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Synthesis of (2*E*)-3-{2-[(substituted benzyl)oxy]phenyl}acrylaldehydes as novel anti-inflammatory agents

Li-Jiau Huang,[a,*] Jih-Pyang Wang,[a,b,*] Yu-Chi Lai[a] and Sheng-Chu Kuo[a]

[a]*Graduate Institute of Pharmaceutical Chemistry, China Medical University, Taichung 40402, Taiwan, ROC*
[b]*Department of Education and Research, Taichung Veterans General Hospital, Taichung 407, Taiwan, ROC*

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Abstract—As part of our continuing effort for development of novel anti-inflammatory agents, the highly potential agent **CCY1a**, which we reported recently, was selected as lead compound to synthesize a series of its derivatives for evaluation. Most of the newly synthesized compounds exhibited superior inhibitory activity than both the lead compound and the positive control (trifluoperazine) toward fMLP-stimulated neutrophil superoxide formation. (2*E*)-3-[2-(Benzyloxy)-5-methoxyphenyl]-acrylaldehyde (**31**) was among the most potent with action mechanism different from **CCY1a** in that it does not act as cAMP-elevating agent but inhibits the increase in cellular Ca^{2+} with greater potency.

In our previous work,[1] several regioisomers of benzyloxybenzaldehyde were synthesized and determined to have significant inhibitory activity toward neutrophil superoxide anion generation. Among these compounds, 2-benzyloxybenzaldehyde (**1**, **CCY1a**) was the most promising one, which was further identified as an indirect adenylyl cyclase activator,[2] through the release of endogenous adenosine. The inhibition of superoxide anion generation by **CCY1a** in neutrophils is attributed partly to its cAMP-elevating activity, and partly to the blockade of external Ca^{2+} entry and phospholipase D activation via cAMP-independent mechanisms.[2–4]

In the present work, **CCY1a** was selected as lead compound and a series of 3-{2-[(substituted benzyl)oxy]phenyl}acrylaldehydes were synthesized and their effect on neutrophil superoxide formation and cAMP-elevating activity were evaluated.

The (2*E*)-3-{2-[(substituted benzyl)oxy]phenyl}acrylaldehydes (**15–26**) were synthesized according to the synthetic method of **CCY1a**.[1] As shown in Scheme 1, when cinnamic aldehyde (**2**) was reacted with a variety of substituted benzyl chlorides (**3–14**) and K_2CO_3 in EtOH, the corresponding target compounds (**15–26**) were obtained. On the other hand, as illustrated in Scheme 2, 2-(substituted benzyloxy)-5-methoxybenzaldehyde (**27–30**),[5] which was prepared from 2-hydroxy-5-methoxybenzaldehyde and substituted benzyl chloride (**3–6**), was treated with equal mole of acetaldehyde at low temperature to undergo aldol condensation which resulted in the formation of (2*E*)-3-[2-(substituted benzyloxy)-5-methoxyphenyl]acrylaldehyde (**31–34**). Finally, compounds **31–33** were treated with hydroxylamine to afford the corresponding oximes **35–37**. All the synthetic compounds were characterized by their spectral characteristics.[6]

Superoxide anion formation was measured in terms of superoxide dismutase inhibitable cytochrome c reduction.[7] Briefly, the assay mixture contained the cell suspension and 0.5 mg/mL of cytochrome *c* (ΔA_{550}), the reference mixture also received 6.6 μg/mL of superoxide dismutase. Reaction was initiated by stimulating with 0.3 μM formyl-Met-Leu-Phe (fMLP) or 3 nM phorbol 12-myristate 13-acetate (PMA).

