Synthesis, Characterisation and Biological Activity Studies of Substituted 6H-12H-benzopyrano [4, 3-b] quinolin-6-one

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***Abstract*— The reaction of 4-arylaminocoumarin with phosphorousoxychloridedimethylformamide led to 6H-1-benzopyrano [4,3-b] quinoline-6-one derivatives in very good yield under Vilsmeier-Haack condition. The antitubercular and other chemotherapeutic activity were found promising in few molecules. The purity of all the compounds is checked by TLC. The structures of new compounds were confirmed on the basis of UV, IR, and Mass spectral studies.**

***Index Terms*—4-arylaminocoumarin, 6H-12H-benzopyrano [4,3-b] quinolin-6-one derivatives, antitubercularactivity, antimicrobial activity, spectroscopic structural confirmation**

I. INTRODUCTION

Natural and synthetic quinolines and their derivatives are known for their exoticmanifoldapplications[1,2]. Some of the substitutedchromenoquinolinesare drug that modulates the transcriptional activity of human progesterone receptor[3]. These sorts of compounds are glucocorticoid receptor agonist, antagonist, and androgen receptor antagonist[4.] These are also useful in the treatment of osteoporosis, inflammatory bowel diseases, estrogen dependent cancers, anxiety disorders[5]. Only a few reports are available in the literature for the synthesis of 6H-chromeno[4,3-b]quinolines. This literature survey and the establishment of the privileged scaffold Chromenoquinolin as an active therapeutic agent inspire us to the synthesis of Substituted 6H-12H-Chromeno [4,3-b] quinolin-6-on**es.**

It has been established[6] that certain simple synthetic (e.g., β-Propiolactone) and complex natural (e.g. afatoxin) compounds with lactone function possess considerable anticarcinogenic activity. Hence it was of interest to prepare for investigation the compounds of molecular structure akin to those of confirmed nitrogen heterocyclic anticarcinogens (i.e. the angular benzacridines and banzocarbazoles), but with a lactone ring.

The ring system of 6H-1-benzopyrano [4,3-b] quinoline-6-ones can be synthesized by several methods [7-10].

Other analogs of 6,12-dihydro-1-benzopyrano [4,3-b] [1,h] benz- othiazine-6-ones were studied in detail for their biological profile and possible multidrug resistance (mdr) reversal in tumor cells [11,12].

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The benzopyranoquinolinecompounds are reported to have anticarcinogenic and also antipsoriatic activities. The new mono- functionally drugs such as pyridopsoralene do not usually produce skin photo toxicity [13,14], which make typical use easier.

Further, recently nitrogen heterocycles fused with lactone ring were found to be active against human promyelocytic leukemic HL-60 Cells[17].

As quinolinocoumarin found to be used as bioactive compounds, further work also suggested need for modification of structural aspects of such molecules[18].

II. CHEMISTRY:

The key intermediate 4-hydroxycoumarin derivative has been prepared by the Shah and Shah method[15, 16].4-Arylaminocoumarins were prepared by reacting different 4-hydroxycoumarins with several appropriate amines.The high reactivity to electrophiles of coumarin ring at the 3-position[17, 18] and the possibility of synthesizing with the fact that the reaction of 4-arylaminocoumarin with phosphorous oxychloridedimethylformamide led to 6H-1-benzopyrano [4,3-b] quinoline-6-one derivatives in very good yield under Vilsmeier-Haack condition.

The purity of all thecompoundsis checked by TLC. The structures of new compounds were confirmed on the basis of UV, IR, and Mass spectral studies.

The series of compounds synthesized in this chapter are substituted on the benzenoid part of different substituents at different positions by methyl or benzo groups, while that on benzenoid part of quinoline bearing chloro, fluoro, and methoxy group to study effect of substituents on the possible biological activity.

III. RESULTS AND DISCUSSION:

Antimicrobial profile of substituted 6H, 12H-chromeno [4,3-b] quinolin-6-ones.

