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Synthesis and biological screening of new 1,3-diphenylpyrazoles with different heterocyclic moieties at position-4

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1,3-Diphenyl-1*H*-pyrazole-4-carboxaldehyde (**1**) was reacted with barbituric acid, thiobarbituric acid, some activated nitriles and/or acetophenone to give the condensation products **2a**, **b**, **3a**–**c** and **4**, respectively. The reaction of **1** with hydrazine hydrate, semicarbazide or thiosemicarbazide afforded the corresponding azomethines **5a**–**c**. The compounds **3a**, **b**, **4** and **5a**, **c** were subjected for different sequence reactions to produce the title compounds. The antibacterial and antifungal activity of some selected derivatives were evaluated.

1. Introduction

The pyrazole nucleus in general and its chemistry [1–5] has found considerable attention during the decades due to outstanding biological activities as antianxiety [6, 7], antipyretic, analgesic and antiinflammatory drugs [8, 9] as well as its good antibacterial and antifungal properties [10–14]. All these findings prompted us to introduce several pharmacophores such as pyran, pyridine, pyrimidine or thiazole moieties into the pyrazole system hoping to get compounds with enhanced potency. Also, some of the synthesized compounds were screened *in vitro* for their antibacterial and antifungal activities.

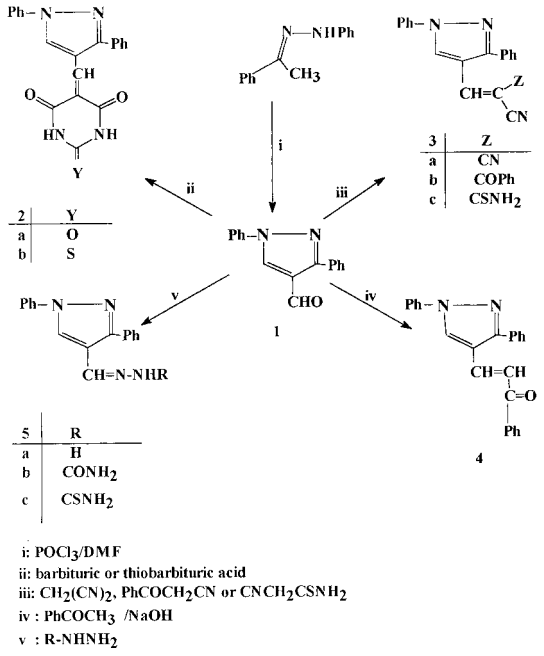
2. Investigations, results and discussion

2.1. Chemistry

Our approach to the target heterocyclic compounds was achieved by the synthesis of 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde (**1**) from acetophenone phenylhydrazone and Vilsmeier reagent [15]. Compound **1** was reacted with some active methylene compounds namely; barbituric acid, thiobarbituric acid, malononitrile, ω-cyanoacetophenone or cyanothioacetamide to give the condensation products **2a**, **b** and **3a**–**c**, respectively. Also, the chalcone **4** was prepared by condensation of **1** with acetophenone as reported before [14]. On the other hand, the reaction of **1** with hydrazine hydrate, semicarbazide and thiosemicarbazide furnished the corresponding azomethines **5a**–**c** (Scheme 1).

Most of the latter compounds (**3a**, **b**, **4** and **5a**, **c**) were used as key intermediates in the synthesis of the desired pyrazoles via their interaction with different reagents.

Scheme 1



Thus, the reaction of **3a** or **3b** with 3-methyl-1-phenyl-2-pyrazolin-5-one in the presence of triethylamine did not give the expected pyrazolopyrans **6a**, **b**. Instead, only one compound was isolated, which was identified as 4-(1,3-diphenyl-1 *H*-pyrazol-4-yl)methylidene-3-methyl-1-phenyl-2-pyrazolin-5-one (**7**). Also, treatment of **3a** with hydrazine hydrate in refluxing ethanol furnished a product with a m.p. of 335 °C. Based on the spectral and elemental analyses, the structure of this product was assigned as bis(azomethinopyrazole) **9**, not as 3,5-diaminopyrazole **8** as reported for a similar function [17]. The structure of **7** and **9** was further confirmed by independent synthesis via direct condensation of **1** with 3-methyl-1-phenyl-2-pyrazolin-5-one or with compound **5a**, respectively (Scheme 2). In contrast, the interaction of **3a** with ethyl acetoacetate in methylene chloride containing triethylamine gave the pyrazolylpyran **10**.

