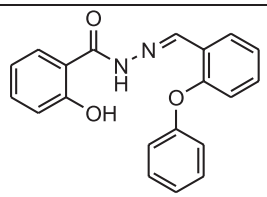
Figure 5: Synthesis pathway of target compounds (hydrazine derivatives)

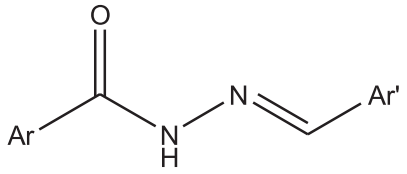
Synthesis of target compounds

General procedure for the preparation of target compounds 20-23

A mixture of hydrazide 14-17 (2 mmol) and aldehydes 18-19 (2.05 mmol) was stirred at room temperature for 3-5 hr, in the presence hydrochloric acid as a catalyst. The end of the reaction was observed by TLC, and then the mixture was neutralized by 10% aqueous solution of sodium bicarbonate. The resulting precipitate was filtered, washed with 20 ml water, dried and crystallized by ethanol (Table 1).

Table 1: Physical properties of synthesized compounds

Compound No	Molecular Formula	Structure	Molecular Weight	MP°C	yield %
20	$C_{26}H_{19}N_2ClO_2S$		458.5	145-147	64%
21	$C_{26}H_{20}N_2O_3S$		440	183-185	73%
22	$C_{26}H_{20}N_2O_4S$		456	127-129	65%
23	$C_{20}H_{16}N_2O_3$		332	138-140	



Spectral data of selected compounds

Compound 20: IR (KBr): ν cm-1, 3328(NH), 1684(C=O), 1638(C=N).
1H-NMR (DMSO-d6): δ ppm 11.26(s, 1H, NH), 8.17 (s, 1H, CH=N), 7.86(d, J=8.0Hz, 1H, aromatic), 7.67-6.94 (m, 12H, aromatic), 6.92-6.88(m, 4H, aromatic).

Compound 21: IR (KBr): ν cm-1, 3314(NH), 1687(C=O), 1638(C=N), 1059(S=O). 1H-NMR (DMSO-d6): δ ppm 11.10(s, 1H, NH), 8.29(s, 1H, CH=N), 7.98(d, J=7.8Hz, 1H, aromatic), 7.83-7.22(m, 13H, aromatic), 6.97-6.96(m, 4H, aromatic).

Compound 22: IR (KBr): ν cm-1, 3315(NH), 1680(C=O), 1638(C=N), 1306, 1154(SO2).
1H-NMR (DMSO-d6): δ ppm 10.98(s, 1H, NH), 8.30(s, 1H, N=CH), 8.05(d, J=7.8Hz, 1H, aromatic), 7.97(d, J=8.2Hz, 1H, aromatic) 7.90-7.20(m, 12H, aromatic), 6.98-6.89(m, 4H, aromatic).

Compound 23: IR (KBr): ν cm-1, 3325(OH, NH), 1686(C=O), 1639(C=N).
1H-NMR (DMSO-d6) δ ppm: 11.70(s, 1H, NH), 9.93(bs, 1H, OH), 8.16(s, 1H, N=CH), 7.78-7.01(m, 8H, aromatic), 6.97-6.88(m, 5H, aromatic).

Pharmacology

Male NMRI mice weighting 20-25 g (from animal house of Faculty of Pharmacy, TUMS) were used for abdominal constriction test (writhing test). The animals were housed in colony cages under constant temperature (22 ± 2°C) and a 12 h light/dark schedule. Animals were allowed free access to standard diet and tap water except during the experiment. The animals were allowed to habituate to the laboratory environment for 2 h, before the experiments were initiated. An approval of study protocol was obtained from TUMS ethical committee and all ethical
considerations for use of laboratory animals were carefully observed. A suspension of compounds in saline and tween 80 (4%w/v) was prepared and administered intraperitoneally (IP) (30 mg/kg; 0.2 ml/20g). Mefenamic acid (Hakim Pharmaceutical Co) (30 mg/kg, IP) (Almasirad et al., 2011) was used as standard drug under the same conditions. The control group received vehicle (0.2 ml/20g, IP) alone.

Analgesic Activity

The analgesic activity of the compounds was determined in vivo by the by acetic acid induced writhing method (0.6%; 0.1 ml/10g) in mice (Almasirad et al., 2005). An acetic acid solution was administered IP 30 minutes after administration of compounds. Antinociception was recorded by counting the number of writhes immediately after injection of acetic acid and during 30 minutes. The analgesic activity was quantified as the percentage of inhibition that was calculated according to the following formula:

Percentage inhibition of writhing = (1-T/S) × 100
where S and T are the number of writhes in the control and drug administered groups, respectively.

Statistics

The data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey multicomparison test. Differences with $P < 0.05$ between experimental groups were considered statistically significant.

Results

The structures of target compounds were confirmed using FT-IR, 1H-NMR spectra. Pharmacological activities are summarized in Table 2. All compounds except compound 24 were active analgesic agents. The analgesic activity of compounds 20 and 21 was found to be comparable with mefenamic acid.

Table 2: Effects of Compounds 20 - 23 and mefenamic acid in the abdominal constrictions induced by acetic acid in mice.

Compound	Dose (mg/kg)1	Constriction No. (mean ± SEM)	Inhibition (%)2	P value
Control	-	63.5±16.77	-	-
mefenamic acid	30	8.167±3.312	87.13	P < 0.001
20	30	11.00±4.427	82.67	P < 0.001
21	30	10.5±9.311	83.46	P < 0.001
22	30	20.50±10.71	67.71	P < 0.001
23	30	68.83±22.89	-0.08	P > 0.05

1- Number of animals in each group n= 6; 2 % inhibition obtained by comparison with vehicle control group

Discussion

Pharmacological tests showed that both 2-phenoxybenzyliden and 4-phenoxybenzyliden moieties are potent compounds. Presence of a fenamate-like structure in the aroyl part of the compounds 20-22 has a critical role in their activity. Substitution of the fenamate like structure in aroyl part with another aryl group (compound 23) has a deleterious effect on the analgesic activity of the compounds.
Comparison of compounds 20 and 21 with 22 showed that sulfur or sulfoxide was the best linker in the aroyl part of the target compounds and oxidation to sulfone had a decrescent effect on analgesic potency.

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