Comparative antimicrobial study of these compounds shows that VCA-9 and VCA-28 are active against Candida albicans, while compound VCA-16 is active against bacterial strain Staph.aureus 209p. The compounds VCA-16 and VCA-28 are active as antifungal against Aspergillusfumigatus While VCA-16, VCA-28 shows some promise against Candida glabrata H05.

No promising activity was observed in case of VCA-6, VCA-11, VCA-13, VCA-17, VCA-19, VCA-23, VCA-25, VCA-27 and VCA-30.
All synthesized compounds were screened against seven different strains comprising of gram +ve and gram –ve bacteria and fungi. Out of which eight were found active against Staph. aureus 209p. Three were found active against E. Coli ESS 2231. Four were found active against Candida albicans ATCC 10231. Three were found active against Candida HO5.

The antitubercularactivity was found in one molecule.

IV. SPECTRAL ANALYSIS:

The constitutions of newly synthesized compounds were supported by UV, IR, and Mass spectra study. The details are as under.

A. Ultra Violet spectral study:

The UV spectra of newly synthesized compounds were taken in ELICO SL 159 UV-VIS spectrophotometer. The UV spectra were taken in DMF and also in other acidic and alkaline condition. The bathochromic as well as hypsochromic shifts are recorded. The UV spectral trend and changes in electronic transfer bands (ET bands) are mentioned in Table. It is observed that the in most of the cases λ_{max} values were observed at 274, 277, 280, 301, 304, 310, 337 and 340 nm. The other ET bands have appeared at 214, 235, 241, 244, 271, 361, 394 and 436nm range. As UV spectra of compounds are taken in acidic and alkaline medium, characteristic blue and red shifts are recorded and also changes in ET bands.

UV spectral study of substituted 6H, 12H-chromeno [4,3-b] quin- olin-6-ones.

(1) The λ_{max} and other λ values shown below in (1) DMF (N); (2) Acidic (A); (3) Alkaline (B) medium.

(2) All spectra are taken in DMF.
(3) The λ values are shown in nm and Extinction Coefficient (ε) values are shown in brackets.

Code	λ_1(ε)	λ_2 (ε)	λ_3 (ε)	λ_4(ε)	λ_5 (ε)
VCA-1 (N)	214 (0.345)	271 (0.507)	**340 (0.749)**	-	-
VCA-1 (A)	214 (0.287)	274 (0.484)	**340 (0.736)**	-	-
VCA-1 (B)	214 (0.236)	**277 (0.611)** 298 (0.503)	-	-	436 (0.077)
VCA-1 9(N)	214 (0.345) 244 (0.196)	277 (0.686)	**337 (0.825)**	-	-
VCA-1 9(A)	214 (0.315) 244 (0.138)	277 (0.607)	**337 (0.812)**	-	-
VCA-1 9(B)	241 (0.176)	-	**301 (0.576)**	-	-
VCA-2 3(N)	-	**280 (0.868)**	-	361 (0.172)	-
VCA-2 3(A)	-	**274 (1.552)**	-	361 (0.167)	-
VCA-2 3(B)	235 (0.097)	**271 (0.445)**	-	394 (0.159)	-
VCA-2 9(N)	214 (0.345) 244 (0.196)	271 (0.686)	**304 (0.772)**	-	-
VCA-2 9(A)	244 (0.234)	271 (0.680)	**310 (0.702)**	-	-
VCA-2 9(B)	214 (0.287) 244 (0.176)	**280(0.720)**	-	364 (0.575)	-

☞ Dark value indicates λ_{max} of compound in different media.

B. Infra Red (IR) spectral study:

The infrared spectra were recorded on SHIMADZU FT IR-8400 spectrophotometer by KBr pellet method. The IR (KBr) spectra of all compound showed band at 1700-1752cm^{-1} due to carbonyl stretching vibration of ketones. While ether linkage (C-O-C asym) and (C-O-C sym) appeared at region of 1200-1275 cm^{-1} and 1020-1075 cm^{-1} respectively. C-C and C-O gave stretching vibration in the region of 1150-1200 cm^{-1} while C-C and C-O band showed between 1000-1100 cm^{-1}. Stretching vibration from (C-H asym) observed at 2950-2975 cm^{-1} and for (C-H sym) showed band at 2860-2880 cm^{-1}.