The reaction of chalcone **4** with thiourea in refluxing ethanol containing sodium ethoxide yielded pyrazolylpyrimidinethione **11** in a good yield. Also, the cyclocondensation of **4** with 3-amino-1,2,4-triazole in refluxing acetic acid furnished 4,7-dihydro-7-(1,3-diphenyl-1 H-pyrazol-4-yl)-5-phenyl-s-triazolo[1,5-*a*]pyrimidine (**12**). Compound **4** was fused with ethyl cyanoacetate in the presence of ammonium acetate to give the pyrazolylpyridone **13**. The thioxo analogue **14** was obtained by reaction of **4** with cyanothioacetamide in the presence of triethylamine as a basic catalyst [18] (Scheme 3).

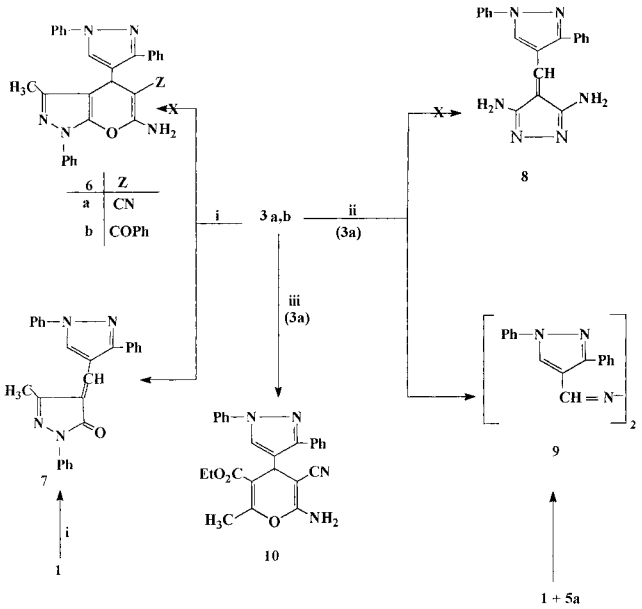
The ternary condensation of **11** with chloroacetic acid and benzaldehyde, in the presence of fused sodium acetate and acetic anhydride, resulted in the formation of the benzylidinethiazolopyrimidine **16**. When the latter reaction was performed again without benzaldehyde, the product was identified as thiazolopyrimidine derivative **15**. The structure of **16** was further confirmed by an independent synthesis via interaction of **15** with benzaldehyde in the presence of piperidine (Scheme 4).

Table 1: Antibacterial and antifungal activities of some new pyrazole derivatives
(diameter of inhibition zones)

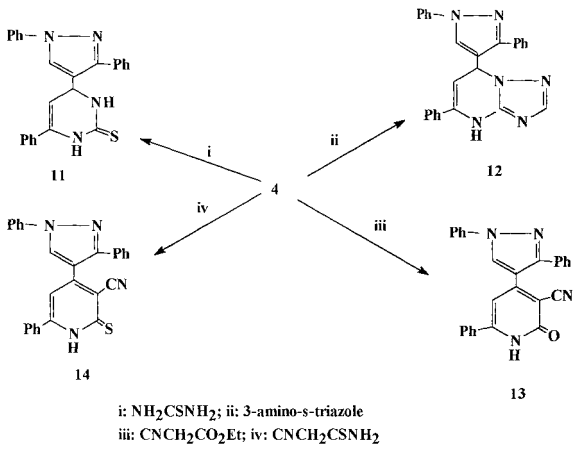
Compd.	*B. cereus*	*E. coli*	*Botrytis*	*G. candidum*	*C. albicans*
2b	18	–	–	–	–
3c	30	–	20	12	–
5c	20	–	–	–	–
13b	36	–	–	–	–
17c	9	–	–	–	–
18a	30	–	20	14	–
18b	30	–	–	–	–
19	22	–	10	11	–
20	26	–	10	12	–
21a	36	–	30	16	–
21b	24	–	–	–	–

–: No inhibition zone

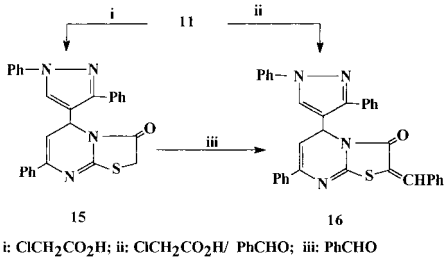
Scheme 2



Scheme 3



Scheme 4



The reaction of **14** with some α-halocarbonyl compounds namely; phenacyl bromide, ethyl chloroacetate and/or chloroacetamide afforded the corresponding S-alkylated products **17a–c**. Heating of **17a–c** in ethanol containing sodium ethoxide led to the formation of the pyrazolylthienopyridines **18a–c**. The condensation of **18c** with triethyl orthoformate in refluxing acetic anhydride furnished the pyrazolylpyridothienopyrimidine **19** (Scheme 5).

