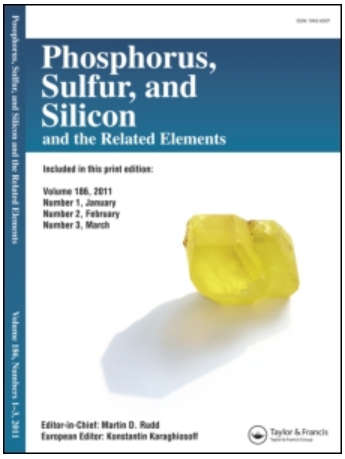

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Synthesis of N 1 -Substituted, N 3 -[P -(3-Ethoxy-Carbonyl-4,5-Dihydronaphtho[1,2- c]Pyrazol-2-YL)Benzenesulfonyl]Urea and Thiourea Derivatives. Class of Cyclooxygenase-2 Inhibitors

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SYNTHESIS OF N^1-SUBSTITUTED, N^3-[*P*-(3-ETHOXYCARBONYL-4,5-DIHYDRONAPHTHO[1,2-*c*]PYRAZOL-2-YL)BENZENESULFONYL]UREA AND THIOUREA DERIVATIVES. CLASS OF CYCLOOXYGENASE-2 INHIBITORS

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*Several urea and thiourea derivatives (**2a–f**) were prepared by the reaction of dihydronaphthopyrazolylbenzenesulfonamide (**1**) with the corresponding isocyanates and isothiocyanates, respectively. The benzenesulfonylthioureas (**2d**,**e**) were cyclized with ethyl bromoacetate, ethyl β-bromopropionate and α-bromoacetophenones to give the corresponding 4-oxothiazolidine (**3a**,**b**), 4-oxo-5,6-dihydrothiazine (**4a**,**b**) and thiazoline derivatives (**5a–d**) respectively.*

Keywords: Dihydrothiazine; thiazolidine; thiazoline

INTRODUCTION

A number of selective inhibitors of cyclooxygenase-2 (COX-2) were shown to possess antiinflammatory activity with little or no gastric side effects (Figure 1).[1,2] To date, two distinct structural classes of molecules have been reported as selective inhibitors of COX-2, NS-398[3] and L-745, 337[4] are members of the methanesulfonanilide class of inhibitors, and DUP 697,[5] SC-57666[6–8] and SC-58125[9] are few of the many examples of the tricyclic inhibitors class.[10–13] Recently,[14] it was found that within the 1,5-diarylpyrazole class of COX-2 inhibitors, the *p*-sulfamoylphenyl group was essential for good COX-2 inhibitors potency and in vivo efficacy.

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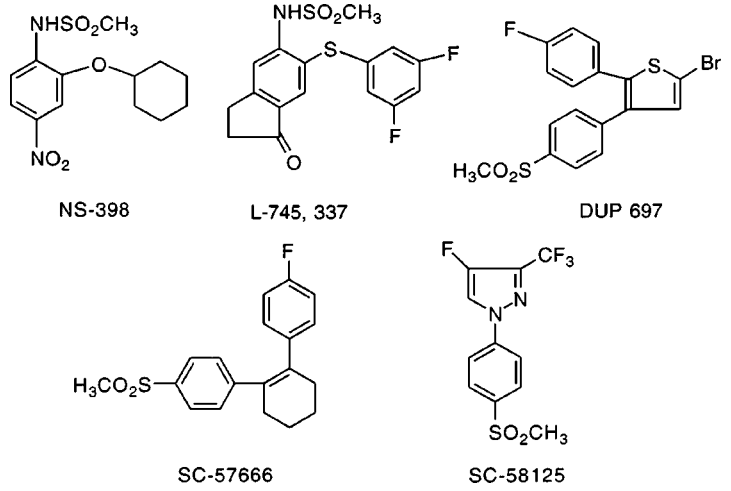


