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Note

Synthesis of some new pyrazolines and isoxazoles carrying 4-methylthiophenyl moiety as potential analgesic and anti-inflammatory agents

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A series of new pyrazolines **3a-m** and isoxazoles **4a-k** have been synthesized from 4-acetylthioanisole, **1** with aryl aldehydes through α, β-unsaturated ketones. The structures of the newly synthesized compounds have been confirmed on the basis of elemental analysis and spectral studies. The newly synthesized title compounds have been tested for their analgesic and anti-inflammatory activity. Some of the compounds exhibited encouraging results.

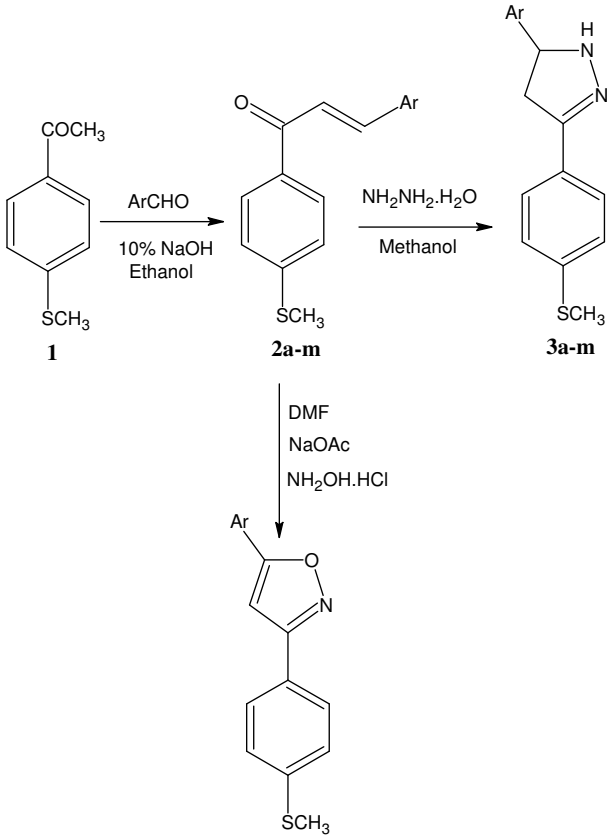
Keywords: 4-Acetylthioanisole, arylaldehydes, propenones, pyrazolines, isoxazoles, analgesic, anti-inflammatory activity

Pyrazolines and isoxazoles have been found to be associated with diverse biological activities and numerous reports have appeared in the literature, which highlighted their chemistry and use. Pyrazole derivatives were shown to possess many biological activities including antibacterial[1], antifungal[2], anti-inflammatory[3], anti-depressant[4], anti-tumor[5], muscle relaxant[6], anti-arthritic[7], analgesic[8] and anticonvulsant[9] properties. Also, varied medicinal activities such as anti-inflammatory[10], antibacterial[11], anti-convulsant[12], antibiotic[13], anti-tubercular[14], anti-fungal[15] and anxiolytic activity[16] have been reported for isoxazole derivatives. Moreover, it has been established that introduction of thiophenyl group in strategic positions of many molecules altered the biological activity considerably[17-19]. Keeping this in view, it has been planned to synthesize the new pyrazolines **3a-m** and isoxazoles **4a-k** containing methylthio phenyl group in position 3 and aryl groups in position 5 and evaluate their *in vivo* analgesic and anti-inflammatory properties. The present study describes the synthesis of hitherto unreported (2*E*)-3-(aryl/heteroaryl)-1-[4-(methylthio) phenyl] prop-2-en-1-one **2a-h** and their cyclized products *viz.*, 5-(aryl/heteroaryl)-3-[4-(methylthio)phenyl]-4,5-dihydro-1*H*-pyrazoles, **3a-m** and 5-(aryl/heteroaryl)-3-[4-(methylthio)phenyl]isoxazoles, **4a-k**, starting from 4-methylthioacetophenone. It also includes analgesic and anti-inflammatory studies of title compounds.

Results and Discussion

The reaction sequences for the synthesis of title compounds are shown in **Scheme I**. The key intermediates 1-[4-(methylthio)phenyl]-3-aryl/heteroaryl-propen-1-ones **2a-m** were prepared by treating 4-acetylthioanisole, **1** with substituted aryl/heteroaryl aldehydes in presence of sodium hydroxide according to Claisen-Schmidt condensation. These propenones **2a-m** are used as suitable precursors for the synthesis of pyrazolines **3a-m** and isoxazoles **4a-k**. The intermediates **2a-m**, when treated with hydrazine hydrate in ethanol afforded 3-[4-(methylthio)phenyl]-5-aryl/heteroarylpyrazolines **3a-m**. On the other hand, the compounds **2a-k** on treatment with hydroxylamine hydrochloride in dimethylformamide and sodium acetate yielded 3-[4-(methylthio)phenyl]-5-aryl/heteroarylisoxazoles **4a-k**. All the newly synthesized compounds were characterized by analytical, FTIR, ^{1}H and ^{13}C NMR and mass spectral data. The characterization data of all the new compounds are summarized in **Tables I** and **II**. The newly synthesized compounds were screened for their analgesic and anti-inflammatory activities and results of the screening studies are tabulated in **Tables III** and **IV** respectively.