When thiosemicarbazone **5c** was allowed to react with phenacyl bromide in the presence of fused sodium acetate, the thiazoline derivative **20** was obtained. As well, the reaction of **5c** with ethyl chloroacetate or methyl α-bromopropionate gave the corresponding thiazolidinones **21a**, **b**. These reactions were assumed to proceed via S-alkylation followed by dehydration or loss of an alcohol molecule (Scheme 6).

The structures of all the synthesized compounds were confirmed on the basis of their elemental analyses, IR and ^{1}H NMR spectral data. Moreover, the MS spectra of both **20** and **21b** were recorded and showed the corresponding molecular ion peak and a peak at m/z 246 due to 4-azamethino-1,3-diphenylpyrazole fragment (**22**) which formed as a result of the cleavage of the acyclic N–N bond (Scheme 7).

Table 2: Characterization data of all newly synthesized compounds

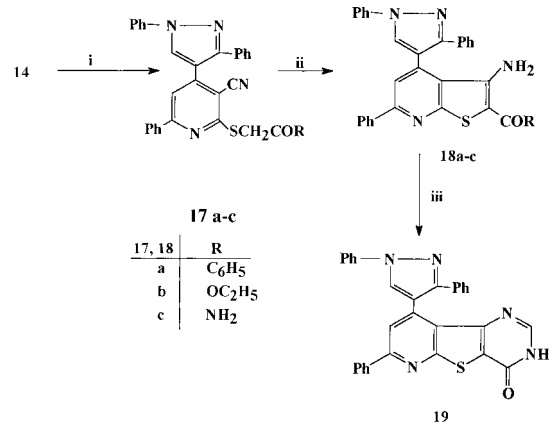
Compd.	M.P. °C (Yield/%)	Mol. Formula* (M.Wt.)	IR (cm^{-1})	^1H NMR (ppm)
2a	>360 (56)	$C_{20}H_{14}N_4O_3$ (358.4)	3200 (NH) 1725 (CO) 1700 (CO)	
2b	>360 (49)	$C_{20}H_{14}N_4O_2S$ (374.3)	3130 (NH) 1700 (CO) 1650 (NCS)	
3a	202 (81)	$C_{19}H_{12}N_4$ (296.3)	2200 (CN) 1590 (C=C)	($CDCl_3$): 7.4–7.9 (m, 11 H, Ar-H + CH pyrazole); 9.0 (s, 1 H, CH=C)
3b	197 (68)	$C_{25}H_{17}N_3O$ (375.4)	2200 (CN) 1640 (CO)	($CDCl_3$): 7.2–8.1 (m, 15 H, Ar-H); 8.3 (s, 1 H, CH pyrazole); 9.3 (s, 1 H, CH=C)
3c	262 (85)	$C_{19}H_{14}N_4S$ (330.3)	3300, 3100 (NH_2) 2200 (CN) 1640 (NCS)	
5a	118 (85)	$C_{16}H_{14}N_4$ (262.3)	3390, 3300 (NH_2)	($CDCl_3$): 5.4 (br, 2 H, NH_2); 7.2–7.9 (m, 10 H, Ar-H); 8.3 (s, 1 H, CH pyrazole); 8.6 (s, 1 H, N=CH)
5b	242 (65)	$C_{17}H_{15}N_5O$ (305.3)	3320, 3220 (NH_2) 3150 (NH) 1680 (CO)	
5c	230 (84)	$C_{17}H_{15}N_5S$ (321.3)	3300, 3230 (NH_2) 3130 (NH)	
7	250 (70)	$C_{26}H_{20}N_4O$ (404.5)	1640 (CO) 1580 (C=C)	($CDCl_3$): 2.3 (s, 3 H, CH_3); 7.0–8.1 (m, 15 H, Ar-H); 8.3 (s, 1 H, CH pyrazole), 10.3 (s, 1 H, CH=C)
9	335 (40)	$C_{32}H_{24}N_6$ (492.6)	1610 (C=N)	
10	230 (35)	$C_{25}H_{22}N_4O_3$ (426.5)	3400, 3300 (NH_2) 2200 (CN) 1700 (CO)	($CDCl_3$): 1.1–1.3 (t, 3 H, CH_3); 2.4 (s, 3 H, CH_3); 3.9–4.3 (q, 2 H, CH_2); 4.5 (s, 2 H, NH_2); 4.9 (s, 1 H, CH pyran); 7.2–7.9 (m, 11 H, Ar-H + CH pyrazole)
11	215 (83)	$C_{25}H_{20}N_4S$ (408-4)	3180 (NH) 1640 (NCS)	(DMSO-d_6): 5.2 (m, 1 H, CH pyrimidine); 4.5 (m, 1 H, CH pyrimidine); 7.3–9.0 (m, 15 H, Ar-H); 8.4 (s, 1 H, CH pyrazole); 9.2 (s, 1 H, NH); 9.8 (s, 1 H, NH)