According to the data in Table 1, converting the –CHO moiety of lead compound (**CCY1a**) into –CH=CH–CHO (**15**) improved its activity significantly. Moreover, the addition of a Cl atom into the *ortho*

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* Corresponding authors. Tel.: +886 4 22053366 1007; fax: +886 04 22055105 (L.J.H.); tel.: +886 04 23592525 2043; fax: +886 04 23592705 (J.P.W.); e-mail addresses: ljhuang@mail.cmu.edu.tw; w1994@vghtc.vghtc.gov.tw

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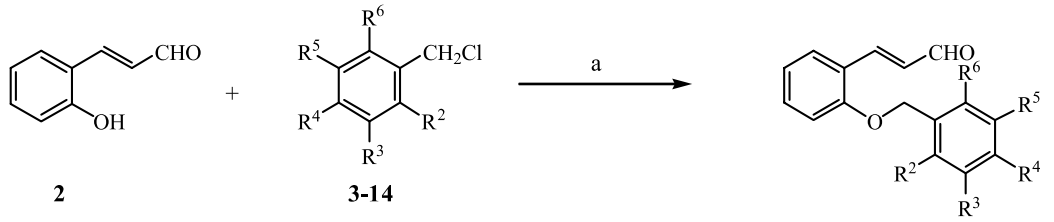
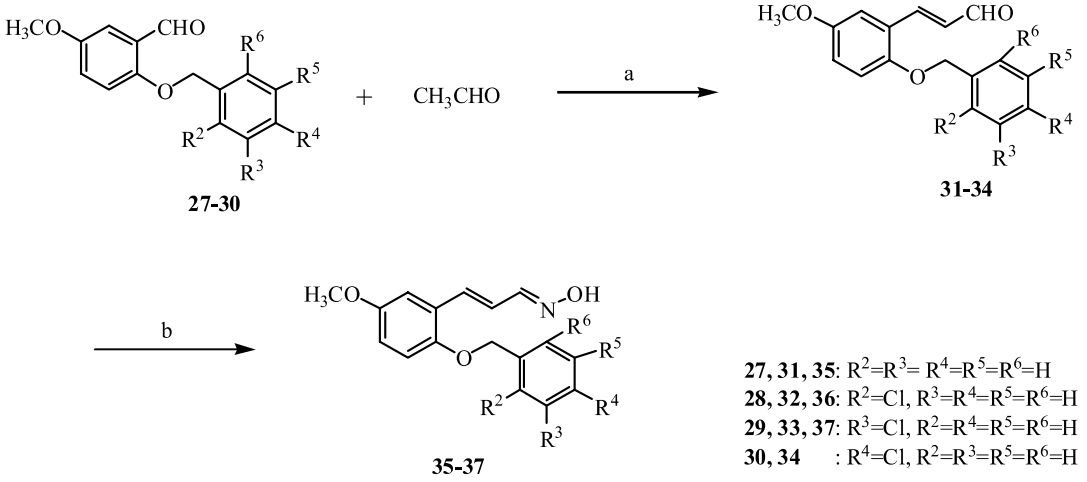


3, 15: $R^2=R^3=R^4=R^5=R^6=H$
4, 16: $R^2=Cl$, $R^3=R^4=R^5=R^6=H$
5, 17: $R^3=Cl$, $R^2=R^4=R^5=R^6=H$
6, 18: $R^4=Cl$, $R^2=R^3=R^5=R^6=H$
7, 19: $R^2=F$, $R^3=R^4=R^5=R^6=H$
8, 20: $R^3=F$, $R^2=R^4=R^5=R^6=H$
9, 21: $R^4=CH_3$, $R^2=R^3=R^5=R^6=H$
10, 22: $R^4=OCH_3$, $R^2=R^3=R^5=R^6=H$
11, 23: $R^3=R^4=Cl$, $R^2=R^5=R^6=H$
12, 24: $R^2=R^3=Cl$, $R^4=R^5=R^6=H$
13, 25: $R^2=R^4=Cl$, $R^3=R^5=R^6=H$
14, 26: $R^2=R^6=Cl$, $R^3=R^4=R^5=H$

Scheme 1. Reagents and conditions: (a) K_2CO_3, KI/ethanol, reflux.