IR Spectral Analysis of 2-Methyl-9-fluoro-6H, 12H-chromeno[4,3-b]quinolin-6-one(VCA-23).
IR (KBr) cm^{-1}: 1732.0 (C=O str); 1191.9(C-C & C-O str); 756.0(C-C & C-O band); 1222.8 (C-O-C asym); 1018.3 (C-O-C sym); 1562.2(C=C); 3062.7 (C-Hstrasym); 2881.4 (C-Hstrsym).

C. Mass spectral study:

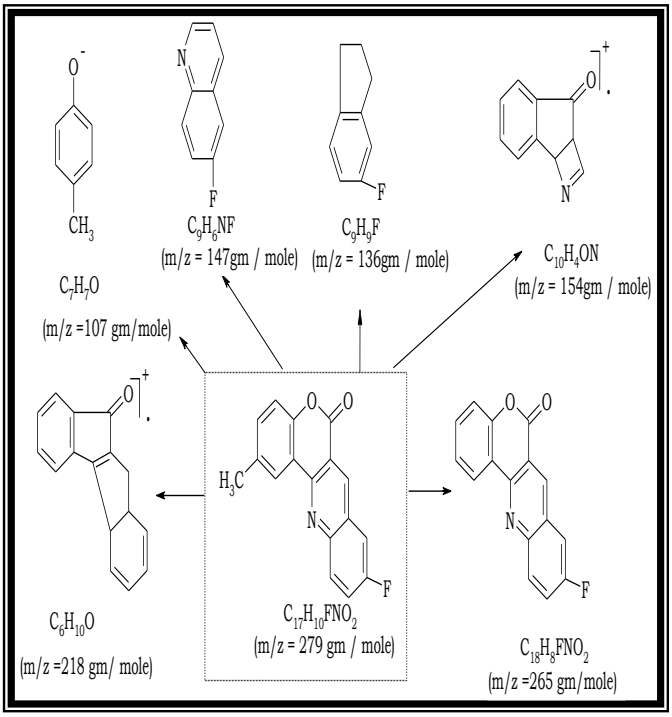
Mass spectra were recorded on JEOL SX-120/DX-6000 spectrometer.

All the newly synthesized compounds gave typical molecular ion peak according to their molecular weight. In addition, they also shows base peak.

Mass Spectra of 2-Methyl-9-fluoro-6H, 12H-chromeno [4,3-b] quinolin-6-one(VCA-23).

(FAB): M.Wt. = 279 gm/moles : [m/e (%)]; (M+1) **280 (75.99);** 270 (14.66); 266 (5.99); 242 (12.66); 220 (4.66); 209 (6.66); 178(4.66); **154 (100)**; 149 (10.66); 136 (73.33); 107 (11.99).

Possible Mass fragmentation of 2-Methyl-9-fluoro-6H, 12H-chrome-no[4,3-b]quinolin-6-one (VCA-23).



V. EXPERIMENTAL:

Preparation of 4-Hydroxycoumarins :

It was prepared according to the method described by Shah and coworkers[15, 16].

Preparation of 4-(3'-Chloroaminophenyl) coumarin[19]:

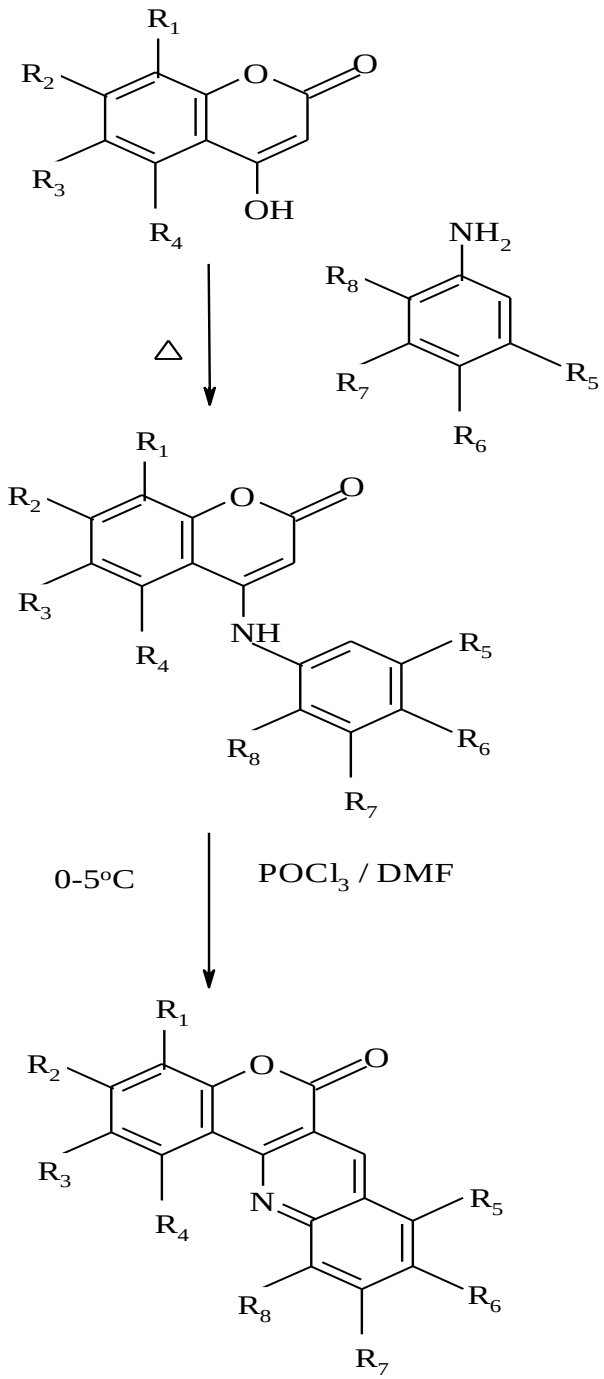
4-hydroxycoumarin (1.62 gm., 0.01 moles) was mixed with 3-chloro aniline (1.27 gm., 0.01 moles) and heated up to 150-175ºC with continuous stirring. The resulting mass then cooled and then treated with methanol (25 ml) and solid product formed was filtered. Then it washed with 0.1 M sodium hydroxide solution to remove unreacted 4-hydroxycoumarin and subsequently washed with excess water. It was dried and crystallized from acetonitrile, m. p. 236ºC (Reported m. p. = 237ºC[19]), yield 55 %.

Similarly, other substituted 4-arylaminocoumarins were prepared.

Preparation of substituted 6H-12H-Chromeno [4,3-b] quinolin-6-ones[19]:

The previously chilled phosphorous oxychloride (0.0035 moles) was added drop wise to dimethylformamide (DMF) (0.031 moles) by maintaining the temperature below 5ºC in ice-salt bath during 15 minutes. 4-(substituted arylamino) coumarin was (0.08 moles) added to the above solution in a single portion and allowed to stand at room temperature for few minutes. After that, the reaction mixture was heated on water bath for 2-3 hrs. Then the mixture was cooled and reaction mass was poured into the crushed ice. The crude product isolated was filtered; washed with cold water, dried and crystallized from ethanol, yield 65 %.Similarly, other compounds of these series were prepared by adopting the same reaction method.

REACTION SCHEME:



Where,

R_1, R_2, R_3, R_4 = H, CH_3, diCH_3, etc.

R_5, R_6, R_7, R_8 = H, F, Cl, benzo, phenyl, di Cl, etc.

VI. ANTITUBERCULAR ACTIVITY:

The antitubercular and other chemotherapeutic activity were found promising in few molecules. The antitubercularactivity screening was done for some newly synthesized compounds against Mycobacterium Tuberculosis out of which VCA – 16 has shown the resistance.

