SYNTHESIS AND SPECTRAL STUDIES OF SOME NOVEL PYRAZOLE DERIVATIVES FROM CHALCONES PRECURSORS

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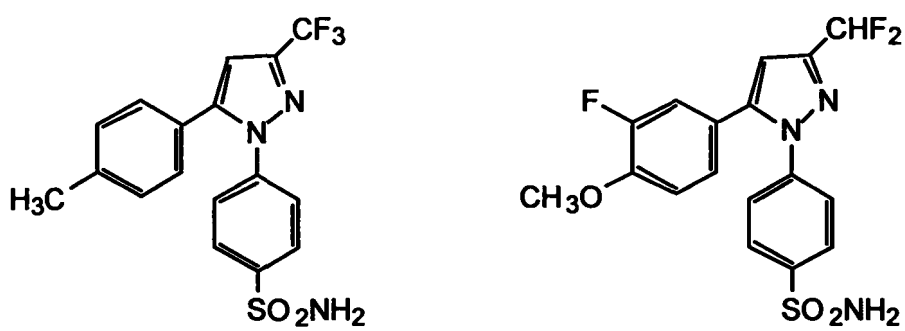
Absract: Chalcones **1a-c** were prepared by a base catalyzed *Claisen-Schmidt* condensation reaction. The dibromoderivatives **2a-c** were obtained by treatment of chalcones with bromine in chloroform. Pyrazoles **4a-e** were obtained either by refluxing of dibromochalcones **2a-c** with benzoylhydrazines in dry pyridine or condensation of **1a-c** with benzoylhydrazines to give hydrazones **3a-e**. Subsequent treatment of **3a-e** with 30% hydrochloric acid gave the corresponding pyrazoles. The structures of all newly synthesized compounds are characterized using spectral methods.

Keywords: Chalcones, Dibromochalcones, Benzoylhydrazones, Pyrazoles.

Introduction:

The importance of the pyrazole ring system[1-10] in synthetic products with pharmacodynamic applications attracted my attention to prepare a new derivatives of these compounds. Numerous compounds of therapeutic importance[11-14] including a number of marketed drugs, such as Celecoxib (Celebrex®) or Deracoxib (Fig.1)[15-16]. Due to the importance of these pharmacological properties, significant efforts toward the synthesis of this kind of compounds have been carried out in the last years.[13,14,17] For these reasons and to continue my interest in the synthesis of pyrazoles from chalcones precursors, some new derivatives of this class are prepared.