27, 31, 35: $R^2=R^3=R^4=R^5=R^6=H$
28, 32, 36: $R^2=Cl$, $R^3=R^4=R^5=R^6=H$
29, 33, 37: $R^3=Cl$, $R^2=R^4=R^5=R^6=H$
30, 34 : $R^4=Cl$, $R^2=R^3=R^5=R^6=H$

Scheme 2. Reagents and conditions: (a) 20% NaOH/ethanol, 0 °C; (b) $NH_2OH \cdot HCl$, CH_3COONa/ethanol, reflux.

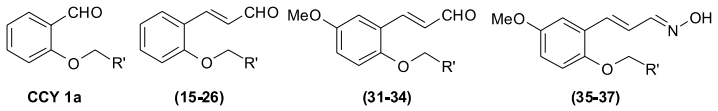
position of the benzyl group in compound **15** resulted in compound **16** with further improved activity. Meanwhile, the placement of the same Cl atom in the *meta* position (**17**) appeared to be functionless, whereas a Cl atom in *para* position (**18**) resulted in reduced activity. In order approaches, it was found that the substitution of the *ortho* Cl of compound **16**, or the *meta* Cl of **17** with F atom, resulted in compounds **19** and **20** with a slight improvement in their activity. Then our attempt to modify compound **15** by adding a CH_3 group onto its *para* position at benzyl group resulted in compound **21** with only about half the activity.

Results on the effect of all dichlorobenzyl derivatives (**23**–**26**) on neutrophil superoxide anion formation indicated that only 3,4-dichlorobenzyl derivatives (**23**) demonstrated significant activity. Neither its 2,3-dichloro (**24**), 2,4-dichloro (**25**) nor 2,6-dichloro (**26**) isomers show any significant activity. Excitingly, the incorporation of an OCH_3 group into the 4 position at the benzyloxy group (**22**) and the 5 position at the phenyl group (**31**) of compound **15** resulted in significant boost of activity.

In particular, the IC_{50} value for compound **31** was determined as 2.6 μM which is about 6 times more active than the lead compound **CCY1a** or the positive control (trifluoperazine). After introduction of a Cl atom onto the benzyl group of compound **31** at either the *ortho*-(**32**), *meta*-(**33**) or *para*-location (**34**), only the 3-chlorobenzyl derivatives (**33**) maintain significant inhibitory activity against superoxide formation. Our attempt in derivatization of compound **31** into an oxime (**35**) resulted in 50% lower activity, whereas similar derivatization of compound **32** resulted in compound **36** with improved activity in 30 μM concentration. On the other hand, all the compounds were tested for their inhibitory activity against PMA-stimulated superoxide anion formation. The result indicated that, unlike the positive control TFP, none of the tested compounds showed significant activity in the test concentration range 1–30 μM. This seems to suggest that, the action mechanism of the test compounds differs when tested against superoxide anion generation by different stimulants.

Summarizing all the above findings, compound **31** was found to demonstrate the greatest inhibitory activity against fMLP-induced superoxide anion formation of

Table 1. The inhibitory effects of **15**–**26** and **31**–**37** on the neutrophil superoxide formation



Animal: Rat (Sprague Dawley) Inducer: fMLP (0.3 μM)/cytochalasin B (5 μg/mL)
Inducer: PMA (3 nM)