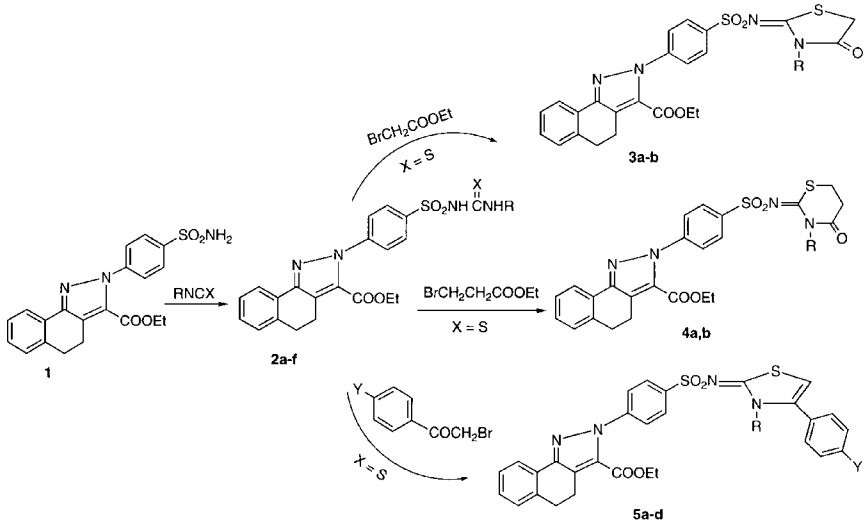
FIGURE 1 Selective Inhibitors of Cyclooxygenase-2

In continuation of our previous work[15–20] in the synthesis of pyrazole compounds containing sulfonamide moieties, many new pyrazole derivatives were synthesized as a class of cyclooxygenase-2 inhibitors.

DISCUSSION

Urea and thiourea derivatives were prepared by the reactions of pyrazole derivative[8] (**1**) with isocyanates and isothiocyanates to give the corresponding dihydronaphthopyrazolylbenzenesulfonylureas (**2a–c**) and thioureas (**2d–f**) respectively. The data are shown in Scheme 1 and Table I.

The infrared spectra of the urea and thiourea derivatives (**2a–f**) revealed an ester carbonyl absorption at 1701–1724 cm^{-1}, two bands for the symmetrical and asymmetrical vibrations of the SO_2 group at 1140–1190 cm^{-1} and 1310–1375 cm^{-1} as well as a urea carbonyl stretching at 1644–1652 cm^{-1} in case of compounds (**2a–c**) and thiocarbonyl stretching at 1085–1109 cm^{-1} in case of compounds (**2d–f**). The NH bands appeared at 3132–3350 cm^{-1} (Table II). Their ^1H NMR Spectral data are summarized in Table III. They showed a multiplet in the region δ 2.96–3.30 for H-5 and H-4, as well as a triplet of three protons intensity at δ 1.34–1.47 and a quartet of two protons intensity at δ 4.35–4.45 for the CH_3 and CH_2 of the ester group, respectively (Table III). Further evidence concerining the structure of the forgoing urea and thiourea derivatives (**2a–f**) has been derived from their ^{13}C NMR spectra which revealed the expected number of signals for



SCHEME 1

the mentioned compounds as well as the C=O and C=S signals at δ 176.00 and 205.00 for the urea and thiourea derivatives, respectively (Table IV).

Cyclization of the benzenesulfonylthioureas (**2d–f**) with ethyl bromacetate, ethyl β-bromoprpionate and α-bromoacetophenones yielded the corresponding 4-oxothiazoldine, 4-oxo-5,6-dihydrothiazine and thiazoline derivatives (**3a**,**b**), (**4a**,**b**), and (**5a–d**) respectively. The results of the reactions are summarized in Scheme 1 and Table V.