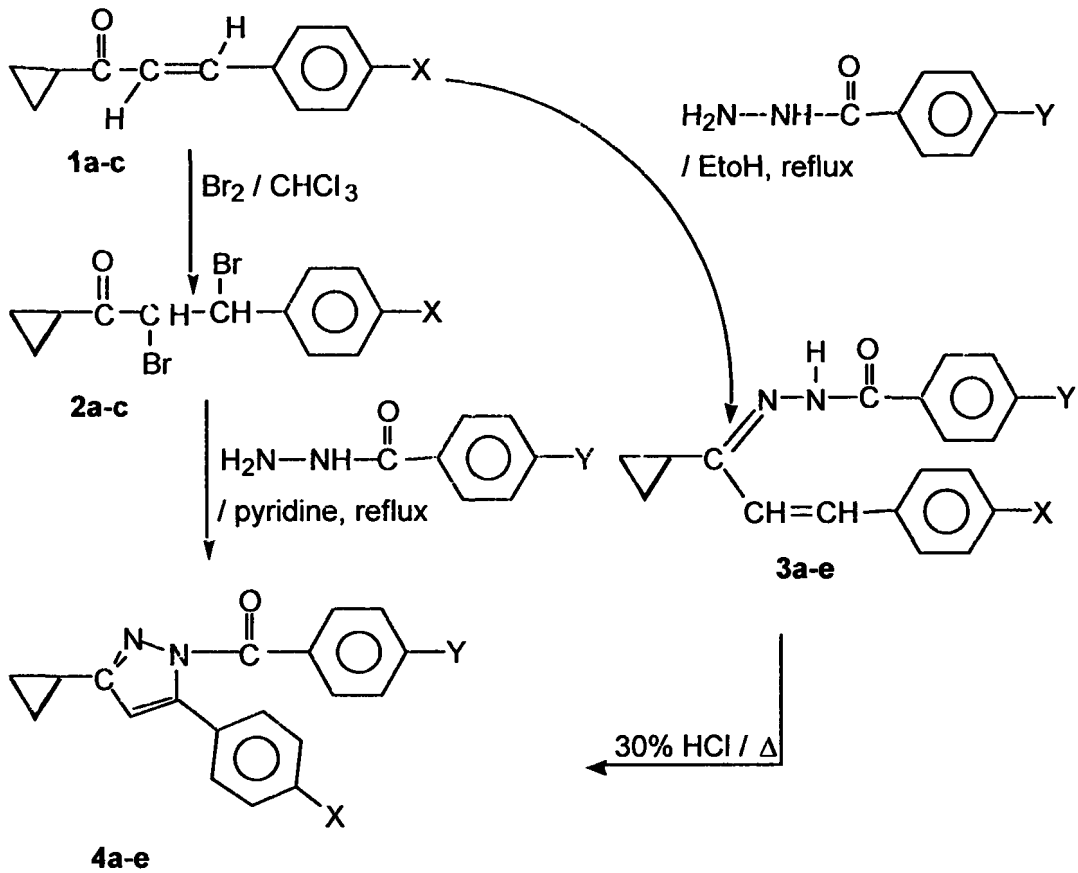
Celecoxib **Deracoxib**

Figure 1

Results and Discussion

Chalcones **1a-c** were synthesized by a base catalyzed *Claisen-Schmidt* condensation reaction [18-19] of appropriately substituted benzaldehyde and cyclopropylmethyl ketone[20]. The method is attractive since it specifically generates the (*E*)-isomer[21].

The dibromochalcones **2a-c** were prepared by adding bromine dropwise to the clear solution of **1a-c** in chloroform to afford the corresponding compounds **2a-c**. The results are shown in scheme 1 and Table 1.



Scheme 1

Condensation of (*E*)-isomers **1a-c** with benzoylhydrazines results in formation of hydrazone derivatives **3a-e**. The IR spectra of these hydrazones show the characteristic bands for vinyl HC=CH at 1486–1613, C=N at 1528–1644, C=O at 1634–1694 and NH at 3338–3424 cm^{-1}. The ^1H NMR spectra showed the presence of a singlet at δ=10.90-11.32 ppm for the NH proton, aromatic protons at 9.70–10.95 ppm, two doublets at δ = 6.40–6.50 ppm and δ 6.70–6.81 ppm characteristic for the olefinic –CH=CH protons. The cyclopropyl ring-protons appeared as 2 multiplets in the range 0.65–1.40 ppm (CH) and 1.13–2.51 ppm ($2CH_2$) respectively. The results are shown in Table 2. The structures of all isolated hydrazones was confirmed using mass spectra. For example, the mass spectra of **3a** showed the presence of the molecular ion peaks at *m/z* =324 and 326 in a ratio 3:1 indicating a chlorine isotope. The base peaks which appeared at *m/z* = 139 and 141 confirmed the existance of chlorine isotope. Other different fragments which support a hydrazone structure are shown in Scheme 2.

The pyrazole derivatives **4a-e** were obtained by treatment of hydrazones **3a-e** with 30% hydrochloric acid. The IR of **4a-e** showed the characteristic bands for C=C–Ar at 1515–1592, C=N at 1600–1619 and amide cabonyl band at 1661–1683 cm^{-1}, while the ^1H NMR spectra showed a singlet at δ 6.43–7.10 ppm for the pyrazole–H–4. Other

characteristic signals for **4a-e** are shown in Table 2. The mass spectra for all isolated pyrazoles were also determined. For example, the mass spectra of **4d** showed molecular ion peaks at *m/z*= 402, 404 and 406 while, the base peaks appeared at *m/z* = 139 and 141 as a result of chlorine isotope contribution. The fragmentation pathways of **4d** is outlined in scheme 3. Finally, the pyrazole structure was confirmed by preparation through another route. Therefore, refluxing of dibromochalcones **2a-c** with benzolyhydrazines in dry pyridine afford **4a-e**. The mp and all spectral data of the pyrazole derivatives obtained from dibromochalcones precursors were completely identical with those obtained from hydrazone precursors.

