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Uses of piperonal in the synthesis of novel prop-2-enoyl amides, esters, heterocyclic systems and study of their antibacterial activities

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Novel (*E*)-3-(benzo[d][1,3]dioxol-5-yl)-2-cyanoacryloyl chloride **4** was condensed with several mono-; 1,2-; 1,3- and 1,4-bi-nucleophilic reagents containing nitrogen and oxygen to give new 2-propenoylamide and ester derivatives. Some of these amides cyclised under the reaction conditions and/or with $POCl_3$ to give new derivatives of heterocyclic systems. Antibacterial activities were tested for nine of these products.

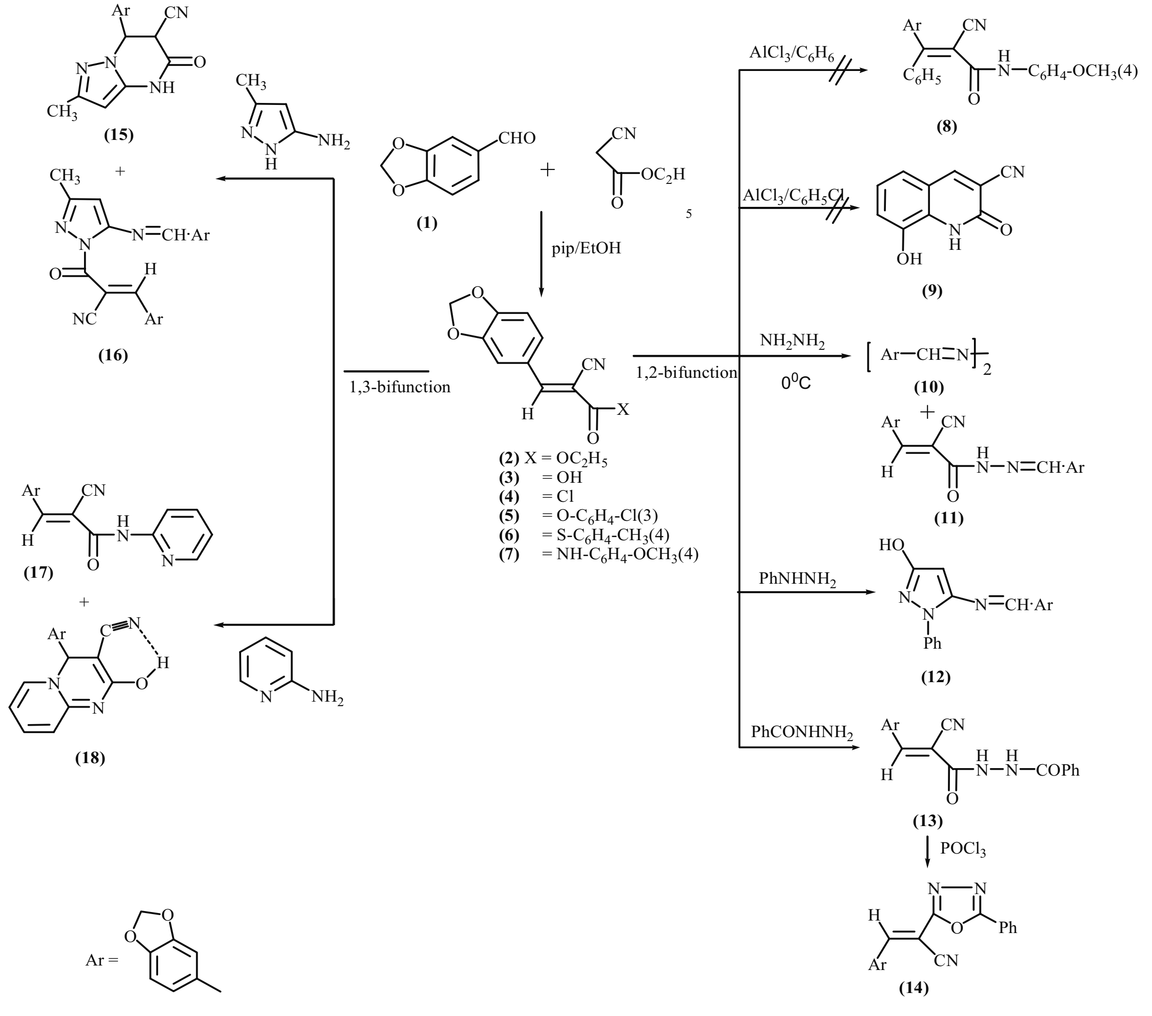
Keywords: piperonal, prop-2-enoyl amides, esters antibacterials

Piperonal is a suitable substrate to several products of commercial importance.[1] The recent wide importance of prop-2-enoylamides,[2] 2-propenoates,[3-6] besides the interesting biological and pharmacological activities of many heterocyclic systems, like, benzimidazoles,[7-9] benzoxazoles,[7-10] benzoxazines,[11,12] oxadiazoles,[13] and pyrazoles[14] have encouraged us to gather these moietes hoping to produce new compounds with expected biological activity.

Discussion

In continuation[15-19] of our interest in the synthesis and reactivity of 2-propenoylchlorides toward some nitrogen and oxygen nucleophilic reagents, we report here the synthesis of novel (*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)-2-cyanoacryloyl chloride **4** via the common route condensation of piperonal **1** with ethyl cyanoacetate in presence of piperidine, to give a quantitative yield of the corresponding (*E*)-ethyl 3-(benzo[*d*][1,3]dioxol-5-yl)-2-cyanoacrylate **2**.[20] Hydrolysis of **2** in alcoholic solution of sodium hydroxide (1 : 1 mole) gave the corresponding acid[21] **3**, which was identified as a precursor of herbicides,[22] agrochemical and pharmaceutical intermediates.[23] Refluxing the acid **3** in thionyl chloride yielded the new 2-cyanoacryloyl chloride **4** in good yield (Scheme 1).