The formation of pyrazolines was confirmed by FTIR, ^{1}H and ^{13}C NMR, mass spectral data and elemental analysis. The IR spectrum of compound **3a** exhibited peaks due to groups NH, CH_3, C=N and C=C at 3347, 2916, 1586 and 1494 cm^{-1} respectively. Its ^{1}H NMR spectrum showed pairs of doublets of doublet in the region δ 2.95-3.03 (J = 8.4 Hz, 8.4 Hz) and 3.36-3.45 (J = 10.5 Hz, 10.5 Hz) respectively, due to geminal and vicinal coupling of CH_2 protons of the pyrazoline ring. Further, the CH proton of the ring resonated as a doublet of doublets at δ 4.83-4.89



Scheme I

(J = 8.4 Hz, 8.9 Hz) due to vicinal coupling with the two magnetically non-equivalent protons of the methylene group at position 4 of the pyrazoline ring. The appearance of doublets at δ 7.12, 7.58 and multiplet at 7.21-7.25 was due to aromatic protons of 4-methylthiophenyl and 4-methylphenyl moieties respectively. Its ^{13}C NMR spectrum showed peaks at δ 15.45, 21.04, 41.21, 63.96, 126.07, 126.17, 126.30, 129.43, 129.54, 137.44, 139.39, 139.72 and 150.86 which were due to SCH_3, CH_3, CH_2, CH of pyrazoline, C_3 and C_5 of methylthiophenyl, C_2 and C_6 of methylphenyl, C_3 and C_5 of methylphenyl, C_2 and C_6 of methylthiophenyl, C_1 of methylthiophenyl, C_4 of methylphenyl, C_1 of methylphenyl, C_4 of methylthiophenyl and C_3 of pyrazole ring. The peaks due to quaternary carbon atoms disappeared on DEPT experimentation. Further, ESI mass spectrum showed the base peak at *m/z* 283 (M+1) which is in agreement with the molecular formula $C_{17}H_{18}N_2S$.

The conversion of propenones **2a-k** to isoxazoles **4a-k** was confirmed by FTIR, ^{1}H and ^{13}C NMR and mass spectral studies in addition to elemental analysis. IR spectrum of **4b** showed absorption bands at 3113, 1595, 1489, 1020 and 816 cm^{-1} indicating the presence of CH_3, C=N, C=C, C-O-C and N-O groups respectively. Its ^{1}H NMR spectrum displayed two singlets at δ 2.50 and 6.79 due to SCH_3 and CH of isoxazole ring respectively. Further, two doublets appeared at δ 7.30 and 7.48 which were due to four

Table I — Characterization data of propenones **2a-h**

Compd	Ar	Mol. formula	Mol. wt	m.p. (°C)	Yield (%)	% Found (Calcd) C	H	N
2a	4,4′- Biphenyl	$C_{22}H_{18}OS$	330.44	122-24	92	79.90 (79.96	5.43 5.46	0.0 0.0)
2b	2-Amino-3-pyridyl	$C_{15}H_{14}N_2OS$	270.35	116-20	94	66.29 (66.34	5.30 5.34	10.40 10.44)
2c	8-Quinolinyl	$C_{19}H_{15}NOS$	305.39	76-78	90	74.79 (74.75	4.99 4.95	4.63 4.61)
2d	4-Methoxy-2,3,6-trimethylphenyl	$C_{20}H_{22}O_2S$	326.45	120-22	91	73.62 (73.65	6.83 6.80	0.0 0.0)
2e	2-Bromo-6-nitro phenyl	$C_{16}H_{12}BrNO_3S$	378.24	110-15	92	50.88 (50.85	3.26 3.29	3.76 3.76)
2f	2,4,5-Trichloro phenyl	$C_{16}H_{11}Cl_3OS$	357.68	130-32	85	53.77 (53.73	3.13 3.15	0.0 0.0)
2g	2-Furyl	$C_{14}H_{12}O_2S$	244.31	120-22	78	68.88 (68.84	4.98 4.95	0.0 0.0)
2h	6-Methoxy-2-naphthyl	$C_{21}H_{18}O_2S$	334.43	130-32	88	75.46 (75.42	5.48 5.44	0.0 0.0)