12	272 (54)	$C_{26}H_{20}N_6$ (416.5)	3180 (NH)	(TFA): 5.5 (d, 1 H, CH pyrimidine); 6.7 (d, 1 H, CH pyrimidine); 7.3–7.8 (m, 15 H, Ar-H); 8.3 (s, 1 H, CH triazole); 8.7 (s, 1 H, CH pyrazole)
13	331 (43)	$C_{27}H_{18}N_4O$ (414.5)	3100 (NH) 2200 (CN) 1640 (CO)	(TFA): 6.7 (s, 1 H, CH pyridine); 7.2–7.8 (m, 15 H, Ar-H); 8.7 (s, 1 H, CH pyrazole)
14	273 (59)	$C_{27}H_{18}N_4S$ (430.5)	3150 (NH) 2200 (CN)	
15	150 (70)	$C_{27}H_{20}N_4OS$ (448.4)	1720 (CO)	($CDCl_3$): 3.7 (s, 2 H, CH_2); 5.7 (d, 1 H, CH pyrimidine); 6.0 (d, 1 H, CH pyrimidine); 6.8–7.9 (m, 15 H, Ar-H); 8.0 (s, 1 H, CH pyrazole)
16	260 (86)	$C_{34}H_{24}N_4OS$ (536.5)	1700 (CO)	($CDCl_3$): 5.7 (d, 1 H, CH pyrimidine); 6.1 (d, 1 H, CH pyrimidine) 7.2–7.8 (m, 20 H, Ar-H); 8.0 (s, 1 H, CH=C); 8.4 (s, 1 H, CH pyrazole).
17a	210 (80)	$C_{35}H_{24}N_4OS$ (548.6)	2200 (CN) 1680 (CO)	($CDCl_3$): 4.8 (s, 2 H, CH_2); 6.8–8.1 (m, 21 H, Ar-H + CH pyridine); 8.5 (s, 1 H, CH pyrazole)
17b	159 (75)	$C_{31}H_{24}N_4O_2S$ (516.5)	2200 (CN) 1730 (CO)	($CDCl_3$): 1.1–1.3 (t, 3 H, CH_3); 4.1–4.3 (m, 4 H, 2 CH_2); 7.2–7.9 (m, 16 H, Ar-H + CH pyridine); 8,5 (s, 1 H, CH pyrazole)
17c	240 (76)	$C_{29}H_{21}N_5OS$ (487.5)	3400, 3200 (NH_2) 2200 (CN) 1640 (CO)	($CDCl_3$): 4.0 (s, 2 H, CH_2); 7.2–7.9 (m, 18 H, Ar-H + CH pyridine + NH_2); 8.5 (s, 1 H, CH pyrazole)
18a	308 (91)	$C_{35}H_{24}N_4OS$ (548.6)	3450, 3300 (NH_2) 1620 (CO)	
18b	224 (81)	$C_{31}H_{24}N_4O_2S$ (516.5)	3480, 3350 (NH_2) 1660 (CO)	($CDCl_3$): 1.2–1.5 (t, 3 H, CH_3); 4.1–4.4 (q, 2 H, CH_2); 5.9 (s, 2 H, NH_2); 7.1–8.3 (m, 17 H, Ar-H + CH pyridine + CH pyrazole)
18c	245 (82)	$C_{29}H_{21}N_5OS$ (487.5)	3430, 3300, 3120 (2 NH_2) 1650 (CO)	
19	287 (68)	$C_{30}H_{19}N_5OS$ (497.5)	3200–2400 (NH) 1650 (CO)	(TFA): 6.7 (s, 1 H, CH pyridine); 7.2–7.8 (m, 15 H, Ar-H); 8,5 (s, 1 H, CH pyrimidine); 8.7 (s, 1 H, CH pyrazole)

Table 2: Continued

Compd.	M.P. °C (Yield/%)	Mol. Formula* (M.Wt.)	IR (cm^{-1})	^{1}H NMR (ppm)
20**	162 (75)	$C_{25}H_{19}N_5S$ (421.4)	3420 (NH)	($CDCl_3$): 6.8 (s, 1 H, CH thiazoline); 7.0–7.8 (m, 17 H, Ar-H + NH + CH=N); 8.3 (s, 1 H, CH pyrazole)
21a	315 (85)	$C_{19}H_{15}N_5OS$ (361.4)	3100 (NH) 1700 (CO)	(DMSO-d_6): 3.9 (s, 2 H, CH_2); 7.3–8.1 (m, 11 H, Ar-H + NH); 8.5 (s, 1 H, CH pyrazole); 8.9 (s, 1 H, CH=N)
21b**	257 (75)	$C_{20}H_{17}N_5OS$ (375.4)	3100 (NH) 1700 (CO)	(DMSO-d_6): 1.6–1.7 (d, 3 H, CH_3); 3.9–4.1 (q, 1 H, CH thiazolidinone); 7-3–7.9 (m, 11 H Ar-H + NH); 8.4 (s, 1 H, CH pyrazole); 8.6 (s, 1 H, CH=N)