The infrared spectra of compounds (**3a**,**b**) showed a cyclic carbonyl absorption at 1728–1746 cm^{-1}, two bands at 1335–1382 cm^{-1} and 1172–1180 cm^{-1} for the SO_2N group as well as an ester carbonyl stretching at 1713–1721 cm^{-1} (Table VI). The high value of stretching vibrations for amide carbonyl of **3a**,**b** would be attributed to the proximity of the imine function to the amide moiety. The ^1H NMR spectral data further supported the suggested structures. They displayed a multiplet at δ 3.20–3.34 for H-4 and H-5, a triplet of three protons intensity at δ 1.37–1.40 and a quartet of two protons intensity at δ 4.45–4.53 for the CH_3 and CH_2 of the ester group respectively. In addition, compounds (**3a**,**b**) revealed a singlet of two protons intensity at δ 3.92–4.13 for H-5′ of thiazolidinone moiety while, compounds (**4a**,**b**) showed a multiplet of four protons intensity at δ 4.43–4.48 due to H-5′ and H-6′ of the thiazinone ring (Table VII).

Further evidence concerning the structure of the thiazolidinone (**3a**) has been derived from its mass spectrum which showed no molecular ion peak, but it gave fragments that confirmed the structure.

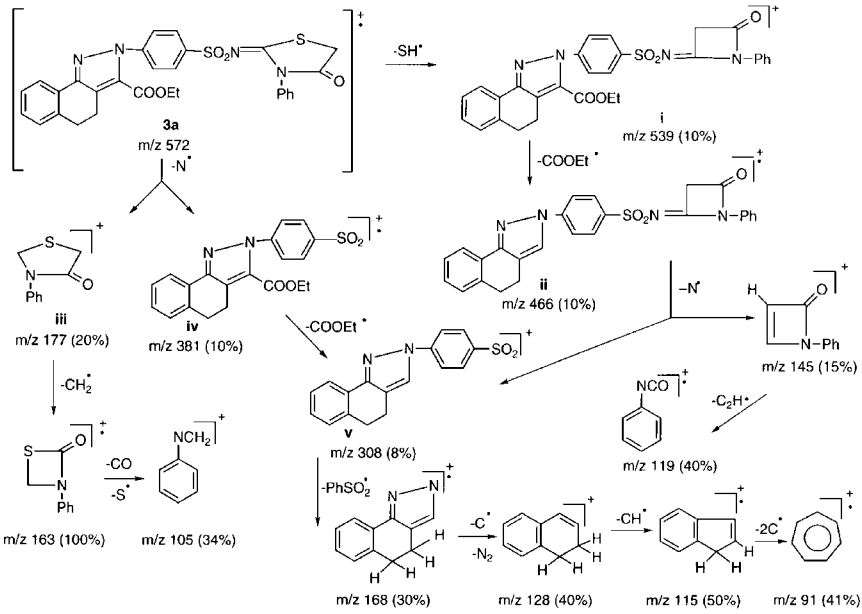
TABLE I Characterization Data of Compounds (**2a–f**)

Cpd	R	X	Yield (%)	m.p.	m.f.	Anal. Calcd				Found			
						C	H	N	S	C	H	N	S
2a	Ph	O	83	190	$C_{27}H_{24}N_4O_5S$	62.80	4.65	10.85	6.20	62.52	4.31	10.49	6.00
2b	Naphthyl	O	85	229	$C_{31}H_{26}N_4O_5S$	65.72	4.59	9.89	5.65	65.46	4.23	9.54	5.35
2c	Cyclohexyl	O	80	210	$C_{27}H_{30}N_4O_5S$	62.07	5.75	10.73	6.13	62.15	5.85	10.45	6.24
2d	Ph	S	87	202	$C_{27}H_{24}N_4O_4S_2$	60.90	4.51	10.53	12.03	60.73	4.81	10.75	11.96
2e	Benzyl	S	82	177	$C_{28}H_{26}N_4O_4S_2$	61.54	4.76	10.26	11.72	61.22	5.02	9.92	11.50
2f	Allyl	S	78	173	$C_{24}H_{24}N_4O_4S_2$	58.06	4.84	11.29	12.90	58.22	4.72	11.08	13.05

TABLE II IR Spectral Data of Pyrazolebenzenesulfonylurea and Thiourea Derivatives (**2a–f**)