Experimental :

All melting points are uncorrected. IR spectra were recorded using potassium bromide method on a Perkin-Elmer 1650 spectrophotometer (Faculty of Scinece, Alexandria University, Alex, Egypt). H^1-NMR spectra were determined on a varian EM-390, 90 MHZ spectrophotometer, using TMS as internal standard. Mass spectra were recorded on 70 ev on Hawlett-packared 5988 mass spectrophotometer. (Faculty of Science, Cairo University, Cairo, Egypt). Microanalyses were operated at Faculty of Science, Cairo University, Cairo, Egypt.

General Procedure for Preparation of *E*-1-cyclopropyl-3-*p*-(substituted-phenyl)-2-propenones 1a-c:

To a cold solution of sodium hydroxide (3g in 50 ml aqueous ethanol 60%), cylopropylmethyl ketone (0.1 mole), was added dropwise (30 min.), while rapidly stirring and the temperature kept below 20°C, the desired *p*-substituted benzaldehyde (0.1 mole) was then added dropwise (30 min). After five hours, the mixture was left overnight in refregirator. The separated solid was filtered, washed with water and dried, then recrystallized from ehanol as colourless needles. The physical properties and all the spectral data are as shown in the litleture[20]

General procedure for Preparation of Erythro-2,3-dibromo-1-cylopropyl-3-(*p*-subtituted-phenyl-1-propanones 2a-c:

A solution of bromine in chloroform (0.05 mole) was added dropwise (20 min to a cold stirred to a cold solution of the chalcones **1a-c** (0.05 mole) in chloroform. The reaction mixture was left overnight at room temperature. The solid was filtered off, washed successively with water, dried and recrystallized from ethanol. The physical properties and all spectral data of the dibromo derivatives are identical with those in the litleture[20].

General Procedure for Preparation of 1-cyclopropyl-3-(*p*-subtituted-phenyl)-2-propene-1-aroyl hydrazones 3a-e

A solution of chalcones **1a-c** in ethanol (0.01 mole) was refluxed with the appropriate aroyl hydrazines (0.01 mole) in glacidal acetic acid for about six hours, then the reaction mixture was poured onto crushed ice and was kept overnight at room temperature, the separated solid was filtered off, washed successively with water and dried, then recrytallized form methanol.

General Procedure for Preparation of 1-aroyl-3-cyclopropyl-5-(*p*-substituted) pyrazoles 4a-e

A solution of the appropriate hydrazone **3a-e** (0.02 mol) in 30% hydrochloric acid was refluxed for about two hours, the reaction mixture was concentrated, the separated solid was filtered off, washed with water, dried and recrystallized from methanol.