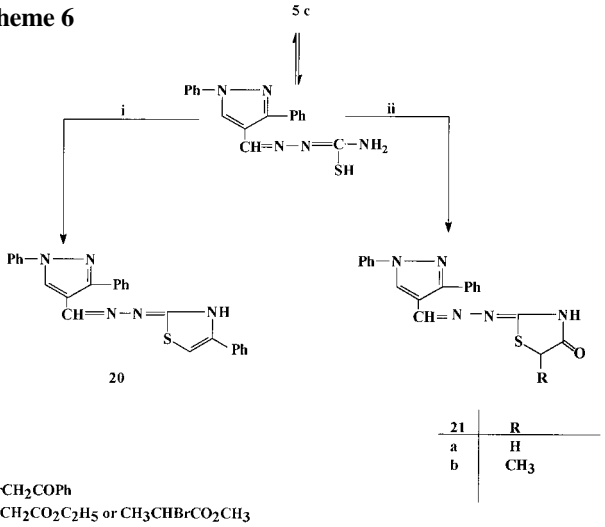
* Satisfactory elemental analyses were obtained for all compounds
** MS of **20**: 421 (M^+, 18%); 246 (21%); 176 (100%). ** MS of **21b**: 375 (M^+, 65%); 246 (100%)

Scheme 5



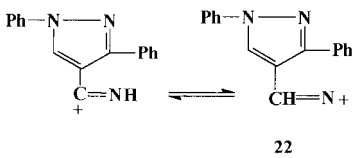
i: $PhCOCH_2Br$, $ClCH_2CO_2Et$ or $ClCH_2CONH_2$
ii: EtONa
iii: $CH(OEt)_3$

Scheme 6



i: $BrCH_2COPh$
ii: $ClCH_2CO_2C_2H_5$ or $CH_3CHBrCO_2CH_3$

Scheme 7



2.2. *Biological activity*

Eleven compounds were screened *in vitro* for their antimicrobial acitivities against two strains of bacteria (*Bacillus cereus, Escherichia coli*), two strains of fungi (*Botrytis, Geotrichum candidum*) and one strain of yeast (*Candida albicans*) using the filter paper disc method [19, 20]. The results revealed that all the tested compounds exhibit moderate to strong activity against *bacillus cereus* and are inactive against *Escherichia coli*. However, only five compounds (**3a**, **18a**, **19**, **20** and **21a**) showed considerable potency against the two fungal species used. None of the tested compounds were active against *Candida alibicans* (Table 1).

3. Experimental

Meltings points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded in KBr on a Pye-Unicam SP 3-100 spectrophotometer (ν_{max} in cm^{-1}), ^{1}H NMR spectra on a Varian EM 390 90 MHz spectrometer using TMS as internal reference (chemical shifts in δ values) and MS spectra on SSQ-7000 apparatus. The elemental analyses were carried out on a Perkin-Elemer 240C elemental analyzer. The characterization data of all newly synthesized compounds are given in Table 2.

3.1. *1,3-Diphenyl-1 H-pyrazole-4-carboxaldehyde* (1)

This compound was prepared according to a reported method [15].

3.2. *Condensation of 1 with barbituric acid and thiobarbituric acid: Formation of compounds* **2a, b**

A mixture of **1** (2.48 g, 0.01 mol) and barbituric or thiobarbituric acid (0.01 mol) in C_2H_5OH (30 ml) containing triethylamine (0.1 ml) was heated under reflux for 1 h. The solid thus formed on cooling was collected and recrystallized from dioxane as orange needles of **2a**, **b**.

3.3. *Condensation of 1 with activated nitriles: Formation of acrylonitriles* **3a–c**

To a mixture of **1** (2.48 g, 0.01 mol) and malononitrile, ω-cyanoacetophenone or cyanothioacetamide (0.01 mol) in C_2H_5OH (30 ml), piperidine (0.1 ml) was added. The resulting mixture was heated under reflux for 5 min and left to cool. The precipitate thus formed was collected and recrystallized from C_2H_5OH/dioxane to give the acrylonitrile derivatives **3a**, **3b** and **3c**, respectively.