Condensation of **4** with mono-nucleophilic reagents, like *m*-chlorophenol, *p*-methylthiophenol and/or *p*-anisidine in dry benzene in the presence of Et_3N at room temperature afforded



Scheme 1

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the corresponding ester **5**, thiolester **6**, and amide **7** (Scheme 1). In contrast to Wang *et al.*,[24] treatment of **7** with $AlCl_3$ in benzene and/or chlorobenzene gave unchanged product rather than Michael adduct **8**/or quinoline derivative **9** (Scheme 1).

Condensation of **4** with 1,2-binucleophilic reagent like hydrazine hydrate at 0 °C gave a mixture of azine **10** and (*2E,N'E*)-3-(benzo[*d*][1,3]dioxol-5-yl)-N'-(benzo[*d*][1,3]dioxol-5-ylmethylene)-2-cyanoacrylohydrazide **11** (Scheme 1). The structure of azine **10** was supported by comparison with authentic sample[25] and besides the analytical and spectral data. The same reaction at room temperature gave only the azine **10** as a sole product.

On the other hand, reaction of phenylhydrazine with acid chloride **4** gave the unexpected product (*E*)-5-(benzo[*d*][1,3]dioxol-5-ylmethyleneamino)-1-phenyl-1*H*-pyrazol-3-ol **12** (Scheme 1).

The formation of **10**, **11**, and **12** can be explained according to the pathway shown in Scheme 2.

With benzoylhydrazine, the expected N,N'-diacylhydrazine **13** was obtained in good yield which, upon heating with $POCl_3$, produced the corresponding dehydrating product, 1,3,4-oxadiazole derivative **14** (Scheme 1).

Furthermore, condensation of **4** with 1,3-binucleophilic reagent, such as, 5-amino-3-methyl-1*H*-pyrazole, yielded a mixture of fused heterocyclic compound, pyrazolo[1,5-*a*]pyrimidin-5-one derivative **15** and 1-(-acryloyl)-5-methyleneamino-3-methylpyrazole derivative **16** (Scheme 1).

Formation of **15** and **16** can be explained according to the pathway shown in Scheme 3.

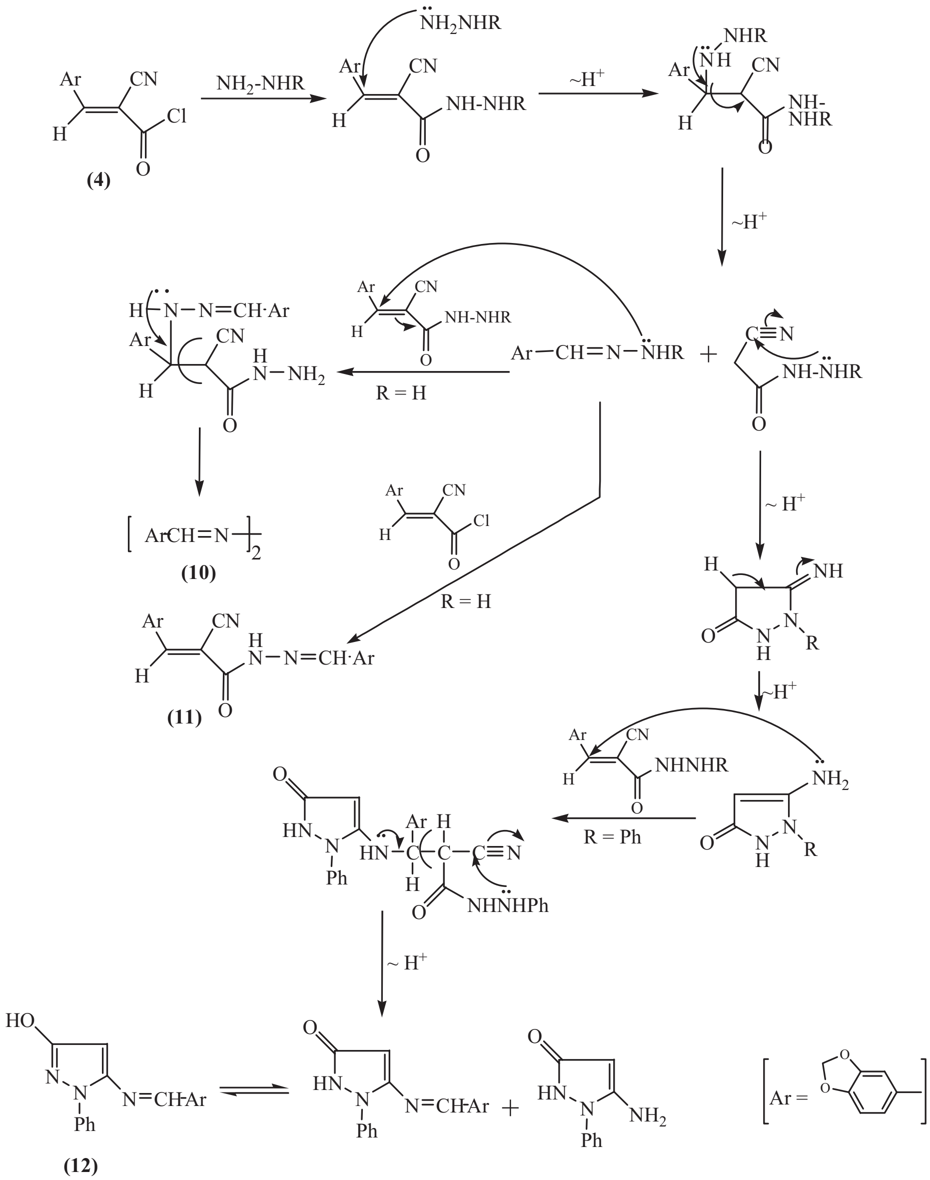
Treatment of **4** with 2-aminopyridine afforded a mixture of *N*-(pyridine-2-yl)acrylamide **17** and pyrido[1,2-*a*]pyrimidine derivative **18** (Scheme 1).

Formation of **17** and **18** can be explained by the mechanism shown in Scheme 4.