Table II — Characterization data of compounds **3a-m** and **4a-k**

Compd	Ar	Mol. formula	Mol. wt	m.p. (°C)	Yield (%)	% Found (Calcd) C	H	N
3a	4-Methylphenyl	$C_{17}H_{18}N_2S$	282.40	114-16	78	71.69 (71.66	6.03 6.01	10.42 10.44)
3b	Phenyl	$C_{16}H_{16}N_2S$	268.37	90-92	78	72.29 (72.32	6.45 6.42	9.90 9.92)
3c	4-Methoxyphenyl	$C_{17}H_{18}N_2OS$	298.40	115-18	76	68.44 (68.42	6.05 6.08	9.36 9.39)
3d	4-Chlorophenyl	$C_{16}H_{15}ClN_2S$	302.82	118-20	85	63.44 (63.46	4.95 4.99	9.29 9.25)
3e	Biphenyl	$C_{22}H_{20}N_2S$	344.47	120-23	80	76.73 (76.71	5.82 5.85	8.15 8.13)
3f	3.4-Dimethoxyphenyl	$C_{18}H_{20}N_2O_2S$	328.43	110-12	68	65.85 (65.83	6.16 6.14	8.56 8.53)
3g	2-Amino-3-pyridyl	$C_{15}H_{16}N_4S$	284.38	126-28	73	63.38 (63.35	5.66 5.67	19.72 19.70)
3h	4-Quinolinyl	$C_{19}H_{17}N_3S$	319.42	110-12	67	72.36 (72.38	5.77 5.79	8.06 8.04)
3i	4-Methoxy-2,3,6-trimethyl phenyl	$C_{20}H_{24}N_2OS$	340.48	118-20	81	70.56 (70.55	7.3 7.1	8.26 8.23)
3j	2-Bromo-6-nitrophenyl	$C_{16}H_{14}Br\ N_3O_2S$	392.27	120-22	65	48.96 (48.99	3.63 3.67	10.74 10.71)
3k	2,4,5-Trichlorophenyl	$C_{16}H_{13}Cl_3N_2S$	371.71	130-32	75	51.72 (51.7	3.55 3.53	7.56 7.54)
3l	2-Furyl	$C_{14}H_{14}N_2OS$	258.34	100-02	83	65.12 (65.09	5.48 5.46	10.87 10.84)
3m	6-Methoxy-2-naphthyl	$C_{21}H_{20}N_2OS$	348.46	148-50	90	71.46 (71.44	5.34 5.36	13.12 13.15)
4a	4-Methylphenyl	$C_{17}H_{15}NOS$	281.37	156-58	75	71.86 (71.84	5.93 4.90	5.22 5.24)
4b	Phenyl	$C_{16}H_{13}NOS$	267.34	146-48	77	72.59 (72.57	5.40 5.37	4.96 4.98)
4c	4-Methoxyphenyl	$C_{17}H_{15}NO_2S$	297.37	155-58	76	68.64 (68.66	5.05 5.08	4.76 4.71)
4d	4-Chlorophenyl	$C_{16}H_{12}ClNOS$	301.79	210-12	85	63.64 (63.68	4.05 4.01	4.67 4.64)
4e	Biphenyl	$C_{22}H_{17}NOS$	343.44	148-50	86	76.96 (76.94	4.95 4.99	4.04 4.08)
4f	3.4-Dimethoxyphenyl	$C_{18}H_{17}NO_3S$	327.39	125-27	68	66.05 (66.03	5.26 5.23	4.26 4.28)
4g	2-Amino-3-pyridyl	$C_{15}H_{13}\ N_3OS$	283.34	130-32	75	63.56 (63.58	4.65 4.61	14.80 14.83)
4h	4-Methoxy-2,3,6-trimethyl phenyl	$C_{20}H_{21}NO_2S$	339.45	136-38	81	72.63 (72.60	4.96 4.93	4.05 4.03)
4i	2-Bromo-6-nitrophenyl	$C_{16}H_{11}Br\ N_2O_3S$	391.24	116-18	66	70.74 (70.77	6.27 6.24	4.15 4.13)
4j	2,4,5-Trichlorophenyl	$C_{16}H_{10}Cl_3NOS$	370.68	126-28	78	49.16 (49.12	2.86 2.83	7.14 7.16)
4k	6-Methoxy-2-naphthyl	$C_{21}H_{17}NO_2S$	347.43	150-52	90	51.87 (51.84	2.75 2.72	3.75 3.78)

