Synthesis of some Alkyl/Chloro/Methoxy-substituted-4-(substituted-phenoxymethyl)-2*H*-1-benzopyran-2-ones as Potential Antifungal Agents

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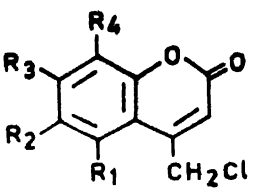
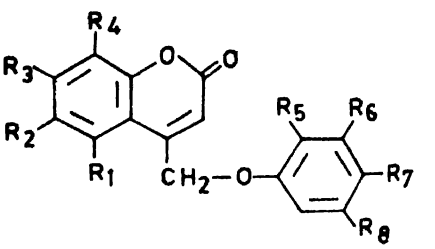
In continuation of our earlier work on alkyl substituted-2*H*-1-benzopyran-2-ones as potential antifungal agents[1,2], it was thought of interest to synthesise 6-chloro-5,7-dimethyl-/8-methoxy-/8-methoxy-6-(2-propenyl)-4-(substituted-phenoxymethyl)-2*H*-1-benzopyran-2-ones (**4**−**18**) and evaluate their antifungal activity against plant pathogenic fungi, the results of which are reported in this communication.



(**1**–**3**)



(**4**–**18**)

1 ; $R_1=R_3=CH_3$, $R_4=H$, $R_2=Cl$
2 ; $R_4=OCH_3$, $R_1=R_2=R_3=H$
3 ; $R_1=R_3=H$, $R_2=-CH_2-CH=CH_2$, $R_4=OCH_3$
$R_1=R_3=CH_3$, $R_4=H$, $R_2=Cl$
4 ; $R_5=H$, $R_6=H$, $R_7=Cl$, $R_8=H$
5 ; $R_5=H$, $R_6=Cl$, $R_7=Cl$, $R_8=H$
6 ; $R_5=Cl$, $R_6=H$, $R_7=Cl$, $R_8=Cl$
7 ; $R_5=H$, $R_6=H$, $R_7=NO_2$, $R_8=H$
8 ; $R_5=H$, $R_6=H$, $R_7=(CH_3)_3$, $R_8=H$
$R_4=OCH_3$, $R_1=R_2=R_3=H$
9 ; $R_5=H$, $R_6=H$, $R_7=Cl$, $R_8=H$
10 ; $R_5=H$, $R_6=Cl$, $R_7=Cl$, $R_8=H$
11 ; $R_5=Cl$, $R_6=H$, $R_7=Cl$, $R_8=Cl$
12 ; $R_5=H$, $R_6=H$, $R_7=NO_2$, $R_8=H$
13 ; $R_5=H$, $R_6=H$, $R_7=CH_3$, $R_8=H$
$R_1=R_3=H$, $R_2=-CH_2\ CH=CH_2$, $R_4=OCH_3$
14 ; $R_5=H$, $R_6=H$, $R_7=Cl$, $R_8=H$
15 ; $R_5=H$, $R_6=Cl$, $R_7=Cl$, $R_8=H$
16 ; $R_5=Cl$, $R_6=H$, $R_7=Cl$, $R_8=Cl$
17 ; $R_5=H$, $R_6=H$, $R_7=NO_2$, $R_8=H$
18 ; $R_5=H$, $R_6=H$, $R_7=C(CH_3)_3$, $R_8=H$

Results and Discussion

The condensation of 4-chloro-3,5-dimethyl-, 2-methxoy-, and 4-(2-propenyl)-2-methoxyphenols with ethyl 4-chloroacetoacetate in presence of 73% sulphuric acid at ambient temperature yielded 6-chloro-4-chloromethyl-5,7-dimethyl-, 4-chloromethyl-8-methoxy- and 6-(2-propenyl)-4-chloromethyl-8-methoxy-2*H*-1-benzopyran-2-ones (**1**−**3**), respectively. These compounds on treatment with various substituted phenols such of 4-chlorophenol, 3,4-dichlorophenol, 2,4,5-trichlorophenol, 4-nitrophenol, 4-*t*-butylphenol/4-methylphenol afforded the corresponding 6-chloro-5,7-dimethyl/8-methoxy/8-methoxy-6-(2-propenyl-4-(substituted-phenoxymethyl)-2*H*-1-benzopyran-2-ones (**4**−**18**).

In the pmr spectrum of **1** the diagnostic C_3-H and C_4-CH_2Cl protons appeared as singlets integrating for one and two protons at δ 6.40 and 4.50 respectively. The methyl protons at positions 5 and 7 could also be picked up as singlets at δ 2.30 and 2.35 respectively. Compound **3** showed singlets at δ 6.63, 7.38 and 7.27 each integrating for one proton at positions 3, 5 and 7 respectively, while other singlets at δ 4.68 and 3.85 integrating for two and three protons were assigned to C_4-CH_2Cl and OCH_3 functionalities respectively. The appearance of side-chain benzylic protons as doublet (J 7.0 Hz) at δ 3.21 and the olefinic protons as multiplets

centred at δ 5.55 (CH_2=CH) and 4.90 (CH_2=CH) were in agreement with the assigned structure. Similarly, **4** showed a triplet at δ 6.59 and a doublet at 5.20 each (*J* 2.0 Hz), a diagnostic pattern for allylic coupling for protons at C_3-H and C_4-CH_2O. The *ortho*-coupled doublet centred at δ 6.90 (*J* 9.0 Hz) was assigned to aromatic protons, *ortho* to CH_2-O functionality of phenoxy moiety while the singlet integrating for six protons at δ 2.40 stood for both the aromatic methyl groups merged together and the remaining aromatic protons at δ 7.0−7.50 as multiplet supported the assigned structure. Thus, the pmr spectra of all the compounds were in accordance with the proposed structure and the 2-pyrone structure of all the compounds followed from the mode of synthesis and was further supported by the appearance of bands around 1 710 cm^{-1} in their ir spectra[3].