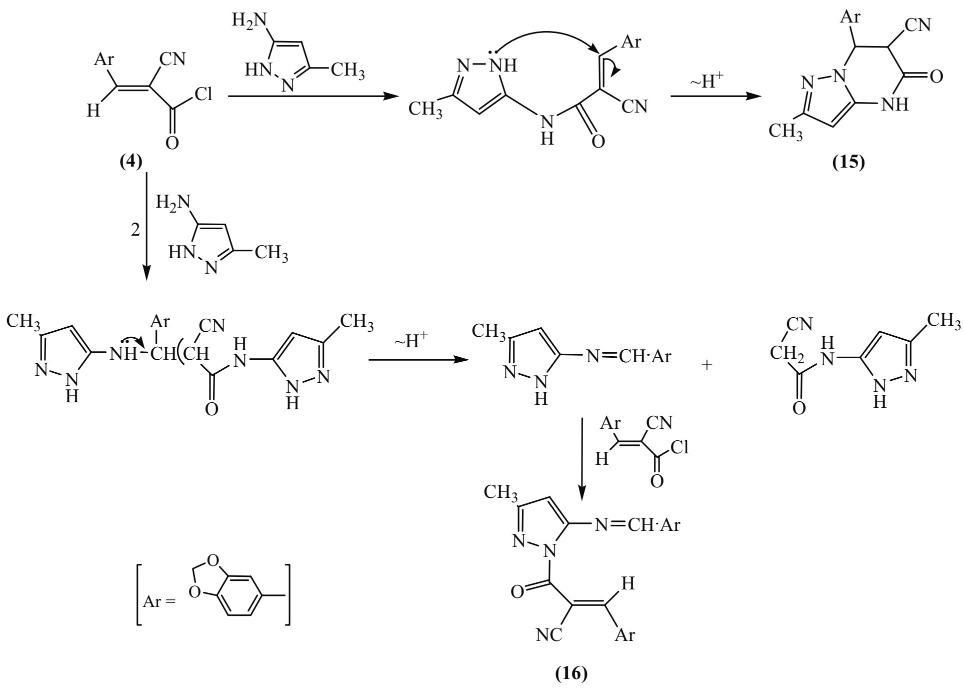
Condensation of acid chloride **4** with 1,4-binucleophilic reagents, namely, 2-aminoethanol, 2-aminophenol, anthranilic acid and *o*-phenylendiamine is shown in Scheme 5.

With 2-aminoethanol, acid chloride **4** yielded the corresponding amide-ester **19** (Scheme 5).

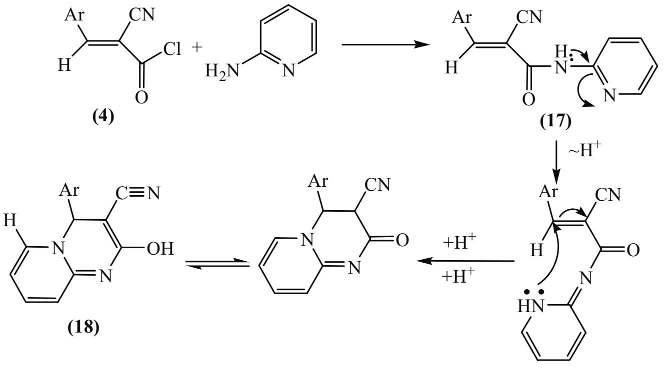
Reaction of **4** with 2-aminophenol gave the acrylamide **20**, which dehydrated in presence of $POCl_3$ to give the benzoxazole derivative **21** in good yield (Scheme 5). This compound was previously prepared by condensation of 2-cyanomethylbenzoxazole with piperonal in Et_3N at room temperature.[10]



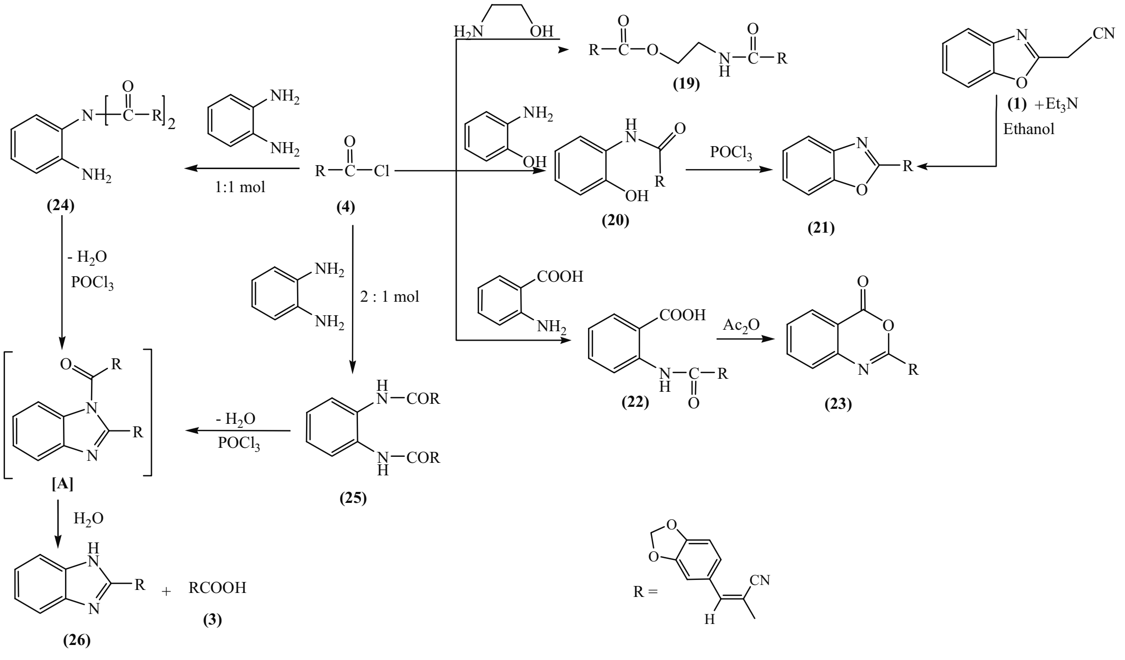
Scheme 2



Scheme 3



Scheme 4



Scheme 5

With anthranilic acid, acid chloride **4** afforded the *N*-acylanthranilic acid **22**, which cyclised in the presence of acetic anhydride to give the benzoxazinone derivative **23** (Scheme 5).