Table III — Analgesic activity by tail-flick method

Compd	Dose (mg/kg) body weight	Average (±SE) reaction time (sec): Time after drug treatment (min) 0	30	60	90
Control 1 mL (1 % Tween 80)	-	3.89 (± 0.043)	4.04 (±0.039)	4.06 (±0.03)	4.01 (±0.07)
Standard Analgin	25	4.74* (±0.033)	5.86** (±0.076)	7.3** (±0.13)	8.79** (±0.21)
3a	50	4.39* (±0.033)	5.18** (±0.11)	6.85** (±0.33)	7.37** (±0.18)
3c	50	3.83 (±0.072)	4.02 (±0.076)	5.18* (±0.36)	5.41* (±0.23)
3e	50	3.81 (±0.108)	4.04 (±0.52)	4.80 (±0.078)	5.11* (±0.03)
3f	50	3.63 (±0.174)	4.98* (±0.067)	5.60* (±0.16)	6.42** (±0.19)
3g	50	4.83* (±0.04)	5.72* (±0.154)	7.44** (±0.24)	7.94** (±0.074)
3i	50	4.26 (±0.073)	5.23* (±0.193)	5.57* (±0.21)	6.60** (±0.24)
3k	50	4.77* (±0.052)	5.81* (±0.045)	7.07** (±0.058)	8.52** (±0.15)
3m	50	3.80 (±0.149)	4.17 (±0.213)	4.99* (±0.04)	6.00* (±0.18)
4a	50	3.92 (±0.104)	4.15 (±0.034)	5.59** (±0.20)	6.61** (±0.20)
4c	50	4.21 (±0.087)	4.74* (±0.158)	5.54* (±0.19)	6.29** (±0.14)
4d	50	4.00 (±0.043)	4.95* (±0.31)	5.95* (0.30)	6.37* (±0.17)
4e	50	3.91 (±0.14)	4.94* (±0.14)	6.15** (±0.19)	7.15** (±0.11)
4f	50	4.31 (±0.067)	4.82* (±0.08)	5.36** (±0.22)	6.19** (±0.18)
4g	50	3.80 (±0.286)	4.66* (±0.17)	5.53** (±0.22)	6.54** (±0.17)
4h	50	3.88 (±0.102)	4.45 (±0.124)	5.32* (±0.16)	6.17** (±0.16)
4k	50	3.73 (±0.191)	4.82* (±0.086)	5.43* (±0.21)	6.36* (±0.16)

Significance levels *P<0.05, **P<0.01 compared with respective control (ANOVA followed by Dunnet's test). Each value represents ±SE (n=6)

aromatic protons of 4-methylthiophenyl moiety while multiplet appeared at δ 7.75-7.84 was due to five protons of phenyl group. In ^{13}C NMR spectrum of **4b**, signals at δ 15.31, 97.25, 125.81, 126.09, 126.23, 127.08, 127.42, 128.90, 128.98, 141.22, 162.47 and 170.35 were due to SCH_3, C_4 of isoxazole, C_3 and C_5 of methylthiophenyl moiety, C_2 and C_6 of methylthiophenyl moiety, C_2 and C_6 of phenyl moiety, C_3 and C_5 of phenyl moiety, C_1 of methylthiophenyl moiety, C_4 of methylthiophenyl moiety, C_4 of phenyl moiety, C_1 of phenyl moiety, C_5 of isoxazole and C_3 of isoxazole ring respectively. On DEPT experimentation, peaks due to quaternary carbon atoms disappeared. Further, ESI mass spectrum showed molecular ion peak at *m/z* 268 (M+1) which is consistent with molecular formula $C_{16}H_{13}NOS$.