A. ANTIBACTERIAL ACTIVITY [20 - 23]*:*

The purified products were screened for their antibacterial activity. The nutrient agar medium was prepared by the usual method was inoculated aseptically with 0.5 ml for 24 hours old subcultures of staph. Aureus 209p and E.Coli ESS 2231 in separate conical flask at 40-50^{0}C and mixed well by gentle shaking. About 25 ml of the medium were poured and evenly spread in petri-dish (13 cm in diameter) and 10 mm bore in agar medium and filled with 0.05 ml solution of sample in 10 % DMSO in methanol. The plates were incubated at 37^0 for 24 hours and he control was also maintained with 0.05 ml of 10% DMSO in methanol in similar manner. The zones of inhibition of the bacterial growth were measured.

1. Concentration used : 1 mg/ml well/disc).
2. (-) denotes no activity.
3. (h) shows hazy.

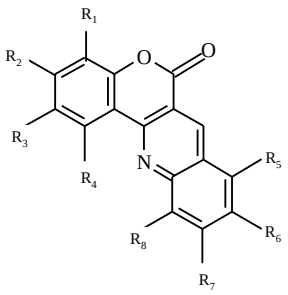
B. ANTIFUNGAL ACTIVITY [21 - 23] *:*

Aspergillusfumigatus, Candida albicans, Candida albicans ATCC 10231, Candida krusei G03, Candida glabrata H05 were employed for testing antifungal activity using well method. The control used was Fluconazole.

Note:

4. Solvent used : 10 % DMSO in methanol.
5. Concentration used : 1 mg/ml well/disc).
6. (-) denotes no activity.
7. (h) shows hazy.

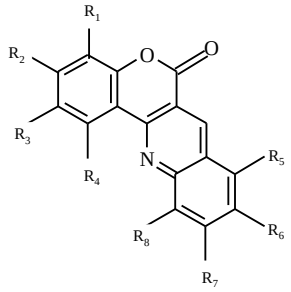
TableA : Antimicrobial profile of substituted 6H,12-H-chromeno [4,3-b]quinolin-6-ones.



Code	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Antimicrobial Activity					
									Antibacterial		Antifungal			
									Staph. Aureus 209-p	E.coli ESS 2231	Aspergillus fumigants	Candida albicans	Candida krusei G03	Candida glabrata H05
VCA-6	CH_3	CH_3	H	H	H	H	Cl	H	-	-	-	-	-	-
VCA-9	-Benzo-		H	H	H	H	-Benzo-		-	12h	-	10	-	-
VCA-11	H	H	CH_3	H	H	H	-Benzo-		-	-	-	11h	-	-
VCA-13	H	H	-Benzo-		H	H	H	C_6H_5	-	-	-	-	-	-
VCA-16	H	H	CH_3	H	H	H	H	C_6H_5	14	15h	14	12h	11h	12
VCA-17	CH_3	CH_3	H	H	H	H	H	C_6H_5	-	-	-	10h	-	-
VCA-19	H	H	H	H	H	F	H	H	-	-	-	-	-	-
VCA-23	H	H	CH_3	H	H	F	H	H	-	-	-	-	-	-
VCA-25	H	H	CH_3	H	H	Br	H	H	-	-	-	10h	-	-
VCA-27	-Benzo-		H	H	H	Cl	Cl	H	-	-	-	14h	-	-
VCA-28	H	CH_3	Cl	H	H	Cl	Cl	H	-	-	14	12	10h	9
VCA-30	H	H	CH_3	H	H	Cl	Cl	H	-	-	-	-	-	-

Table No:-1

Physical and analytical data of substituted 6-H-1-benzopyrano [4,3-b] qunioline-6-ones.