Treatment of acid chloride **4** with *o*-phenylendiamine at 1 : 1 mole and, at 2 : 1 mole afforded the *N,N*-bis[prop-2-enoyl]-*o*-phenylendiamine derivative **24** and/or *N,N′*-bis[prop-2-enoyl]-*o*-phenylendiamine derivative **25**. Dehydration of both **24** and **25** with $POCl_3$ yielded the corresponding benzimidazole derivative **26** and the acid **3** via the hydrolysis of the intermediate [A] (Scheme 5).

Fragmentation pattern of (*E*)-ethyl 3-(benzo[*d*][1,3]dioxol-5-yl)-2-cyanoacrylate shown in Scheme 6.

Experimental

Melting points reported are uncorrected. IR spectra were recorded on Pye Unicam SP 1200 spectrophotometer using the KBr wafer technique. ^1H NMR spectra were determined on a Varian FT-200, and a Bruker AC-200 MHz using TMS as internal standard. All chemical shifts (δ) are expressed in ppm. All the NH or OH protons are disappeared on addition of D_2O. The mass spectra were determined using MP model MS-5988 and Shimadzu single focusing mass spectrophotometer (70 eV). Elemental analysis were investigated by Elementar analyser Vario EL III. Physical data are reported in Table 1, spectral data in Tables 2 and 3.

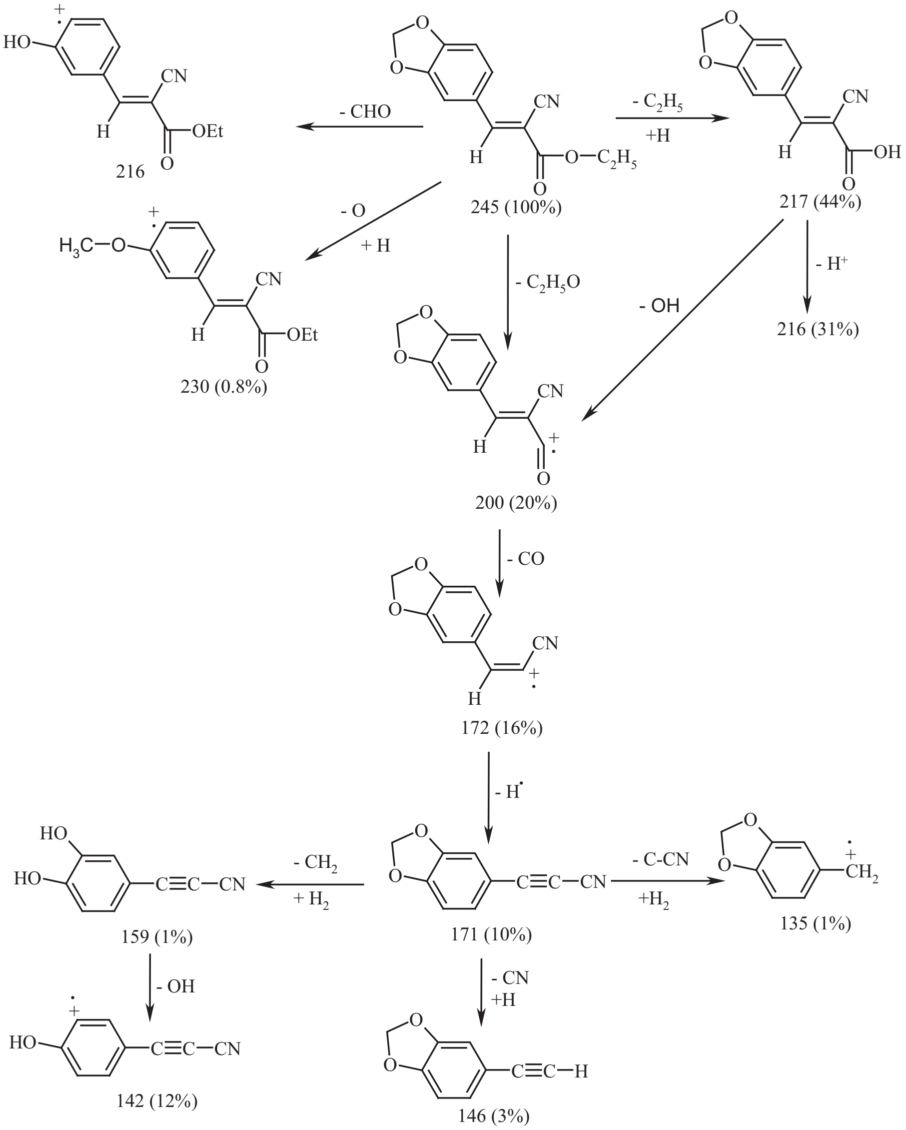
(E)-Ethyl 3-(benzo[d][1,3]dioxol-5-yl)-2-cyanoacrylate[20] (**2**): A mixture of piperonal **1** (15 g, 0.1 mol), ethyl cyanoacetate (11.3 g, 0.10 mol) and drops of piperidine in ethanol (100 ml) was refluxed for 1 h. The solid formed after cooling was filtered, dried and crystallised to give **2**.

(E)-3-(Benzo[d][1,3]dioxol-5-yl)-2-cyanoacrylic acid[21] (**3**): To a solution of **2** (12.50 g, 0.05 mol) in ethanol (50 ml), sodium hydroxide in ethanol (1.15 g, 0.05 mol, 10 ml) was added. The reaction mixture was stirred at room temperature for 1 h then poured on crushed ice (50 g) and acidified with cold dilute hydrochloric acid. The solid separated was filtered, washed with water, dried and crystallised to give **3**.