Table IV — Anti-inflammatory activity by paw oedema method

Compd	Dose (mg/kg)	Average (±SE) reaction time (sec). Time after drug treatment (min). 0 hr	1 hr	2 hr	3 hr	4 hr
Control (1 % Tween 80)	1 mL (1%)	1.52 (± 0.037)	1.57 (±0.066)	1.61 (±0.064)	1.63 (±0.037)	1.61 (±0.03)
Standard (Diclofenic sodium)	50	1.60 (±0.05)	1.45 (±0.0298)	1.26* (±0.04)	0.99*** (±0.033)	0.82*** (±0.014)
3a	50	1.40 (±0.042)	1.41 (±0.048)	1.30* (±0.02)	1.25** (±0.012)	1.11** (±0.04)
3f	50	1.44 (±0.060)	1.47 (±0.037)	1.33 (±0.014)	1.34 (±0.018)	1.4 (±0.030)
3g	50	1.48 (±0.043)	1.45 (±0.048)	1.28* (±0.02)	1.15** (±0.018)	1.11** (±0.04)
3i	50	1.52 (±0.09)	1.46 (±0.03)	1.32 (±0.022)	1.22* (±0.023)	1.18** (±0.022)
3k	50	1.52 (±0.033)	1.47 (±0.034)	1.26* (±0.025)	1.18** (±0.013)	1.00** (±0.025)
4c	50	1.42 (±0.032)	1.33 (±0.033)	1.27 (±0.011)	1.24* (±0.020)	1.28* (±0.045)
4e	50	1.48 (±0.031)	1.51 (±0.023)	1.28 (±0.028)	1.21* (±0.033)	1.19* (±0.03)
4f	50	1.48 (±0.09)	1.49 (±0.037)	1.38 (±0.022)	1.26* (±0.023)	1.19* (±0.056)
4g	50	1.46 (±0.063)	1.45 (±0.046)	1.29* (±0.021)	1.20* (±0.019)	1.19* (±0.022)

Significance levels * P< 0.05, ** P< 0.01, *** P< 0.001 compared with respective control (ANOVA followed by Dunnett's test). Each value represents ±SE (n=6)

Biological activity

Analgesic activity

Test for analgesic activity was performed by tail-flick technique[20,21] using Wister albino mice (25-30 g) of either sex selected by random sampling technique. Analgin 25 mg/kg was administered as a standard for comparison, and test compounds at dose level of 50 mg/kg were administered orally. The reaction time was recorded at 0, 30, 60 and 90 min after treatment, cut off time was 10 s. The percent analgesic activity was calculated. The results are summarized in **Table III**.

Anti-inflammatory activity

Anti-inflammatory activity was evaluated for the selected title compounds **3a-m** and **4a-k** by carra-geenan paw oedema test in rats[22]. Acute inflammation was produced by sub plantar injection of 0.1 mL of 1% suspension of carrageenan in 1% Tween-80, in the right hind paw of the rats. Diclofenac sodium 25 mg/kg, b.w. suspended in 1% Tween-80 was used as the standard drug for comparison and test compounds having dose level of 25 mg/kg, b.w. suspended in 1% Tween-80 were administered orally. The paw volume was measured using the mercury displacement technique with the help of plethysmograph (Ugo Basile, Italy) immediately before and 0.5, 1.0, 2.0, 3.0 and 4.0 hr after the carrageenan injection. The results are summarized in **Table IV**.

Significance levels * P< 0.05, ** P< 0.01, *** P< 0.001 compared with respective control (ANOVA followed by Dunnett's test). Each value represents ±SE (n=6)

Experimental Section

Melting points are uncorrected and were determined in open capillaries using Serwell Instruments Inc, India melting point apparatus. Homogeneity of the compounds was checked by thin layer chromatography (TLC) on a silica coated aluminum sheet (silica gel $60F_{254}$) using chloroform and methanol (9:1, v/v). IR spectra were recorded on Nicolet Avatar 330-FTIR Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 MHz NMR spectrometer using TMS as an internal

standard. Chemical shifts are reported in ppm (δ) and signals are described as singlet (s), doublet (d), triplet (t), quartet (q), broad (br) and multiplet (m). The FAB mass spectra were recorded on a Jeol SX 102/DA-6000 spectrometer/data system using Argon/Xenon (6 KV, 10 mA) FAB gas, at 70 eV and ESI mass spectra were recorded on a Micromass Quattro II triple quadrupole mass spectrometer. Elemental analysis was carried out using FlashEA 1112 Series, CHNSO Analyzer (Thermo). Solvents and reagents were purchased from the commercial vendors in the appropriate grade and were used as received.

Procedure for preparation of 4-acetylthioanisole, 1

4-Acetylthioanisole was prepared by Friedel Craft's acylation of thioanisole using aluminium chloride catalyst, as reported by Holla *et al*.[23]

General procedure for preparation of propenones, 2a-m

A clear solution of aromatic aldehydes (0.01 mole) in 10 mL of ethanol was added to the mixture of 4-acetylthioanisole (0.01 mole, 1.664 g) in 15 mL of ethanol, aqueous sodium hydroxide (40%, 6 mL) with stirring at 20°C and stirring was continued at RT for 24 hr. The contents were poured into about 200 g of crushed ice, and the solid product separated was filtered, dried and crystallized from ethyl acetate. Physical and elemental analysis data of **2a-h** are given in **Table I**. The physical and characterization data of some of these compounds, *viz.,* **2i-m** agree with the reported literature values.