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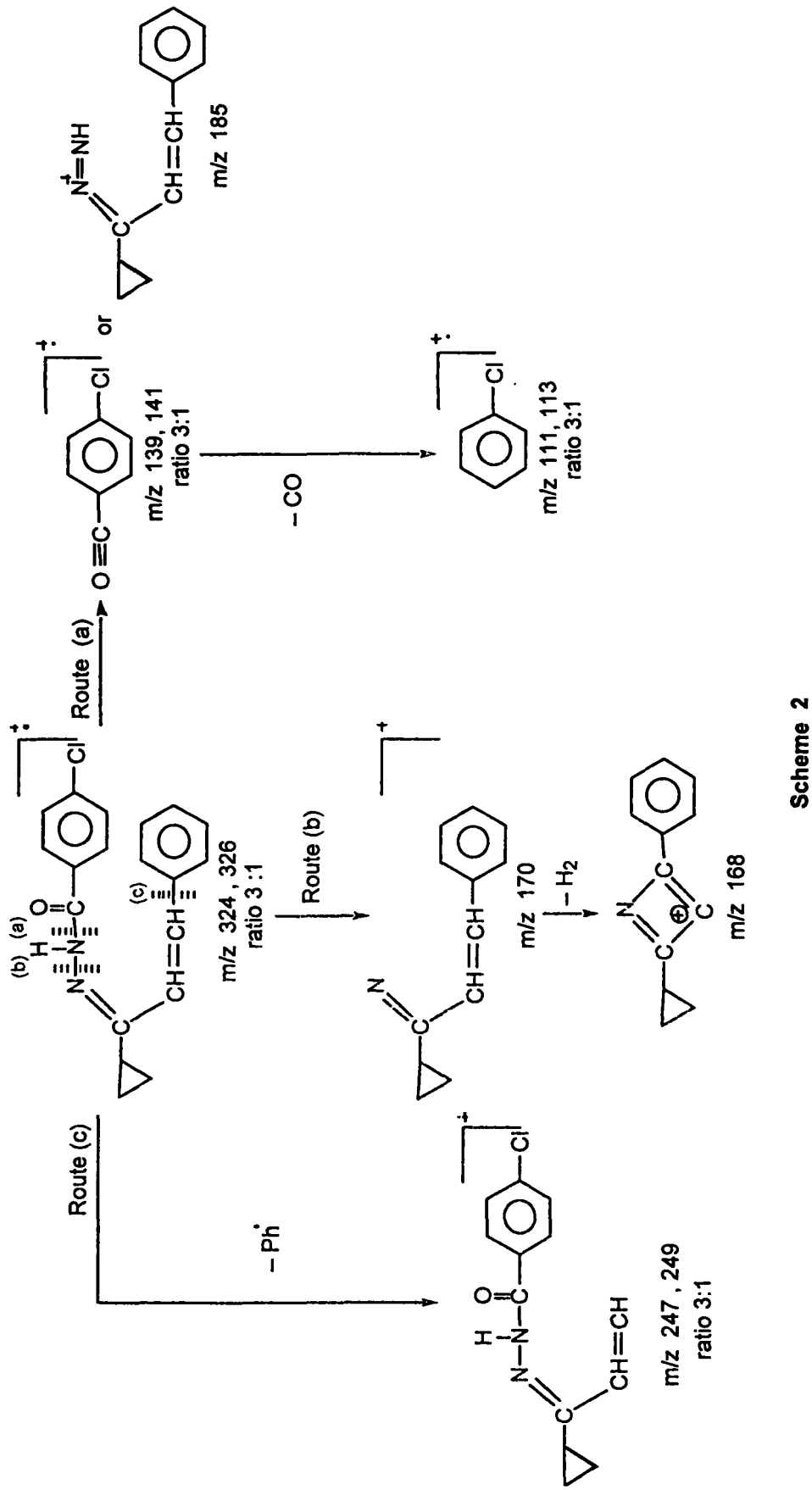
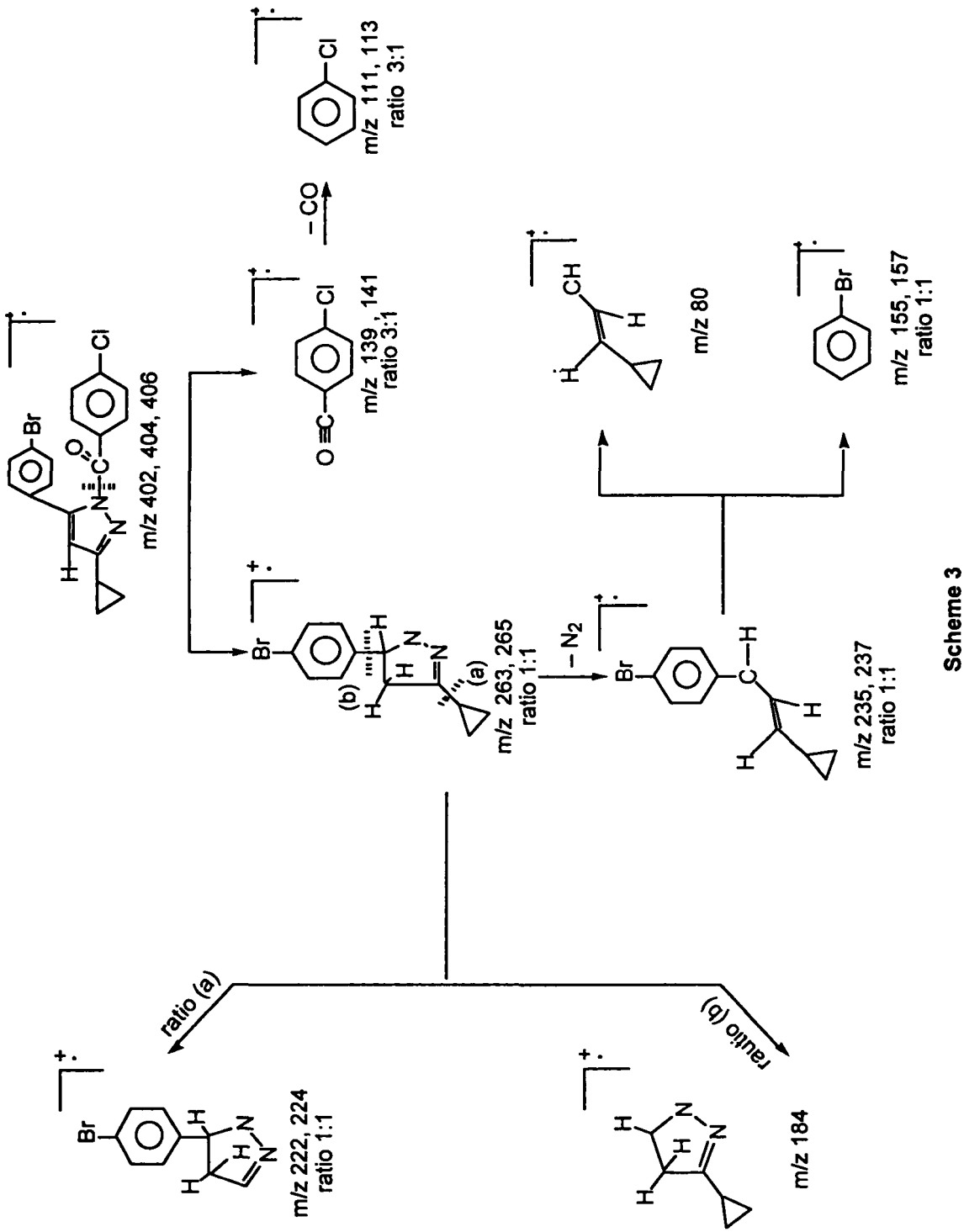