(E)-3-(Benzo[d][1,3]dioxol-5-yl)-2-cyanoacryloyl chloride (**4**): A mixture of **3** (10 g) and thionyl chloride (15 ml) was heated on water bath for 3 h. The excess $SOCl_2$ was distilled under reduced pressure, the solid separated was collected, triturated with petroleum ether 40–60 °C, dried and crystallised to give **4**.

(E)-3-Chlorophenyl 3-(benzo[d][1,3]dioxol-5-yl)-2-cyanoacrylate (**5**): A mixture of **4** (1.18 g, 0.005 mol), triethylamine (0.505 g, 0.005 mol), *m*-chlorophenol (0.64 g, 0.005 mol) in dry benzene (50 ml), was stirred at room temperature for 2 h. The solid separated was filtered, washed with water (80 ml) to remove the Et_3NHCl salt, dried and crystallised to give **5**.

(E)-S-p-Tolyl 3-(benzo[d][1,3]dioxol-5-yl)-2-cyanoprop-2-enethioate (**6**): A mixture of **4** (1.18 g, 0.005 mol), triethylamine (0.505 g, 0.005 mol) and 4-mercaptotoluene (0.62 g, 0.005 mol) in dry benzene (50 ml) was stirred at room temperature for 2 h. The solid separated was filtered; the filtrate was concentrated till dryness. The residue was crystallised to give **6**.



Scheme 6

Table 1 Physical data of synthesised compounds

Compd. no.	M.p/°C	Yield/%	Colour (solvent)	Molecular formula (M wt)	Analysis calculated/found		
					C%	H%	N%
2	94–96[a]	90	Yellow	$C_{13}H_{11}NO_4$	63.67	4.52	5.71
			(ethanol)	(245.23)	63.56	4.42	5.53
3	224–226[b]	98	Yellow	$C_{11}H_7NO_4$	60.83	3.25	6.45
			(ethanol)	(217.17)	60.98	3.41	6.29
4	109–110	93	Yellow	$C_{11}H_6NClO_3$	56.07	2.57	5.94
			(toluene)	(235..62)	56.12	2.44	6.01
5	124–126	85	Yellow	$C_{17}H_{10}NClO_4$	62.30	3.08	4.27
			(toluene)	(327.72)	62.15	3.21	4.06
6	169–170	94	Yellow	$C_{18}H_{13}NO_3S$	66.85	4.05	4.33
			(toluene)	(323.35)	67.00	4.09	4.52
7	188–190	82	Green	$C_{18}H_{14}N_2O_4$	67.07	4.38	8.69
			(toluene)	(322.31)	66.82	4.36	8.33
10	208–210	79	Yellow	$C_{16}H_{12}N_2O_4$	64.86	4.08	9.45
			(toluene)	(296.28)	65.01	4.23	9.67
11	228–230	62	Yellow	$C_{19}H_{13}N_3O_5$	62.81	3.60	11.56
			(toluene)	(363.31)	62.65	3.75	11.41
12	165–170	92	Green	$C_{17}H_{13}N_3O_3$	66.44	4.26	13.67
			(benzene)	(307.29)	66.28	4.41	13.52
13	178–180	78	Yellow	$C_{18}H_{13}N_3O_4$	64.47	3.91	12.53
			(toluene)	(335.30)	64.19	4.17	12.44
14	230–232	45	Yellow	$C_{18}H_{11}N_3O_3$	68.13	3.49	13.24
			(toluene)	(317.29)	67.97	3.33	13.09
16	150–154	34	colourless	$C_{15}H_{12}N_4O_3$	60.80	4.08	18.91
			(pet.80–100–Toluene)	(296.28)	60.95	3.92	18.75
17	170–172	23	Yellow	$C_{23}H_{16}N_4O_5$	64.48	3.76	13.08
			(toluene)	(428.39)	64.63	3.92	12.93
18	158–160	43	colourless	$C_{16}H_{11}N_3O_3$	65.53	3.78	14.33
			(pet.80–100–Toluene)	(293.27)	65.54	3.77	14.34
19	180–182	32	White	$C_{16}H_{11}N_3O_3$	65.53	3.78	14.33
			(toluene)	(293.27)	65.52	3.63	14.32
20	188–190	80	Green	$C_{24}H_{17}N_3O_7$	62.74	3.73	9.15
			(toluene)	(459.40)	63.00	3.62	9.03
21	209–210[c]	72	Yellow	$C_{17}H_{12}N_2O_4$	66.23	3.92	9.09
			(toluene)	(308.29)	66.01	4.02	9.25
22	208–210	92	Yellow	$C_{18}H_{12}N_2O_5$	64.28	3.60	8.33
			(toluene)	(336.30)	64.30	3.51	8.55
23	260–262	86	Yellow	$C_{18}H_{10}N_2O_4$	67.92	3.17	8.80
			(toluene + EtOH)	(318.28)	68.08	3.02	8.64
24	159–160	87	Yellow	$C_{28}H_{18}N_4O_6$	66.40	3.58	11.06
			(toluene + pet. 80–100)	(506.45)	66.49	3.32	11.01
25	259–260	75	Yellow	$C_{28}H_{18}N_4O_6$	66.40	3.58	11.06
			(toluene)	(506.45)	66.67	3.82	10.90
26	262–264	62	Yellow	$C_{17}H_{11}N_3O_2$	70.58	3.83	14.52
		(toluene)	(289.28)	70.73	3.98	14.67	

[a]Lit.[20] m.p 110 °C, [b]Lit.[21] m.p 223–224 °C, [c]Lit.[10] m.p 238–240 °C

(E)-3-(Benzo[d][1,3]dioxol-5-yl)-2-cyano-N-(4-methoxy-phenyl) acrylamide (**7**): A mixture of **4** (1.18 g, 0.005 mol), triethylamine (0.505 g, 0.005 mol), p-anisidine (0.56 g, 0.005 mol) in dry benzene (50 ml) was stirred at room temperature for 2 h. The solid separated was filtered, washed with water (80 ml), dried and crystallised to give **7**.