General procedure for preparation of pyrazolines, 3a-m

A mixture of **2a-m** (0.01 mole) and 80% of hydrazine hydrate (0.012 mole) in 25 mL of ethanol was refluxed on water bath for 5-6 hr. The reaction mass was then poured into 200 mL of ice-cold water. The solid obtained was filtered, washed with water, dried, and purified by crystallization from ethanol to give **3a-m**. Physical and elemental analysis data of **3a-m** are listed in **Table II**. Spectral data of some of the compounds are given below.

5-(4-Methylphenyl)-3-[4-(methylthio) phenyl]-4,5-dihydro-1*H*-pyrazole, 3a

FTIR: 3347(NH of pyrazoline), 2916 (CH_3), 1586 (C=N), 1494 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): δ 2.25 (s, 3H, CH_3), 2.49 (s, 3H, SCH_3), 2.95-3.03 (dd, 1H, CH_2, *J* = 8.4), 3.36-3.45 (dd, 1H, *J* = CH_2, 10.5 Hz,), 4.83-4.89 (dd, 1H, CH, *J* = 8.4, 8.9 Hz), 7.12 (d, 2H, C_3, C_5-H of 4-methylthio- phenyl moiety, *J* = 8.4), 7.21-7.25 (m, 4H of phenyl moiety, *J* = 4.0), 7.58 (d, 2H, C_2, C_6-H of methylthiophenyl moiety, *J* = 8.4); ^{13}C NMR (75 MHz): δ 15.45 (SCH_3), 21.04 (CH_3), 41.21 (CH_2), 63.96 (CH of pyrazole), 126.07 (C_3 and C_5 of methylthiophenyl moiety), 126.17 (C_2 and C_6 of methylphenyl moiety), 126.30 (C_3 and C_5 of methylphenyl moiety), 129.43 (C_2 and C_6 of methylthio phenyl moiety), 129.54 (C_1 of methylthiophenyl moiety), 137.44 (C_4 of methylphenyl moiety), 139.39 (C_1 of methylphenyl moiety), 139.72 (C_4 of methylthiophenyl moiety), 150.86 (C_3 of pyrazole carbon); MS-ESI: *m/z* (%), 283 (100) [M+1], 305 [M+Na].

3-[4-(Methylthio) phenyl]-5-phenyl-4,5-dihydro-1*H*-pyrazole, 3b

FTIR: 3329 (NH pyrazoline), 2917 (CH_3), 1589 (C=N), 1492 cm^{-1} (C=C); MS-ESI: *m/z* (%), 269 (100) [M+1], 268 [M], 291[M+Na], 291[M-SCH_3].

5-(4-Methoxyphenyl)-3-[4-(methylthio) phenyl]-4,5-dihydro-1*H*-pyrazole, 3c

FTIR: 3340 (NH of pyrazoline), 2934 (CH_3), 1601 (C=N), 1510 (C=C), 1242 cm^{-1} (C-O-C); ^1H NMR ($CDCl_3$): δ 2.49 (s, 3H, SCH_3), 2.94-3.03 (dd, 1H, CH_2, *J* = 9.0), 3.35-3.44 (dd, 1H, CH_2, *J* = 10.8), 3.78 (s, 3H, OCH_3), 4.83-4.89 (dd, 1H, CH, *J* = 9.0), 6.86 (d, 2H, C_3, C_5-H of methylthiophenyl moiety, *J* = 8.5), 7.21-7.29 (m, C_3, C_5, C_2, C_6-H 4-methoxyphenyl moiety, *J* = 8.4), 7.57 (d, 2H, C_2, C_6-H of methylthiophenyl moiety, *J* = 9.0); ^{13}C NMR (75 MHz): δ 15.46 (SCH_3), 41,22 (CH_2), 55.25 (CH of pyrazole) 63.96 (OCH_3), 114.09 (C_3 and C_5 of methoxyphenyl moiety), 126.09 (C_3 and C_5 of methythiophenyl moiety), 126.28 (C_2 and C_6 of methoxyphenyl moiety), 127.43 (C_2 and C_6 of methylthiophenyl moiety), 129.57 (C_1 of methylthiophenyl moiety), 134.39 (C_1 of methoxyphenyl moiety), 139.39 (C_4 of methylthiophenyl moiety), 150.88 (pyrazole carbon), 159.13 (C_4 of methoxyphenyl moiety); MS FAB: *m/z* (%) 298 (100) [M+1], 297(45)[M], 267 [M-OCH_3], 252 [M-SCH_3].