Cpd	R	X	CO (ester)	CO or CS (urea)	SO_2	CH (aliphatic)	NH
2a	Ph	O	1701	1644	1336, 1161	2835–3055	3291
2b	Naphthyl	O	1724	1649	1339, 1157	2830–3060	3312
2c	Cyclohexyl	O	1716	1652	1371, 1182	2854–3058	3350
2d	Ph	S	1720	1109	1371, 1142	2840–3048	3132
2e	Benzyl	S	1723	1097	1347, 1133	2835–3052	3288
2f	Allyl	S	1704	1085	1339, 1158	2850–3062	3262

The most common prominent peaks as well as their fragmentation pathways are shown in Scheme 2. Elimination of HS radical from the molecular ion leads to the weak abundant ion (**i**) at m/z 539, which subsequently loses an ethoxycarbonyl radical giving the weak intense radical cation (**ii**) at m/z 466. Fragmentation of the molecular ion accounts for the observation of the cation (**iii**) at m/z 177 and the radical cation (**iv**) at m/z 381. The weakly abundant peak (**v**) at m/z 308 arising by elimination of ethoxycarbonyl radical from (**iv**). The base peak appeared at m/z 163 which is obtained from (**iii**)



SCHEME 2

TABLE III ^{1}H NMR Spectral Data (δ/ppm)[a] of Pyrazolebenzenesulfonylurea and Thiourea Derivatives (**2a–f**)

Cpd	R	X	H-4 & H-5 (m, 4H)	CH_2 (q, 2H, J = 6.6 Hz)	CH_3 (t, 3H, J = 6.6 Hz)	ArH (m)	Other
2a	Ph	O	2.96	4.38	1.34	6.80–8.32	8.78 (s_b, NH)
2b	Naphthyl	O	3.19	4.45	1.41	6.78–8.30	9.12 (s_b, NH)
2c	Cyclohexyl	O	3.20	4.40	1.40	6.75–8.20	1.65 (2m, 11H, cyclohexyl), 8.82 (s_b, NH)
2d	Ph	S	3.01	4.41	1.35	6.77–8.30	9.12 (s_b, NH)
2e	Benzyl	S	3.11	4.40	1.36	6.80–8.30	4.72 (d, CH_2Ph), 8.70 (t, NH)
2f	Allyl	S	3.30	4.35[b]	1.47	6.68–8.35	5.35 (m, CH_2=CH), 9.02 (t, NH)

[a]Solution in a mixture of $CDCl_3$ and DMSO-d_6.
[b]Multiplet; CH_2 ester + CH_2 allyl.

TABLE IV ^{13}C NMR Spectral Data (δ/ppm)[a] of Pyrazolebenzenesulfonylurea and Thiourea Derivatives (**2a**,**d**)

Cpd	R	X	CH_3	CH_2	C_4	C_5	CO	CS	ArC
2a	Ph	O	13.38	59.81	19.11	28.90	176.00, 177.80		117.59, 121.09, 121.90, 121.94, 122.36, 124.53, 124.72, 125.45, 126.38, 127.35, 127.78, 128.09, 136.25, 136.30, 142.53, 149.31, 161.40
2d	Ph	S	12.68	58.80	18.35	29.00	181.00	205.00	118.77, 120.82, 121.09, 123.36, 123.97, 125.02, 125.42, 125.80, 126.26, 126.58, 126.96, 127.34, 135.33, 137.77, 138.53, 139.31, 160.53

[a]Solution in a mixture of $CDCl_3$ and DMSO-d_6.

TABLE V Characterization Data of Compounds (**3a**,**b**), (**4a**,**b**), and (**5a–d**)