3.4. *1-(1,3-Diphenyl-1 H-pyrazol-4-yl)-3-phenyl-1-propen-3-one* (4)

This compound was prepared according to a reported method [16].

3.5. *Condensation of 1 with amino compounds: Formation of azomethines* **5a–c**

3.5.1. With hydrazine hydrate; Formation of hydrazone **5a**

A mixture of **1** (2.48 g, 0.01 mol) and hydrazine hydrate (3 ml, 0.06 mol) in C_2H_5OH (50 ml) was heated under reflux for 2 h, cooled and diluted with H_2O. The precipitate thus formed was collected and recrystallized from aqueous C_2H_5OH (50%) as white needles.

3.5.2. With semicarbazide: Formation of semicarbazone **5b**

A mixture of **1** (2.48 g, 0.01 mol), semicarbazide HCl (1.13 g, 0.01 mol) and anh. CH_3COONa (2.0 g) in C_2H_5OH (30 ml) was heated under reflux for 2 h. The solid thus formed was collected and recrystallized from dioxane/H_2O mixture (3 : 1) as white crystals.

3.5.3. With thiosemicarbazide: Formation of thiosemicarbazone **5c**

A mixture of **1** (2.48 g, 0.01 mol) and thiosemicarbazide (0.91 g, 0.01 mol) in C_2H_5OH (30 ml) was heated under reflux for 3 h. The precipitated product was collected and recrystallized from a C_2H_5OH/dioxane mixture (2 : 1) as colourless crystals.

3.6. Reaction of **3a, b** *with 3-methyl-1-phenyl-2-pyrazolin-5-one*

To a mixture of **3a** or **3b** (0.01 mol) and 3-Methyl-1-phenyl-2-pyrazolin-5-one (1.74 g, 0.01 mol) in C_2H_5OH (30 ml), triethylamine (0.1 ml) was added. The resulting mixture was heated under reflux for 30 min and left to cool. The precipitated product was collected and recrystallized from C_2H_5OH/dioxane (1 : 1) as orange crystals of **7**.
Compound **7** was also prepared by refluxing a mixture of **1** (2.48 g, 0.01 mol) and 3-methyl-1-phenyl-2-pyrazolin-5-one (1.74 g, 0.01 mol) in C_2H_5OH containing triethylamine (0.1 ml) for 15 min, yield 2.8 g (70%), m.p. 250 °C, mixed m.p. 250 °C.

3.7. Reaction of **3a** *with hydrazine hydrate*

A mixture of **3a** (2.96 g, 0.01 mol) and hydrazine hydrate (0.5 ml, 0.01 mol) in C_2H_5OH (30 ml) was heated under reflux for 2 h, cooled and then diluted with H_2O. The precipitated solid was collected and recrystallized from a benzen/petroleum ether (60/80 °C) mixture (2 : 1) to give white crystals of **9**.
Compound **9** was also synthesized by refluxing a mixture of **5a** (1.31 g, 0.005 mol) and **1** (1.24 g, 0.005 mol) in C_2H_5OH (30 ml) containing a few drops of CH_3COOH for 5 min, yield 2.2 (90%), m.p. 335 °C, mixed m.p. 335 °C.

3.8. 2-Amino-3-cyano-4-(1,3-diphenyl-1 H-pyrazol-4-yl)-5-ethoxycarbonyl-6-methylpyran **(10)**

To a solution of **3a** (2.96 g, 0.01 mol) and ethyl acetoacetate (1.30 g, 0.01 mol) in CH_2Cl_2 (50 ml), triethylamine (0.1 ml) was added. The mixture was heated under reflux for 4 h, concentrated and allowed to cool. The precipitated product was collected and recrystallized from C_2H_5OH as colourless needles.

3.9. 4-(1,3-Diphenyl-1 H-pyrazol-4-yl)-6-phenyl-1,2,3,4-tetrahydropyrimidine-2-thione **(11)**

A mixture of chalcone **4** (3.50 g, 0.01 mol) and thoiurea (0.76 g, 0.01 mol) in ethanolic C_2H_5ONa solution (0.25 g Na in 30 ml abs. C_2H_5OH) was heated under reflux for 2 h, cooled and neutralized with diluted CH_3COOH. The precipitated solid was collected and recrystallized from benzene as fine white needles.

3.10. 4,7-Dihydro-7-(1,3-diphenyl-1 H-pyrazol-4-yl)-5-phenyl-s-triazolo[1,5-a]pyrimidine **(12)**

A mixture of chalcone **4** (3.5 g, 0.01 mol) and 3-amino-s-triazole (0.84 g, 0.01 mol) in CH_3COOH (40 ml) was heated under reflux for 2 h and allowed to cool. The product thus separated was collected and recrystallized from C_2H_5OH to give white crystals of **12**.