Compound	R′	Concentration (μM)	Superoxide formation (nmol/10^6 cells/30 min)			
			fMLP	% inhibition	PMA	% inhibition
Control			2.89 ± 0.30		7.60 ± 0.36	
CCY1a	C_6H_5	3	1.01 ± 0.19**	36.1 ± 6.3	—	—
		10	0.86 ± 0.20**	40.6 ± 5.9	—	—
		30	0.62 ± 0.07**	60.8 ± 1.6	—	—
			IC_{50} = 15.6			
15	C_6H_5	3	1.96 ± 0.19	31.8 ± 3.3**	—	—
		10	1.05 ± 0.16	63.7 ± 2.4**	8.61 ± 0.50	−13.5 ± 6.0
		30	0.48 ± 0.05	83.2 ± 1.4**	9.39 ± 0.49	−23.6 ± 4.8
			IC_{50} = 6.4 ± 0.7			
16	2-Cl-C_6H_4	3	1.69 ± 0.13	40.1 ± 7.5**	—	—
		10	0.82 ± 0.08	71.4 ± 2.3**	9.86 ± 0.27	−30.1 ± 5.4
		30	0.29 ± 0.02	89.7 ± 0.7**	8.39 ± 0.36	−10.9 ± 7.0
			IC_{50} = 4.4 ± 1.1			
17	3-Cl-C_6H_4	3	2.00 ± 0.26	31.2 ± 1.8**	—	—
		10	0.9 ± 90.12	65.7 ± 2.6**	9.85 ± 0.14	−30.1 ± 5.6
		30	0.34 ± 0.04	88.0 ± 1.5**	9.06 ± 0.89	−18.7 ± 7.8
			IC_{50} = 5.9 ± 0.3			
18	4-Cl-C_6H_4	3	2.23 ± 0.20	22.4 ± 1.3	—	—
		10	1.05 ± 0.06	63.1 ± 2.2**	9.41 ± 0.35	−23.9 ± 3.1
		30	0.37 ± 0.02	86.9 ± 1.3**	9.26 ± 0.31	−22.0 ± 3.7
			IC_{50} = 7.4 ± 0.3			
19	2-F-C_6H_4	3	1.48 ± 0.12	47.5 ± 7.0**	—	—
		10	0.72 ± 0.13	75.1 ± 2.3**	9.45 ± 0.64	−24.1 ± 4.3
		30	0.35 ± 0.05	87.6 ± 2.2**	9.82 ± 0.51	−29.4 ± 6.0
			IC_{50} = 3.3 ± 0.8			
20	3-F-C_6H_4	3	1.70 ± .12	40.3 ± 3.6**	—	—
		10	0.76 ± 0.06	73.0 ± 3.4**	8.07 ± 0.26	−6.2 ± 2.3
		30	0.46 ± 0.06	83.9 ± 0.9**	9.38 ± 0.39	−23.7 ± 6.5
			IC_{50} = 4.5 ± 0.7			
21	4-CH_3-C_6H_4	3	2.24 ± 0.15	21.9 ± 2.8	—	—
		10	1.57 ± 0.11	45.1 ± 1.9**	8.53 ± 0.48	−13.2 ± 11.0
		30	0.78 ± 0.12	73.2 ± 1.2**	9.51 ± 0.18	−25.8 ± 7.7
			IC_{50} = 11.0 ± 0.4			
22	4-OCH_3-C_6H_4	3	1.58 ± 0.09	44.6 ± 2.8**	—	—
		10	0.81 ± 0.02	71.3 ± 1.8**	9.45 ± 0.51	−24.5 ± 6.3
		30	0.33 ± 0.09	88.2 ± 3.7**	9.28 ± 0.31	−22.2 ± 1.9
			IC_{50} = 3.8 ± 0.5			
23	3,4-Cl-C_6H_3	1	2.56 ± 0.35	11.7 ± 3.1	—	—
		3	2.03 ± 0.21	29.4 ± 2.4*	—	—
		10	0.60 ± 0.20	79.8 ± 4.4**	7.77 ± 0.29	1.9 ± 6.3
		30	—	—	11.4 ± 0.48	−51.1 ± 8.6*
			IC_{50} = 4.3 ± 0.4			
24	2,3-Cl-C_6H_3	10	2.39 ± 0.27	17.4 ± 0.8	6.72 ± 0.39	11.2 ± 7.2
		30	1.75 ± 0.30	39.9 ± 4.9**	6.29 ± 0.38	17.3 ± 1.2
25	2,4-Cl-C_6H_3	10	2.16 ± 0.17	24.4 ± 4.7	9.29 ± 0.06	−22.7 ± 6.6
		30	1.76 ± 0.33	39.9 ± 5.5**	9.84 ± 0.57	−29.8 ± 8.4
26	2,6-Cl-C_6H_3	10	1.71 ± 0.21	40.3 ± 7.5**	11.4 ± 0.55	−50.6 ± 5.3*
		30	1.54 ± 0.27	46.8 ± 7.6**	12.0 ± 0.14	−59.2 ± 7.6**
31	C_6H_5	1	2.09 ± 0.10	26.7 ± 4.1*	—	—
		3	1.37 ± 0.16	52.24 ± 2.4**	—	—
		10	0.53 ± 0.03	81.2 ± 1.0**	9.42 ± 0.52	−24.0 ± 5.4
		30	—	—	9.19 ± 0.37	−20.9 ± 2.8
			IC_{50} = 2.6 ± 0.2			