Code	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Mol. Formula	Mol. Wt.	R_f value	m.p. ° C	Elemental Analysis *		
													C	H	N
VCA-1	CH_3	H	H	H	H	H	Cl	H	$C_{17}H_{10}ClNO_2$	295.5	0.75	260	69.09 -69.05	3.38 -3.41	4.7 -4.7
VCA-2	H	H	- Benzo -		H	H	Cl	H	$C_{20}H_{10}ClNO_2$	331.5	0.51	180	72.35 -72.41	3 -3.04	4.2 -4.2
VCA-3	- Benzo -		H	H	H	H	Cl	H	$C_{20}H_{10}ClNO_2$	331.5	0.61	230	72.39 -72.41	3.09 -3.04	4.25 -4.2
VCA-4	H	H	CH_3	H	H	H	Cl	H	$C_{17}H_{10}ClNO_2$	295.5	0.39	238	69 -69.05	3.49 -3.41	4.79 -4.7
VCA-5	CH_3	H	H	CH_3	H	H	Cl	H	$C_{18}H_{12}ClNO_2$	309.5	0.44	> 300	69.85 -69.8	3.95 -3.9	4.5 -4.5

* Values in parenthesis denote the calculated % of composition
TLC solvent system Acetone : Benzene (0.5 : 9.5)

Code	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Mol. Formula	Mol. Wt.	R_f value	m.p. ° C	Elemental Analysis *		
													C	H	N
VCA-6	CH_3	CH_3	H	H	H	H	Cl	H	$C_{18}H_{12}ClNO_2$	309.5	0.53	258	69.82 -69.8	3.97 -3.9	4.55 -4.5
VCA-7	CH_3	H	H	H	H_2	H_2	H_2	H_2	$C_{17}H_{15}NO_2$	265	0.44	240	76.95 -76.96	5.77 -5.7	5.3 -5.3
VCA-8	H	H	- Benzo -		H	H	- Benzo -		$C_{24}H_{13}NO_2$	347	0.67	295	82.92 -82.98	3.75 -3.77	4 -4
VCA-9	- Benzo -		H	H	H	H	- Benzo -		$C_{24}H_{13}NO_2$	347	0.41	172	82.9 -82.98	3.7 -3.77	4.07 -4
VCA-10	CH_3	H	H	H	H	H	- Benzo -		$C_{21}H_{13}NO_2$	311	0.45	>300	81.06 -81.01	4.25 -4.21	4.59 -4.5

Code	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Mol. Formula	Mol. Wt.	R_f	m.p. ° C	Elemental Analysis *		
													C	H	N
VCA-11	H	H	CH_3	H	H	H	- Benzo -		$C_{21}H_{13}NO_2$	311	0.51	276	81.04 -81.01	4.17 -4.21	4.51 -4.5
VCA-12	H	CH_3	H	CH_3	H	H	- Benzo -		$C_{22}H_{15}NO_2$	325	0.54	180	81.25 -81.21	4.6 -4.65	4.32 -4.3
VCA-13	H	H	- Benzo -		H	H	H	C_6H_5	$C_{26}H_{15}NO_2$	373	0.6	285	83.6 -83.63	4.1 -4.05	3.79 -3.8
VCA-14	- Benzo -		H	H	H	H	H	C_6H_5	$C_{26}H_{15}NO_2$	373	0.47	250	83.69 -83.63	4.02 -4.05	3.7 -3.8
VCA-15	CH_3	H	H	H	H	H	H	C_6H_5	$C_{23}H_{15}NO_2$	337	0.51	235	81.9 -81.88	4.5 -4.48	4.1 -4.2

* Values in parenthesis denote the calculated % of composition
TLC solvent system Acetone : Benzene (0.5 : 9.5)