Fungitoxicity : The plant pathogenic fungi and the test method used were the same as described earlier[1]. The tested compounds were found to exhibit differential activity against *Colletotrichum falcatum*, *Macrophomina phaseolina* and *Phythium aphanidermatum* fungi. Structure-activity relationship studies showed that compound **7** with most electronegative nitro group at *para*-position in phenoxymethyl moiety was found to be the most toxic against *C. falcatum* and *P. aphanidermatum* with EC_{50} values at 13 and 7 μg ml^{-1} concentrations, respectively. However, compound **8** with *t*-butyl substituent at the same *para*-position showed specificity towards *P. aphanidermatum* with EC_{50} at 32 μg ml^{-1} concentration. With the introduction of methoxy functionality at position-8 instead of alkyl group(s) in 2*H*-1-benzopyran-2-ones, the above observed pattern of toxicity for SAR studies was not maintained and it considerably decreased toxicity against *C. falcatum*. The compounds **11** and **16** were most active against *P. aphanidermatum* and *M. phaseolina* respectively at minimum tested inhibition concentrations of 1 μg ml^{-1}, which deserve further investigations for their possible use in plant disease control.

Experimental

Melting points were determined in a Ganson electrical apparatus and are uncorrected. Homogeniety of the compounds was checked by tlc on silica gel G using benzene or methanol-benzene as the mobile phase. Ir spectra (KBr) were recorded on a Perkin-Elmer 137 spectrophotometer and pmr spectra ($CDCl_3$) on a Varian A60D or R-32 (90 MHz) spectrometer using TMS as internal reference.

*6-Chloro-4-chloromethyl-5,7-dimethyl-2*H*-1-benzopyran-2-one* (**1**) *:* A mixture of 4-chloro-3,5-dimethylphenol (3.12 g, 20 mmol) and ethyl 4-chloroacetoacetate (3.20 g, 20 mmol) was added to sulphuric acid (30 ml ; 73%) with constant stirring and the mixture was left overnight at room temperature. It was then poured over crushed ice and the resulting solid was washed with water, dried and crystallised from benzene-petroleum ether (4.40 g, 84%), m.p. 105−06° (Found ; C, 56.38 ; H, 3.65. $C_{12}H_{10}Cl_2O_2$ requires : C, 56.03 ; H, 3.89%) ; ν_{max} (nujol) 1 715 (C=O) and 780 cm^{-1} (C−Cl) ; δ ($CDCl_3$) 2.30 and 2.35 (2×3H, each s, C_5-CH_3 and C_7-CH_3), 4.50 (2H, s, CH_2Cl), 6.40 (1H, s, C_3-H) and 7.30 (1H, s, C_8-H). In a similar manner, compounds **2** (86%, m.p. 260°d) and **3** (63%, 72−73°) were prepared.

*6-Chloro-4-[(4-chlorophenoxy)methyl]-5,7-dimethyl-2*H*-1-benzopyran-2-one* (**4**) *:* A mixture of **1** (1.26 g, 5 mmol), 4-chlorophenol (0.64 g, 5 mmol), potassium carbonate (2.5 g) and dry acetone (30 ml) was refluxed for 16 h on a steam-bath. The mixture was then evaporated under reduced pressure and the residue triturated with cold water. The resulting solid was dried and crystallised from benzene-petroleum ether (1.07 g, 62%), m.p. 94−95° (Found : C, 61.56 ; H, 4.43. $C_{18}H_{14}Cl_2O_3$ requires : C, 61.89 ; H, 4.01%) ; ν_{max} (nujol) 1 700 (C=O) and 770 cm^{-1} (C−Cl) ; δ ($CDCl_3$) 2.40 (6H, s, 2×CH_3), 5.20 (2H, d, *J* 2.0 Hz, CH_2-O), 6.59 (1H, t, *J* 2.0 Hz, C_3-H), 6.90 (2H, d, *J* 9.0 Hz, C_2'-H and C_6'-H) and 7.0−7.50 (3H, m, ArH). Other compounds were prepared similarly from **1**−**3** respectively : **5** (56%), m.p. 180−82° ; **6** (60%), 224° ; **7** (51%), 107−08° ; **8** (48%), 75−76° ; **9** (36%), 113−14° ; **10** (38%), 123−25° ; **11** (33%), 107−09° ; **12** (43%), 135−36° ; **13** (32%), 115−16° ; **14** (49%), 237° ; **15** (43%), 120−21° ; **16** (51%), 126−27° ; **17** (42%), 95° ; **18** (38%), 106−07°.

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