Table 1 (*continued*)

Compound	R′	Concentration (μM)	Superoxide formation (nmol/10^6 cells/30 min)			
			fMLP	% inhibition	PMA	% inhibition
32	2-Cl-C_6H_4	10	1.89 ± 0.18	34.3 ± 2.6**	8.94 ± 0.59	−17.5 ± 3.7
		30	1.69 ± 0.13	40.9 ± 1.9**	9.63 ± 0.39	−26.9 ± 5.4
33	3-Cl-C_6H_4	1	2.54 ± 0.17	11.4 ± 3.4	—	—
		3	1.82 ± 0.20	36.8 ± 1.4**	—	
		10	0.67 ± 0.22	77.7 ± 5.6**	10.3 ± 0.91	−35.7 ± 8.4
		30	—	—	9.96 ± 0.67	−31.2 ± 7.7
			IC_{50} = 4.2 ± 0.3			
34	4-Cl-C_6H_4	10	2.10 ± 0.21	27.1 ± 0.5*	9.39 ± 0.72	−23.3 ± 6.0
		30	1.90 ± 0.08	33.4 ± 4.3**	9.55 ± 0.66	−25.5 ± 5.8
35	C_6H_5	3	2.03 ± 0.08	41.9 ± 3.4**	—	—
		10	1.05 ± 0.08	70.0 ± 1.3**	4.97 ± 0.88	7.6 ± 12.5
		30	0.48 ± 0.05	86.0 ± 1.9**	6.90 ± 0.76	−29.4 ± 8.3
			IC_{50} = 4.3 ± 0.5			
36	2-Cl-C_6H_4	3	2.45 ± 0.30	29.5 ± 10.5*	—	—
		10	2.09 ± 0.23	40.4 ± 5.8**	5.27 ± 0.64	1.5 ± 7.7
		30	0.78 ± 0.11	77.7 ± 2.9**	7.62 ± 0.12	−44.4 ± 4.7
			IC_{50} = 9.5 ± 1.4			
37	4-Cl-C_6H_4	10	2.53 ± 0.22	27.9 ± 4.6*	11.9 ± 0.25	−124 ± 13.7**
		30	2.41 ± 1.4	31.6 ± 7.9**	12.1 ± 0.15	−132 ± 14.4**
TFP		1	—	—	5.48 ± 0.13	27.6 ± 4.2*
		3	28.0 ± 0.27	1.7 ± 6.6	3.4 ± 0.13	55.4 ± 9.4**
		5	2.1 ± 0.09	24.2 ± 5.3*	—	—
		10	0.54 ± 0.22	79.5 ± 4.2**	1.23 ± 0.16	83.3 ± 5.8**
			IC_{50} = 6.6 ± 0.2		**IC_{50} = 2.7 ± 0.6**	

—, not determined. Trifluoperazine (TFP): positive control.
* $P<0.05$.
** $P<0.01$; N = 3.

neutrophil. Therefore, compound **31** was selected for study of action mechanism.