(E)-1,2-Bis(benzo[d][1,3]dioxal-5-ylmethylene)hydrazine 10 and (2E,N'E)-3-(benzo[d] [1,3]dioxol-5-yl)-N'-(benzo[d][1,3]dioxol-5-ylmethylene)-2-cyanoacrylohydrazide (**11**):

Procedure 1: A mixture of **4** (1.18 g, 0.005 mol), triethylamine (0.505 g, 0.005 mol), hydrazine hydrate (0.22 ml, 0.005 mol) in dry benzene (50 ml) was stirred for 1 h. The solid separated was filtered, washed with water (60 ml), dried and crystallised to give azine **10** as sole product.

Procedure 2: To a solution of **4** (1.18 g, 0.005 mol) in dry toluene (20 ml) in presence of triethylamine (0.505 g, 0.005 mol), hydrazine hydrate (0.24 ml, 0.005 mol) in dry toluene (20 ml) was added dropwise at 0 °C and the reaction mixture was stirred for 1 h. The solid separated was filtered, washed with water (80 ml) and dried. Fraction crystallisation in boiling petroleum–ether 80–100 °C isolates **10** as yellow crystals and the insoluble solid was crystallised from toluene to give **11**.

(E)-5-(Benzo[d][1,3]dioxol-5-ylmethyleneamino)-1-phenyl-1H-pyrazol-3-ol (**12**): A mixture of **4** (1.18 g, 0.005 mol), triethylamine (0.505 g, 0.005 mol), phenyl hydrazine (0.4 g, 0.005 mol) in dry benzene (50 ml) was stirred for 2 h. The solid separated was filtered, washed with water (80 ml) dried and crystallised to give **12**.

(E)-N'-(3-(Benzo[d][1,3]dioxol-5-yl)-2-cyanoacryloyl)benzohydrazide (**13**): A mixture of **4** (1.18 g, 0.005 mol), triethylamine (0.505 g, 0.005 mol), benzoyl hydrazine (0.68 g, 0.005 mol) in dry benzene (50 ml) was stirred for 1 h. The solid separated was filtered, washed with water (80 ml), dried and crystallised to give **13**.

(E)-3-(Benzo[d][1,3]dioxol-5-yl)-2-(5-phenyl-1,3,4-oxadiazol-2-yl) acrylonitrile (**14**): A mixture of **13** (1 g) and phosphorus oxychloride (10 ml) was heated on water bath for 6 h. After cooling the reaction mixture was poured on crushed ice (20 g). The solid separated was filtered, washed with water (50 ml), dried and crystallised to give **14**.

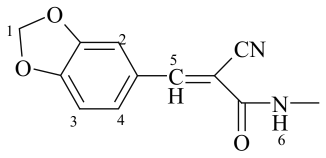
7-(Benzo[d][1,3]dioxol-5-yl)-2-methyl-5-oxo-4,5,6,7-tetrahydropyrazolo [1,5-a]pyrimidine-6-carbonitrile 15 and (E)-3-(benzo [d][1,3]dioxol-5-yl)-2-(5-((E)-benzo[d][1,3] dioxol-5-ylmethyleneamino)-3-methyl-1H-pyrazole-1-carbonyl)acrylonitrile (**16**): A mixture of **4** (1.18 g, 0.005 mol), triethylamine (0.505 g, 0.005 mol) and 3-amino-5-methylpyrazole (0.48 gm, 0.005) in dioxan (50 ml) was refluxed for 2 h. The solid separated was filtered. Filtrate was concentrated till dryness. Fraction crystallisation of the residue in boiling petroleum ether (80–100 °C) gave **15** followed by toluene to give **16**.

(E)-3-(Benzo[d][1,3]dioxol-5-yl)-2-cyano-N-(pyridin-2-yl) acrylamide 17 and 4-(benzo[d][1,3]dioxol-5-yl)-2-hydroxy-4H-pyrido [1,2-a]pyrimidine-3-carbonitrile (**18**): A mixture of **4** (1.18 g, 0.005 mol), triethylamine (0.505 g, 0.005 mol) and 2-aminopyridine (0.47 g, 0.005 mol) in dry benzene (50 ml) was stirred for 2 h. The solid separated was filtered, washed with water (80 ml) and dried.