Code	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Mol. Formula	Mol. Wt.	R_f	m.p. ° C	Elemental Analysis *		
													C	H	N
VCA-16	H	H	CH_3	H	H	H	H	C_6H_5	$C_{23}H_{15}NO_2$	337	0.44	238	81.92 -81.88	4.52 -4.48	4.11 -4.2
VCA-17	CH_3	CH_3	H	H	H	H	H	C_6H_5	$C_{24}H_{17}NO_2$	351	0.62	298	82.1 -82.03	4.9 -4.88	3.92 -4
VCA-18	H	CH_3	H	CH_3	H	H	H	C_6H_5	$C_{24}H_{17}NO_2$	351	0.59	165	82.09 -82.03	4.85 -4.88	3.95 -4
VCA-19	H	H	H	H	H	F	H	H	$C_{16}H_8FNO_2$	264	0.39	282	72.5 -72.45	3 -3.05	5.3 -5.3
VCA-20	H	H	- Benzo -		H	F	H	H	$C_{20}H_{10}FNO_2$	314	0.48	205	76.2 -76.19	3.15 -3.2	4.4 -4.4

Code	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Mol. Formula	Mol. Wt.	R_f	m.p. ° C	Elemental Analysis *		
													C	H	N
VCA-21	- Benzo -		H	H	H	F	H	H	$C_{20}H_{10}FNO_2$	314	0.62	191	76.2 -76.19	3.25 -3.2	4.4 -4.4
VCA-22	H	CH_3	H	CH_3	H	F	H	H	$C_{18}H_{12}FNO_2$	292	0.49	210	73.77 -73.71	4.15 -4.12	4.7 -4.8
VCA-23	H	H	CH_3	H	H	F	H	H	$C_{17}H_{10}FNO_2$	278	0.53	273	73.13 -73.11	3.65 -3.61	5.09 -5
VCA-24	H	H	CH_3	H	H_2	H_2	H_2	H_2	$C_{17}H_{15}NO_2$	265	0.54	245	76.9 -76.96	5.77 -5.7	5.25 -5.3
VCA-25	H	H	CH_3	H	H	Br	H	H	$C_{17}H_{10}BrNO_2$	340	0.44	220	60 -60.02	2.91 -2.96	4.19 -4.1

* Values in parenthesis denote the calculated % of composition

TLC solvent system Acetone : Benzene (0.5 : 9.5)

Code	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Mol. Formula	Mol. Wt.	R_f	m.p. ° C	Elemental Analysis *		
													C	H	N
VCA-26	H	H	- Benzo -		H	Cl	Cl	H	$C_{20}H_9Cl_2NO_2$	365	0.48	217	65.66 -65.6	2.5 -2.48	3.85 -3.8
VCA-27	- Benzo -		H	H	H	Cl	Cl	H	$C_{20}H_9Cl_2NO_2$	365	0.39	215	65.62 -65.6	2.47 -2.48	3.87 -3.8
VCA-28	H	CH_3	Cl	H	H	Cl	Cl	H	$C_{17}H_8Cl_3NO_2$	363.5	0.6	265	56.05 -56	2.2 -2.21	3.85 -3.8
VCA-29	CH_3	H	H	H	H	Cl	Cl	H	$C_{17}H_9Cl_2NO_2$	329	0.55	> 300	61.88 -61.84	2.74 -2.75	4.26 -4.2
VCA-30	H	H	CH_3	H	H	Cl	Cl	H	$C_{17}H_9Cl_2NO_2$	329	0.4	190	61.89 -61.84	2.7 -2.75	4.27 -4.2

Code	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Mol. Formula	Mol. Wt.	R_f	m.p. ° C	Elemental Analysis *		
													C	H	N
VCA-31	CH_3	H	H	CH_3	H	Cl	Cl	H	$C_{18}H_{11}Cl_2NO_2$	343	0.51	210	62.85 -62.81	3.2 -3.22	4.1 -4.1
VCA-32	CH_3	CH_3	H	H	H	Cl	Cl	H	$C_{18}H_{11}Cl_2NO_2$	343	0.57	230	62.87 -62.81	3.29 -3.22	4.01 -4.1
VCA-33	H	CH_3	H	CH_3	H	Cl	Cl	H	$C_{18}H_{11}Cl_2NO_2$	343	0.5	250	62.8 -62.81	3.28 -3.22	4.03 -4.1

* Values in parenthesis denote the calculated % of composition
TLC solvent system Acetone : Benzene (0.5 : 9.5)

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