5-(4-Chlorophenyl)-3-[4-(methylthio) phenyl]-4,5-dihydro-1*H*-pyrazole, 3d

FTIR: 3240 (NH of pyrazoline), 2917 (CH_3), 1587 (C=N), 1488 (C=C), 1091 cm^{-1} (C-O-C); ^1H NMR ($CDCl_3$): δ 2.50 (s, 3H, SCH_3), 2.92-3.01 (dd, 1H,

CH_2, J = 9.0), 3.34-3.45 (dd, 1H, CH_2, J = 10.8 Hz), 4.43-4.49 (dd, 1H, CH, J = 9.0), δ 7.40 (d, 2H, C_3, C_5-H of 4-methylthiophenyl moiety), 7.65 (d, 2H, C_3, C_5-H of 4-chlorophenyl moiety), 7.85 (d, 2H, C_2, C_6-H of 4-methylthiophenyl moiety), 7.93 (d, 2H, C_2, C_6-H of 4-chlorophenyl moiety); MS-FAB: *m/z* (%) 303 (50) [M+1], 302 (60) [M].

5-(3,4-Dimethoxyphenyl)-3-[4-(methylthio) phenyl]-4,5-dihydro-1*H*-pyrazole, 3f

FTIR: 3320 (NH of pyrazoline), 2914 (CH_3), 1617 (C=N), 1590 (C=C), 1194 cm^{-1} (C-O-C); ^1H NMR ($CDCl_3$): δ 2.53 (s, 3H, SCH_3), 2.93-3.00 (dd, 1H, CH_2, J = 9.0), 3.32-3.43 (dd, 1H, CH_2, J = 10.8), 3.94 (OCH_3), 3.97 (OCH_3), 4.46-4.55 (dd, 1H, CH, J = 9.0), 6.70 (d, 1H, C_5-H of 3,4-dimethoxyphenyl moiety), 6.96 (d, 1H, C_3-H of 3,4-dimethoxyphenyl moiety), 7.28-7.46 (m, 3H, C_6-H and C_3, C_5-H of 4-methylthiophenyl moiety), 7.75 (d, 2H, C_2, C_6-H of 4-methylthiophenyl moiety); MS-FAB: *m/z* (%) 329 (80) [M+1], 328 (100) [M] .

General procedure for preparation of isoxazoles, 4a-k

A mixture of propenones, **2a-k** (0.01mole), hydroxylamine hydrochloride (0.012 mole) and sodium acetate (0.04 mole) in 20 mL of dimethylformamide was heated on oil bath at 120°C for 12-13 hr. The reaction mass was then poured into 250 mL of ice-cold water. The solid obtained was filtered, washed with water, dried, and purified by recrystallization from ethanol to give **4a-k**. Physical and elemental analysis data of **4a-k** are listed in **Table II**. Spectral data of some compounds are given below.

5-(4-Methylphenyl)-3-[4-(methylthio)phenyl]isoxazole, 4a

FTIR: 2916 (CH_3), 1496 (C=N), 1430 (C=C), 1098 (C-O-C), 811 cm^{-1} (N-O); ^1H NMR ($CDCl_3$): δ 2.41 (s, 3H, CH_3), 2.53 (s, 3H, SCH_3), 6.74 (s, 1H of isoxazole), 7.25-7.36 (m, 4H of phenyl moiety), 7.70-7.79 (m, 4H of methylthiophenyl moiety); MS-FAB: *m/z* (%) 282 (100) [M+1], 281(50)[M], 267 [M-CH_3], 236 [M-SCH_3].

3-[4-(Methylthio) phenyl]-5-phenylisoxazole, 4b

FTIR: 3113 (CH_3), 1595 (C=N), 1489 (C=C), 1020 (C-O-C), 816 cm^{-1} (N-O); ^1H NMR ($CDCl_3$): δ 2.50 (s, 3H, SCH_3), 6.79 (s, 1H of isoxazole), 7.30 (d, 2H, C_3, C_5-H of methylthiophenyl moiety, J = 8.5), 7.48 (d, 2H, C_2, C_6-H of methylthiophenyl moiety, J = 6.5), 7.75-7.84 (5H, m, phenyl moiety, J = 8.4); ^{13}C NMR (75 MHz): δ 15.31 (SCH_3), 97.25 (C_4 of isoxazole), 125.81 (C_3 and C_5 of methylthiophenyl moiety), 126.09 (C_2 and C_6 of methylthiophenyl moiety), 126.23 (C_2 and C_6 of phenyl moiety), 127.08 (C_3 and C_5 of phenyl moiety), 127.42 (C_1 of methylthiophenyl moiety), 128.90 (C_4 of methylthiophenyl moiety), 128.98 (C_4 of phenyl moiety), 141.22 (C_1 of phenyl moiety), 162.47 (C_5 of isoxazole), 170.35 (C_3 of isoxazole); MS-ESI: *m/z* (%) 268 (40) [M+1], 267 (20) [M], 290 [M+Na], 306 [M+K].