3.11. 3-Cyano-4-(1,3-diphenyl-1 H-pyrazol-4-yl)-6-phenylpyridine-2(1 H)-one **(13)**

A mixture of chalcone **4** (3.5 g, 0.01 mol), ethyl cyanoacetate (2.26 g, 0.02 mol) and CH_3COONH_4 (7.7 g, 0.1 mol) was heated at 150 °C in an oil bath for 5 h. The solid which precipitated after cooling and dilution with H_2O was collected and recrystallized from CH_3COOH as white crystals.

3.12. 3-Cyano-4-(1,3-diphenyl-1 H-pyrazol-4-yl)-6-phenylpyridine-2(1 H)-thione **(14)**

To a suspension of chalcone **4** (7.0 g, 0.02 mol) and cyanothioacetamide (2.0 g, 0.02 mol) in abs. C_2H_5OH (150 ml), triethylamine (1.0 ml) was added. The reaction mixture was heated under reflux for 5 h, concentrated and left to cool. The product thus formed was collected and recrystallized from CH_3COOH as yellow fine needles.

3.13. 2,3-Dihydro-5-(1,3-diphenyl-1 H-pyrazol-4-yl)-7-phenyl-5 H-thiazolo-[2,3-b]pyrimidine-3-one **(15)**

A mixture of **11** (2.04 g, 0.005 mol), chloroacetic acid (1.0 g) and fused CH_3COONa (2.0 g) in 15 ml of CH_3COOH and 15 ml of $(CH_3CO)_2O$ was heated under reflux for 4 h and left to cool. The reaction mixture was diluted with H_2O (30 ml), shaked and allowed to stand for 2 h. The solid obtained was filtered off and crystallized from C_2H_5OH.

3.14. 2-Benzylidene-2,3-dihydro-5-(1,3-diphenyl-1 H-pyrazol-4-yl)-7-phenyl-5H-thiazolo[2,3-b]pyrimidine-3-one **(16)**

3.14.1. Method A

A mixture of **11** (2.04 g, 0.005 mol), chloroacetic acid (1.0 g), benzaldehyde (0.53 g, 0.005 mol) and fused CH_3COONa (2.0 g) in 15 ml of CH_3COOH and 15 ml of $(CH_3CO)_2O$ was heated under reflux for 4 h and left to cool. The reaction mixture was cooled and diluted with H_2O (30 ml). The solid obtained was filtered off and crystallized from CH_3COOH as yellow crystals of **16**.

3.14.2. Method B

To a mixture of **15** (2.24 g, 0.005 mol) and benzaldehyde (0.56 g, 0.005 mol) in abs. C_2H_5OH (15 ml), piperidine (few drops) was added. The mixture was heated under reflux for 2 h. The crystalline product thus obtained after coolling was collected and recrystallized from CH_3COOH, yield 2.0 g (75%).
Compound **16** prepared by methods A and B have the same m.p. and mixed m.p.

3.15. Reaction of 14 with α-halocarbonyl compounds. Formation of thioethers **17a–c**

A mixture of **14** (4.3 g, 0.01 mol) and the respective halocompound (0.01 mol) in C_2H_5OH (60 ml) containing anh. CH_3COONa (1.25 g, 0.015 mol) was refluxed for 2 h. On cooling, the precipitated product was collected by filtration, washed with H_2O, air dried and recrystallized from C_2H_5OH as white needles of **17a–c**.

3.16. Cyclization of compounds **17a–c***: Formation of thienopyridines* **18a–c**

Compounds **17a–c** (0.005 mol) were dissolved in C_2H_5ONa solution (20 mg Na in 40 ml abs. C_2H_5OH) and heated under reflux for 5 min. The yellow solid thus formed after cooling was collected by filtration, washed with H_2O, dried and recrystallized from a $C_2H_5OH/CHCl_3$ mixture as canarian yellow needles of **18a–c**.

3.17. 3,4-Dihydro-9-(1,3-diphenyl-1 H-pyrazol-4-yl)-7-phenyl-4-oxopyrido[3′,2′ : 4,5]thieno[3,2-d]pyrimidine **(19)**

Compound **18c** (2.43 g, 0.005 mol) and $CH(OC_2H_5)_3$ (0.9 g, 0.006 mol) in redistilled $(CH_3CO)_2O$ (15 ml) was heated at 120 °C for 1 h. The solid thus formed after cooling was filtered off, washed with H_2O and recrystallized from CH_3COOH as white crystals.

3.18. Reaction of **5c** *with phenacyl bromide: Formation of thiazoline* **20**

To a mixture of **5c** (1.61 g, 0.005 mol) and phenacyl bromide (1.0 g, 0.005 mol) in C_2H_5OH (30 ml), fused CH_3COONa (1.0 g) was added. The reaction mixture was refluxed for 10 h and left to cool. The precipitated solid was collected and recrystallized from C_2H_5OH as yellow needles of **20**.