Route (a)
Route (b)
Route (c)
m/z 324 , 326
ratio 3 :1
m/z 139, 141
ratio 3:1
m/z 185
m/z 111, 113
ratio 3:1
m/z 170
m/z 168
m/z 247 , 249
ratio 3:1
- CO
- Ph
- H2
or

Scheme 2


m/z 402, 404, 406
m/z 139, 141 ratio 3:1
m/z 111, 113 ratio 3:1
- CO
m/z 263, 265 ratio 1:1
- N2
m/z 80
m/z 155, 157 ratio 1:1
m/z 235, 237 ratio 1:1
ratio (a)
ratio (b)
m/z 222, 224 ratio 1:1
m/z 184

Scheme 3

Table 1. Physical and Analytical Data of Compounds 3a-e and 4a-e.

Compound	X	Y	Yield (%)	m.p (°C)	Molecular Formula	Calculated %			Found %		
						C	H	N	C	H	N
3a	H	Cl	70	175	$C_{19}H_{17}N_2OCl$	70.37	5.25	8.64	70.60	5.24	8.66
3b	Cl	Cl	74	168	$C_{19}H_{16}N_2OCl_2$	63.69	4.47	7.82	63.72	4.51	7.77
3c	Cl	NO_2	76	180	$C_{19}H_{16}N_3O_3Cl$	61.79	4.34	11.38	61.84	4.29	11.44
3d	Br	Cl	79	163	$C_{19}H_{16}N_2OClBr$	56.72	3.99	6.97	56.76	4.03	6.91
3e	Br	NO_2	82	189	$C_{19}H_{16}N_3O_3Br$	55.21	3.87	10.17	55.19	3.77	10.11
4a	H	Cl	72	183	$C_{19}H_{15}N_2OCl$	70.81	4.66	8.70	70.83	4.62	8.66
4b	Cl	Cl	74	195	$C_{19}H_{14}N_2OCl_2$	74.04	3.93	7.87	63.98	3.91	7.88
4c	Cl	NO_2	80	174	$C_{19}H_{14}N_3O_3Cl$	62.13	3.81	11.44	62.16	3.88	11.39
4d	Br	Cl	73	193	$C_{19}H_{14}N_2OClBr$	57.00	3.50	7.00	56.97	3.55	7.08
4e	Br	NO_2	71	167	$C_{19}H_{14}N_3O_3Br$	55.47	3.41	10.22	55.52	3.49	10.21

Table 2. Spectral Data of Compounds 3a-e and 4a-e .

Compound	IR cm^{-1} (KBr)				^1H NMR (δ / ppm)[a]					Mass Spectra	
	C=C	C=N	C=O	NH	Ar-H's and –C–C*H*=CH (m)	–C–CH=C*H*/(d) J = 12 Hz or pyrazolyl H4(s)	N–H (s)	Cycloproyl CH (m)	ring H's 2 (CH_2) (m)	Molecular ions (relative intensity)	Base Peaks (%)
3a	1600	1644	1694	3353	7.32 - 7.98	6.40	10.90	1.93-2.51	0.75-1.39	324(4.1), 326(1.4)	139(100), 141(35)
3b	1486	1528	1634	3424	7.20 - 7.90	6.70	10.95	1.70-2.20	0.65-1.21	358(8.9), 360(3.1), 362(1)	139(100), 141(34)
3c	1541	1595	1676	3503	7.21 - 7.80	6.81	9.70	1.80-2.20	0.70-1.10	369(8.7), 371(2.8)	150(100)
3d	1535	1576	1634	3421	7.26 - 7.89	6.80	9.78	1.13-2.05	0.78-1.00	402(4), 404(3.1), 406(1)	139(100), 141(35)
3e	1613	1637	1689	3338	7.31 - 7.80	6.50	10.80	1.90-2.50	0.70-1.40	413(3.2), 415(3.2)	150(100)
4a	1592	1619	1683	-	7.28 - 7.91[b]	6.43[c]	-	1.96-2.66	0.77-1.44	322(5.3), 324(1.7)	139(100), 141(33)
4b	1477	1506	1644	-	7.22 - 7.91[b]	6.60[c]	-	2.40-2.57	0.78-1.15	356(9.2), 358(3.3),	139(100), 141(35)
4c	1515	1595	1661	-	7.20 - 8.25[b]	6.75[c]	-	2.25-2.50	0.62-1.00	360(1.1)	150(100)
4d	1555	1589	1667	-	7.56 - 7.91[b]	7.02[c]	-	1.40-1.71	0.80-1.24	367(8.7), 369(2.8)	139(100), 141(35)
4e	1520	1600	1662	-	8.09 - 8.43[b]	7.10[c]	-	1.59-2.51	0.78-0.98	400(4), 402(3.1), 404(1.1) 411(3.2), 413(3.2)	150(100)

[a] Solution in DMSO-d6 [b] The chemical shift indicates only Ar-H's [c] Pyrazolyl-H_4 of 4a-e appears as a singlet