Table 2 IR and mass spectra data of prepared compounds

Compd no.	IR ν cm^{-1}			MS (*m/z*) (abundance,%)
	NH, OH	C≡N	C=O	
2	–	2218	1724	245 ($[M^{+\cdot}]$, 100), 217 ($[M – C_2H_4]$, 44), 200 ($[M – OC_2H_5]^{+\cdot}$, 20), 172(16), 171(10), 145(4), 114(25).
3	3400 br-2600	2223	1680	217 ($[M]^{+\cdot}$,100), 216 (79), 200 (4), 172 (33), 146 (5), 116 (10), 114 (39).
4	–	2219	1742	237 ([M + 2], 14), 235 ($[M^{+\cdot}]$, 35), 200 ([M - Cl], 74), 172 ([M – COCl], 11), 170 ($[M – CH_2O\text{-}Cl]$, 100), 146 (2), 114 (34), 64 (17).
5	–	2221	1739	329 ([M + 2], 6), 327 ([M], 18), 200 (96), 199 (100), 172 (5), 170 (66), 146 (0.3), 142 (20), 114 (33).
6	–	2215	1670	323 ($M^{+\cdot}$, 12), 201 (15), 200 (100), 172 (8), 170 (82), 114 (70).
7	3353	2202	1668	322 ($M^{+\cdot}$, 95), 321 ([M – 1], 20), 200 (94), 172 (7), 170 (100), 142 (34), 114 (66).
10	–	–	–	296 ($[M]^{+\cdot}$, 100), 269 (78), 175 (53), 174 (10), 152 (25), 148 (33).
11	3312	2202	1684	363 $[(M]^{+\cdot}$, 22), 362 ($[M – H]^{+\cdot}$, 6), 296 (13), 217(6), 216 (22), 215 (100), 200 (18)
12	3389 br	–	–	307 ($[M]^{+\cdot}$, 100), 306 ($[M]^{+\cdot}$, 32), 291 (6), 200 (9), 188 (19), 186 (42), 174 (52).
13	3342 3167	2207	1688	335 $[(M]^{+\cdot}$, 6), 214 ($[M – (121)]^{+\cdot}$, 15), 200 (13), 172 (2.2), 170 (15), 105 (100).
14	–	2226	–	317 (28), 316 (100), 187 (5), 170 (3), 142 (9), 114 (20)
15	3297	2216	1679	296 ($[M]^{+\cdot}$, 35), 217 (65), 216 (100), 200 (25), 172 (32), 170 (65), 142 (56), 115 (14).
16	–	2223	1670	428 ($[M]^{+\cdot}$, 12), 305 (6), 290 (7), 241 (16), 228 (3), 200 (9), 172 (1), 146 (11), 116 (3), 91 (100).
17	3196	2192	1670	293 ($[M]^{+\cdot}$, 4), 292 ($[M\text{-}1]^{+\cdot}$, 8), 291 (13), 262 (18), 200 (2), 172 (4), 141 (2), 78 (100).
18	3272	2212	1672	293 ($[M]^{+\cdot}$, 4), 290 ($[M\text{-}2]^{+\cdot}$, 9), 264 (4), 224 (12), 207(1).
19	3440	2205	1718 1676	459 ($[M]^{+\cdot}$, 56), 260(4), 254(8), 244(14), 243(22), 241(100), 216(28), 215(16), 200(34), 172(27), 146(9).
20	3386	2206	1674	308 ($[M]^{+\cdot}$, 51), 307 ($[M\text{-}1]^{+\cdot}$, 9), 200(100), 172(9), 146(2)
21	–	2223	–	290 ($[M]^{+\cdot}$, 35), 289 ($[M – 1]^{+\cdot}$, 32), 288 ([M – 2], 11), 216 (14), 200 (100), 114(70), 108(10).
22	3320–2260 br	2210	1682	336 ($M^{+\cdot}$, 70), 335 ($[M^{+\cdot} – 1]$, 5), 319)$[M – OH]^{+\cdot}$, 10), 291 ($[M – CO]^{+\cdot}$, 7), 200 (88), 170 (100).
23	–	2224	1753	318 (M, 100), 317 (45), 292 ($[M^{+\cdot} – CN]$,7), 274 ($[M^{+\cdot} – CO_2]$, 3), 172(2), 146(68), 102(4).
24	3382 3276	2224 2204	1668	307 ($[M – C_{11}H_6NO_3]$, 63), 306 (9), 290 (11), 288 (12), 107 (100).
25	3275	2224 2204	1664	506 ([M], 21), 307 (9), 306 (18), 290 ($M^{+\cdot}$ – NH, 10), 288 (43), 200 (56), 114 (100).
26	3470	2222	–	289 ($[M^{+\cdot}]$, 100), 263 ([M – CN)], 8), 230 (17), 203(5), 116(17)

Table 3 ^{1}H NMR of prepared compounds



Compd no.	C_1–H (s)	C_2–H (s)	C_3–H (d), *J*	C_4–H (d), *J*	C_5–H (s)	NH(s)	Others protons
2	6.19	7.68	7.13, 27	7.65, 28	8.26	–	1.30 (t, 3H, J = 24, 23), 4.30 (q, 2H, J = 23, 23)
4	6.17	7.66	7.12, 28	7.59, 27	8.210	–	–
5	6.23	7.79	7.18, 29	7.63, 29	8.54	–	Ar-H: 7.38 (t, 1H, J = 24, 24), 7.47 (d, 1H, J = 22), 7.49 (d, 1H, J = 28), 7.76 (s, 1H)
6	6.22	7.74	7.16, 29	7.71, 28	8.29	–	2.37 (s, 3H, CH_3), Ar-H: 7.32 (d, 2H, J = 27), 7.40 (d, 2H, J = 26)
7	6.18	7.64	7.14, 27	7.51, 27	8.14	10.12	2.32 (s, 3H, OCH_3), AR-H: 7.55 (d, 2H, J = 31), 6.92 (d, 2H, J = 31)
10	6.09	7.38	7.00, 26	7.33, 27	8.56	–	–
11	6.09, 6.18	7.67, 7.64	7.12, 7.16	7.60, 7.54	8.14, 8.34	11.69	–
13	6.17	7.89	7.12, 26	7.87, 25	8.14	10.49	7.46-7.60 (m, 5H, Ar-H)
17	6.15	7.63	7.09, 28	7.55, 28	8.14	7.48	6.52 (t, 2H, 3`,4`-H, J = 26,26), 7.45 (d, 1H, J = 27), 7.85 (d, 1H, J = 26)
18	6.03	7.65	7.14,26	7.58, 26	–	–	5.46 (s, 1H, C_4-H), 6.81-7.00 (m, 3H, pyridyl), 8.55 (d, 1H, C6-H, J = 25), 9.62 (s, 1H, OH)
19	6.17	7.67	7.14, 28	7.63, 28	8.29	8.54	3.57 (t, 2H, J = 17, 17, CH_2-N), 4.36 (t, 2H, J = 18, 18, CH_2-O)
20	6.16	7.62	7.11, 27	7.55, 25	8.23	9.12	Ar-H: 6.79 (d, 1H, J = 26), 6.89 (t, 1H, J = 24, 26), 6.98 (t, 1H, J = 23, 25), 7.87 (d, 1H, J = 26), 10.10 (s, 1H, OH)
22	6.20	7.70	7.15, 27	7.62	8.33	–	Ar-H: 7.24 (t, 1H, J = 26, 27), 7.65 (t, 1H), 8.05 (d, 1H, J = 26), 8.62 (d, 1H, J = 28), 12.20 (s, 1H, COOH)
24	6.19	7.66	7.13, 27	7.53 × 2, 27	8.24	–	Ar-H: 6.80 (d, 1H, J = 21), 7.01 (t, 1H, J = 25, 26), 7.14 (d, 1H, J = 21), 7.30 (dd, 1H, J = 12, 12), 9.59 (1H, NH), 9.80 (1H, NH)
25	6.19	7.70	7.14, 28	7.64, 27	8.27	9.82	Ar-H: 7.31 (d, 2H, J = 28), 7.54 (d, 2H, J = 27)
26	6.14	7.59	7.13, 27	7.48, 27	8.17	–	3.8 (s, 1H, NH), 7.68 (d, 2H, Ar, J = 27), 7.28 (d, 2H, Ar, J = 20)