3.19. Reaction of **5c** *with α-haloesters. Formation of thiazolidinones* **21a, b**

A mixture of **5c** (1.61 g, 0.005 mol), ethyl α-chloroacetate or methyl α-bromopropionate (0.005 mol) and fused CH_3COONa (1.0 g) in C_2H_5OH (25 ml) was heated under reflux for 10 h, cooled and poured onto ice/H_2O. The precipitate thus formed was collected and crystallized from dioxane to give **21a** or **21b**, respectively.

3.20. Biological screening

The filter paper disc method [19, 20] was performed in Nutrient agar for bacteria and Czapek's Dox agar for fungi. These agar media were inoculated with 0.5 ml of the 24 h liquid cultures. Filter paper discs (5 mm diameter) saturated with each compound solution (10 mg/1 ml of DMSO) were placed on the indicated agar media. The incubation time was 48 h at 28 °C. Discs saturated with DMSO were used as control. The diameter of inhibition zones (mm) were measured and recorded in Table 1.

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Fourier transform infrared spectrometric determination of paracetamol and ibuprofen in tablets

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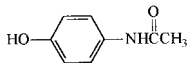
A fourier transform infrared (FTIR) spectrometric technique is described for the simultaneous determination of ibuprofen and paracetamol in two compositions of pharmaceutical tablets. Quantification was carried out by measuring the absorbances at 1684 and 1740 cm^{-1} for paracetamol and ibuprofen, respectively, using the baseline established at 1780 cm^{-1} for measurement correction. The linear correlations with high values of correlation coefficients (0.9999) were obtained at a concentration range of 2.0–10.0 mg ml^{-1} for both analytes. The detection limits were found to be 0.34 and 0.21 mg ml^{-1} for paracetamol and ibuprofen, respectively. A HPLC method was developed as reference method for the determination of both compounds. The results obtained from the FTIR technique are in good agreement with those from HPLC.

1. Introduction

Paracetamol (**1**) is an antipyretic and analgesic compound and ibuprofen (**2**) is a non-steroidal anti-inflammatory analgesic drug [1]. These two drugs are used in combination for the relief of moderate pains. The combined tablets are marketed under various trade names in two compositions, 325 mg of paracetamol and 200 mg or 400 mg of ibuprofen.



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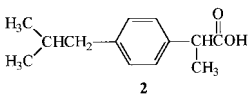

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Many methods have been reported for the determination of paracetamol [2–11] and ibuprofen [12–15]. The combined dosage forms of paracetamol and ibuprofen have been estimated by high performance thin layer chromatography [16] and gas-liquid chromatography [17, 18]. However, no data are available for the direct determination of paracetamol and ibuprofen combinations by FTIR. The goal of this work was to demonstrate an alternative FTIR technique for the simultaneous determination of paracetamol and ibuprofen in tablets which is simple, rapid, accurate and inexpensive.

2. Investigations, results and discussion

The absorbance of a C=O stretch is the interesting band for this study, since it is one of the most prominent band in the spectrum and both paracetamol and ibuprofen contain this group in their structures. Chlorinated solvents such as tetrachloromethane (CCl_4), dichloromethane (CH_2Cl_2) and chloroform ($CHCl_3$) which are transparent in this region cannot be used as solvents for analysis. Ibuprofen can be dissolved in most of the organic solvents

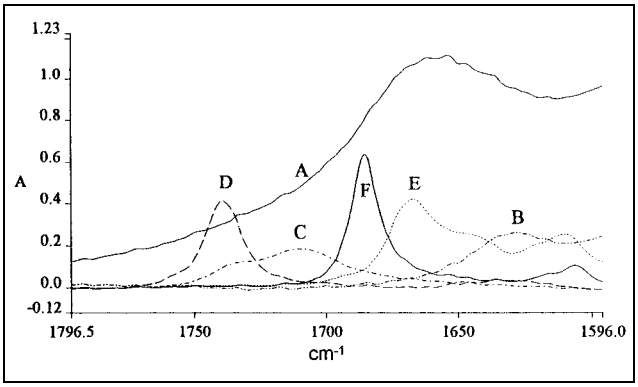

Fig. 1: Spectra of A, methanol; B, acetonitrile, and solvent subtracted absorbance spectra of C, ibuprofen 10 mg ml^{-1} in methanol; D, ibuprofen 10 mg ml^{-1} in acetonitrile; E, paracetamol 10 mg ml^{-1} in methanol; F, paracetamol 10 mg ml^{-1} in acetonitrile