						Anal. Calcd				Found			
Cpd	R	Y	Yield (%)	m.p.	m.f.	C	H	N	S	C	H	N	S
3a	Ph	—	67	219	$C_{29}H_{24}N_4O_5S_2$	60.84	4.19	9.79	11.19	60.92	4.02	10.00	11.25
3b	CH_2Ph	—	77	175	$C_{30}H_{26}N_4O_5S_2$	61.43	4.44	9.56	10.92	61.33	4.56	9.65	11.04
4a	Ph	—	59	116	$C_{30}H_{26}N_4O_5S_2$	61.43	4.44	9.56	10.92	61.56	4.65	9.42	11.08
4b	CH_2Ph	—	64	98	$C_{31}H_{28}N_4O_5S_2$	62.00	4.67	9.33	10.67	61.89	4.77	9.53	10.80
5a	Ph	H	67	186	$C_{35}H_{28}N_4O_4S_2$	66.45	4.43	8.68	10.13	66.58	4.60	8.92	10.24
5b	CH_2Ph	H	67	204	$C_{36}H_{30}N_4O_4S_2$	66.87	4.64	8.67	9.91	66.68	4.45	8.58	10.14
5c	*p*-BrC_6H_4	Br	60	189	$C_{35}H_{27}BrN_4O_4S_2$	59.07	3.80	7.88	9.00	58.99	3.72	7.98	8.88
5d	*p*-$OCH_3C_6H_4$	OCH_3	57	149	$C_{36}H_{30}N_4O_5S_2$	65.26	4.53	8.46	9.67	65.18	4.64	8.62	9.78

TABLE VI IR Spectral Data of Pyrazolethiazolidine (**3a–b**), Thiazine (**4a–b**), and Thiazoline (**5a–d**) Derivatives

Cpd	R	CO (cyclic ketone)	CO (ester)	SO_2	CH (aliphatic)
3a	Ph	1746	1714	1369, 1155	2830–3072
3b	CH_2Ph	1739	1713	1375, 1154	2840–3078
4a	Ph	1732	1716	1370, 1148	2850–3065
4b	CH_2Ph	1728	1714	1369, 1149	2835–3075
5a	Ph		1716	1350, 1154	2835–3058
5b	CH_2Ph		1713	1375, 1158	2850–3078
5c	Ph		1721	1370, 1155	2845–3048
5d	Ph		1716	1370, 1174	2830–3062

by lossing a methylene radical. Other fragmentations are also outlined in Scheme 2.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on Bruker DPX-400FT NMR spectrometers using TMS as internal standard. Mass spectra were determined on a Kratos MS 30. The Infrared spectra were measured on a Nicolet Magna FT 520 spectrophotometer using potassium bromide pellets. Microanalyses were performed on a 2400 Perkin Elmer Series 2 CHNS analyzer. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected.

General Method for Preparation of N^1-Substituted N^3-[*p*-(3-ethoxycarbonyl-4,5-dihydronaphtho[1, 2-*c*]-pyrazol-2-yl)benzenesulfonyl]ureas (2a–c)

A mixture of 3-ethoxycarbonyl-2-*p*-sulfamylphenyl-4,5-dihydronaphtho[1,2-*c*]pyrazole (**1**, 0.5 g, 0.00126 mol), and anhydrous potassium carbonate (0.5 g, 0,0036 mol) in dry acetone (25 ml) was stirred and refluxed for 1 h. At this temperature, a solution of the appropriate amounts of isocyanates (0.00136 mol) in dry acetone (5 ml) was added dropwise, and the reaction mixture stirred and refluxed for 18 h. The acetone was removed under reduced pressure and the solid residue dissolved in water. The crude product was isolated by acidification with 2*M* HCl and purified by recrystallization from ethanol-benzene mixture (2:1) to give cream needles.

TABLE VII ^{1}H NMR Spectral Data (δ/ppm)[a] of Pyrazolethiazolidine (**3a**,**b**), Thiazine (**4a**,**b**), and Thiazoline (**5a–d**) Derivatives

Cpd	R	H-4 & H-5 (m, 4H)	CH_2 (q, 2H, J = 7 Hz)	CH_3 (t, 3H, J = 7 Hz)	ArH	Other
3a	Ph	3.28	4.53	1.47	6.80–8.20	4.13 (s, 2H, CH_2CO)
3b	CH_2Ph	3.22	4.50	1.48	6.78–8.25	3.92 (s, 2H, CH_2CO) 4.97 (s, 2H, CH_2Ph)
4a	Ph	3.34	[b]	1.42	6.77–8.25	4.43 (m, 6H, 3 CH_2)
4b	CH_2Ph	3.31	[b]	1.37	6.80–8.18	4.48 (m, 6H, 3 CH_2), 4.89 (s, 2H, CH_2Ph)
5a	Ph	3.20	4.45	1.41	6.85–8.10	
5b	CH_2Ph	3.29	4.48	1.47	6.80–8.20	4.73 (s, 2H, CH_2Ph)
5c	Ph	3.20	4.45	1.40	6.78–8.10	
5d	Ph	3.23	4.46	1.48	6.79–8.10	3.72 (s, 3H, OCH_3)