Table 4 Antimicrobial and antifungal activities of synthesised compounds

Sample control	*Escherichia coli* (G^+)	*Staphylococcus aureus* (G^-)	*Aspergillus flavus*	*Candida albicans*
(DMSO)	0.0	0.0	0.0	0.0
T[a]	32	34	0.0	0.0
A[b]	0.0	0.0	17	18
4	19	18	0.0	13
7	13	14	0.0	14
11	13	0.0	0.0	0.0
12	21	18	0.0	14
13	0.0	0.0	15	0.0
17	12	12	0.0	0.0
21	12	13	0.0	0.0
25	13	0.0	0.0	0.0
26	12	13	0.0	0.0

[a] Tetracycline; standard antibacterial agent.
[b] Amphotsicine-B; standard antifungal agent.

Fraction crystallisation in boiling petroleum–ether 80–100 °C gave **17** followed by petroleum–ether 80–100 °C-toluene mixture to give **18**.

(E)-3-(Benzo[d][1,3]dioxol-5-yl)-3-cyanoacrylamido)ethyl (E)-3-(benzo[d][1,3]dioxol-5-yl)-2-cyanoacrylate (**19**): A mixture of **4** (1.18 g, 0.005 mol), triethylamine (0.505 g, 0.005 mol), ethanol amine (0.305 g, 0.005 mol) in dry benzene (50 ml) was stirred for 2 h. The solid separated was filtered, washed with water (50 ml), dried and crystallised to give **19**.

(E)-3-(Benzo[d][1,3]dioxol-5-yl)-2-cyano-N-(2-hydroxy-phenyl) acrylamide (**20**): A mixture of **4** (1.18 g, 0.005 mol), triethylamine (0.505 g, 0.005 mol), 2-amino phenol (0.54 g, 0.005 mol) in dry benzene (50 ml) was stirred for 1 h. The solid separated was filtered, washed with water (80 ml), dried and crystallised to give **20**.

(E)-3-(Benzo[d][1,3]dioxol-5-yl)-2-(benzo[d]oxazol-2-yl)acrylonitrile (**21**): A mixture of **20** (1 g) and $POCl_3$ (10 ml) was heated on water bath for 3 h. After cooling, the crushed ice (10 g) was added to the reaction mixture and left overnight. The solid separated was filtered, washed with water, dried and crystallised to give **21**.

(E)-2-(3-(Benzo[d][1,3]dioxol-5-yl)-2-cyanoacrylamido)benzoic acid (**22**): A mixture of **4** (2.35 g, 0.01 mol), triethylamine (1.01 g, 0.01 mol), anthranilic acid (1.37 g, 0.01 mol) in dry benzene (100 ml) was stirred for 1 h. The solid separated was filtered, washed with water (100 ml), dried and crystallised to give **22**.

(E)-3-(Benzo[d][1,3]dioxol-5-yl)-2-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)acrylonitrile (**23**): A mixture of **22** (2 g) and freshly distilled acetic anhydride (5 ml) was heated on a water bath for 6 h. After cooling the solid separated was collected, washed with dry petroleum ether (40–60 °C), dried and crystallised to give **23**.

(E)-N-(2-Aminophenyl)-3-(benzo[d][1,3]dioxol-5-yl)-N-[(E)-3-(benzo[d][1,3]dioxol-5-yl)-2-cyanoacryloyl]-2-cyanoacrylamide (**24**): A mixture of **4** (1.18 g, 0.005 mol), triethylamine (0.505 g, 0.005 mol), *o*-phenylenediamine (0.54 g, 0.005 mol) in dry benzene (50 ml) was stirred for 2 h. The solid separated was filtered, washed with water (80 ml), dried and crystallised to give **24**.

(2E,2'E)-N,N'-(1,2-phenylene)bis(3-(benzo[d][1,3]dioxol-5-yl)-2-cyanoacrylamide (**25**): A mixture of **4** (2.35 g, 0.01 mol), triethylamine (1.01 g, 0.01 mol), o-phenylenediamine (0.54 g, 0.005 mol) in dry benzene (50 ml) was stirred for 2 h. The solid separated was filtered, washed with water (80 ml), dried and crystallised to give **25**.

(E)-3-(Benzo[d][1,3]dioxol-5-yl)-2-(1H-benzo[d]imidazol-2-yl)acrylonitrile (**26**): A mixture of **24** and/or **25** (1 g) and $POCl_3$ (10 ml) was heated on water bath for 3 h. After cooling, the crushed ice (20 g) was added to the reaction mixture and left overnight. The solid separated was filtered, washed with water (40 ml), dried and crystallised to give **26**.

Measurement of antimicrobial and antifungal activities using diffusion disc

The antimicrobial activity was measured in Microanalytical centre, Cairo University, Giza, Egypt.

A filter paper sterilised disc saturated with measured quantity of the sample with concentration of 20 mg ml is placed on plate containing solid bacterial medium (nutrient agar broth) or fungal medium (Dox's medium) which had been heavily seeded with the spore suspension of the tested organism. After inoculation, the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism.[26-29]

The selected samples were screened against Gram-positive; *Staphylococcus aureus* and Gram-negative *Escherichia coli*. Antifungal activity was tested against *Aspergillus flavus* and *Candida albicans*. The recorded resultes were compared with *Tetracycline* and *Amphotsicine-B*, respectively as standard antibacterial and antifungal agents. The results were shown in Table 4.

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