5-(4-Methoxyphenyl)-3-[4-(methylthio)phenyl]isoxazole, 4c

FTIR: 2916 (CH_3), 1496 (C=N), 1430 (C=C), 1098 (C-O-C), 811 cm^{-1} (N-O); ^1H NMR ($CDCl_3$): δ 2.52 (s, 3H, SCH_3), 3.85 (s, 3H, OCH_3), 6.71 (s, 1H of isoxazole), 7.00 (d, 2H, C_3, C_5-H of methylthiophenyl moiety, J = 8.5), 7.30 (d, 2H, C_2, C_6-H of methylthiophenyl moiety, J = 6.5), 7.71-7.80 (4H, m, phenyl moiety, J = 7.5); ^{13}C NMR (75 MHz): δ 15.17 (SCH_3), 55.39 (OCH_3), 95.60 (C_4 of isoxazole), 114.28 (C_3 and C_5 of methoxyphenyl moiety), 120.25 (C_1 of methoxyphenyl moiety), 121.60 (C_4 of methylthiophenyl moiety), 123.96 (C_1 of methylthiophenyl moiety), 126.05 (C_3 and C_5 of methylthiophenyl moiety), 126.20 (C_2 and C_6 of methoxyphenyl moiety), 127.04 (C_2 and C_6 of methylthiophenyl moiety), 141.22 (C_3 of isoxazole), 160.98 (C_1 of phenyl moiety), 162.56 (C_3 of isoxazole); MS-ESI: *m/z* (%) 298 (50) [M+1].

5-(4-Chlorophenyl)-3-[4-(methylthio)phenyl]isoxazole, 4d

FTIR: 2920 (CH_3), 1487 (C=N), 1427 (C=C), 1095 (C-O-C), 811 cm^{-1} (N-O); ^1H NMR ($CDCl_3$): δ 2.50 (s, 3H, SCH_3), 7.42 (d, 2H, C_3, C_5-H of methylthiophenyl moiety), 7.60 (s, 1H of isoxazole), 7.65 (d, 2H, C_3, C_5-H of phenyl moiety), 7.85 (d, 2H, C_2, C_6-H of methylthiophenyl moiety), 7.95 (d, 2H, C_2, C_6-H of chlorophenyl moiety); MS-FAB: *m/z* (%) 325 (50)[M+Na], 267 [M-Cl].

5-(3,4-Dimethoxyphenyl)-3-[4-(methylthio)phenyl]-isoxazole, 4f

FTIR: 2970 (CH_3), 1517 (C=N), 1427 (C=C), 1098 (C-O-C), 811 cm^{-1}(N-O); ^1H NMR (DMSO-d_6) : δ 2.52 (s, 3H, SCH_3), 3.93 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.69 (s.1H of isoxazole), 6.73 (s, 1H, C_2-H of phenyl moiety), 6.94 (d, 1H, C_5-H of phenyl moiety),

7.30 (d, 1H, C_6-H of phenyl moiety), 7.36 (d, C_3, C_5-H of methylthiophenyl moiety), 7.75 (d, 2H, C_2, C_6-H of 4-methylthiophenyl moiety); MS-FAB: *m/z* (%) 328 (100) [M+1], 327(80) [M].

Conclusion

Preliminary analgesic studies of selected title compounds indicate that **3a, 3g, 3k, 4a, 4e, 4f** and **4g** possess very good activity almost comparable with standard Analgin. The compounds **3c, 3f, 3i, 3m, 4c, 4d, 4h** and **4k** possess moderate analgesic activity, while the compound **3e** shows low activity compared to the standard. Both pyrazoles and isoxazoles containing tolyl, 2-amino-3-pyridyl, 2,4,5-trichlorophenyl and biphenyl groups displayed good activity. However, further detailed studies on activity and long term toxicity need to be carried out before any conclusion can be drawn.

Preliminary anti-inflammatory studies of a few selected title compounds reveal that **3a, 3g, 3i,** and **3k,** displayed slightly lower activity than that of standard diclofenac sodium. The compounds **3f, 4c, 4e, 4f** and **4g** possess less activity compared to the standard. Amongst the tested compounds, pyrazolines exhibited better activity than isoxazoles and the substitution at position-5 with groups like *p*-tolyl, 2,4,5-trichlorophenyl, 2-amino-3-pyridyl moieties enhanced the activity to some extent.

This research study reports the successful synthesis of new pyrazolines and isoxazoles carrying 4-methylthiophenyl moiety at position-3. It also reports the analgesic and anti-inflammatory studies of a few selected title compounds. The biological study revealed that a few compounds showed moderate to good activity.

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