[a] Solution in a mixture of $CDCl_3$ and DMSO-d_6.
[b] Overlapped by H-5′ and H-6′ of the thiazine moiety.

General Method for Preparation of N^1-Substituted N^3-[*p*-(3-ethoxycarbonyl-4,5-dihydronaphtho[1,2-*c*]-pyrazol-2-yl)benzenesulfonyl]thioureas (2d–f)

A mixture of 3-ethoxycarbonyl-2-*p*-sulfamylphenyl-4,5-dihydronaphtho[1,2-*c*]pyrazole (**1**, 1 g, 0.0025 mol), anhydrous potassium carbonate (1 g, 0,0072 mol) in dry acetone (25 ml), and the appropriate amounts of isothiocyanates (0.0026 mol) was stirred under reflux for 10 h. The acetone was removed under reduced pressure and the solid residue dissolved in water. The crude product was isolated by acidification with 2*M* HCl. The precipitated product was filtered off, washed with little amount of ethanol, dried, and recrystallized from ethanol to give pale yellow needles.

General Method for Preparation of 3-Substituted-2-[*p*-(3-ethoxycarbonyl-4,5-dihydronaphtho[1,2-*c*]-pyrazol-2-yl)benzenesulfonylimino]-4-oxothiazolidine (3a,b)

A solution of N^1-phenyl-N^3-[*p*-(3-ethoxycarbonyl-4,5-dihydronaphtho [1,2-*c*]pyrazol-2-yl)benzene-sulfonyl]thioureas (**2a**, 0.5 g, 0.00049 mol), or its 3-substituted benzyl derivatives (**2b**, 0.4 g, 0.00073 mol) in absolute ethanol (20 ml) was refluxed with 2.2 equivalent of ethyl bromoacetate and 1.1 equivalent of sodium acetate for 2 h. The reaction mixture was then cooled and poured into ice-cold water. The crude product that separated was filtered off, dried, and recrystallized from ethanol-benzene to give cream needles.

General Method for Preparation of 3-Substituted-2-[*p*-(3-ethoxycarbonyl-4,5-dihydronaphtho[1,2-*c*]-pyrazol-2-yl)benzenesulfonylimino]-4-oxo-5,6-dihydro-1,3-thiazine (4a,b)

A solution of N^1-phenyl-N^3-[*p*-(3-ethoxycarbonyl-4,5-dihydronaphtho [1,2-*c*]pyrazol-2-yl)benzene-sulfonyl]thioureas (**2a**, 0.2 g, 0.00038 mol), or its 3-substituted benzyl derivatives (**2b**, 0.2 g, 0.00037 mol) in absolute ethanol (20 ml) was refluxed with 1 equivalent of ethyl β-bromopropionate and 2 equivalent of sodium acetate for 2 h. The reaction mixture was worked up as previously mentioned for preparation of (**3a**,**b**) to give the corresponding product as cream needles.

General Method for Preparation of 3,4-Disubstituted-2-[*p*-(3-ethoxycarbonyl-4,5-dihydronaphtho[1,2-*c*]pyrazol-2-yl)-benzenesulfonylimino]4-oxo-5,6-dihydro-1,3-thiazoline (5a–d)

A solution of the corresponding thiourea derivative (0.1 g) in absolute ethanol (20 ml) was refluxed with 1 equivalent of 2-bromoacetophenone derivatives, and 2 equivalent of sodium acetate for 2 h. The reaction mixture was worked up as previously mentioned for preparation of (**3a**,**b**) to give the corresponding product as cream needles.

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