We also determined the cAMP-elevating activity of compound **31** in neutrophils by using an enzyme immunoassay kit (Amersham) as the previous report.[1] Surprisingly, compound **31** only slightly elevated the cellular cAMP level at 10 μM and then returned to the baseline at higher concentrations (Fig. 1), unlike **CCY1a**, which produced a concentration-dependent increase in cellular cAMP level. We next determined the effect of compound **31** on intracellular free Ca^{2+} concentration because the fMLP-induced superoxide anion is a Ca^{2+}-dependent process and **CCY1a** also exerts its effect through the inhibition of Ca^{2+} entry.[2] In this experiment, neutrophils were loaded with 5 μM fluo-3 AM for 45 min. After being washed, the cells were resuspended and monitored for the fluorescence change (488/535 nm). Addition of fMLP to fluo-3-loaded cells evoked an initial Ca^{2+} spike, followed by a plateau phase, in the presence of 1 mM extracellular Ca^{2+}.[8] Interestingly, compound **31** was 2.5-fold more potent than **CCY1a** in the inhibition of plateau phase (Fig. 2).

To sum up, the inhibitory activity for all of the above **CCY1a** derivatives against neutrophil superoxide formation was found to be far superior than both their lead compound and the positive control. The action of the most potent compound **31** is attributed at least partly to the blockade of intracellular Ca^{2+} elevation but not to the cAMP-dependent mechanism.

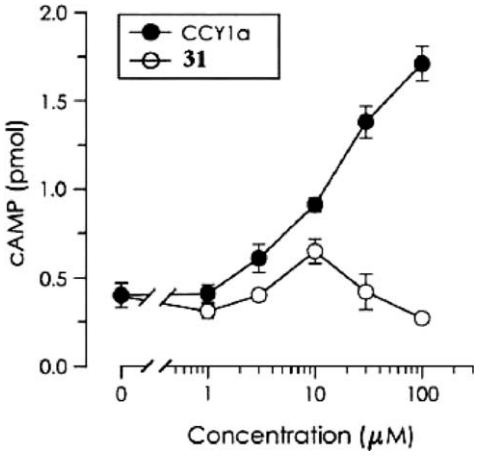


Figure 1. Effect of **CCY1a** and compound **31** on cellular cAMP levels. Cells were treated with DMSO (as basal level), the indicated concentrations of **CCY1a** or compound **31** for 10 min. The cAMP contents were assayed using an enzyme immunoassay kit. Values are means ± SD of three experiments.

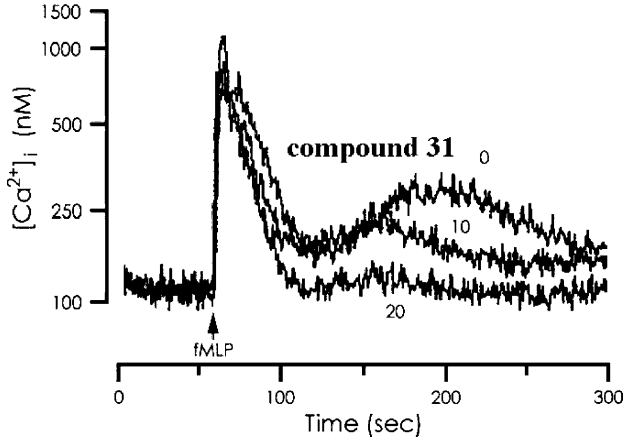


Figure 2. Effect of compound **31** on the fMLP-stimulated elevation of intracellular free Ca^{2+} in neutrophils. Fluo 3-loaded cells in HBSS containing 1 mM Ca^{2+} were pretreated with the indicated concentrations of compound **31** at 37 °C for 1 min before stimulation with 0.3 μM fMLP. The data presented are representative of three independent experiments with similar results.

Acknowledgments

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6. Spectral characteristics for compounds: Compound **15**: yield, 42%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.63 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 16.0 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.29–7.50 (m, 6H), 7.19 (d, J = 8.4 Hz, 1H), 7.02 (dd, J = 7.5, 7.5 Hz, 1H), 6.75 (dd, J = 16.0, 7.8 Hz, 1H), 5.23 (s, 2H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ 194.80, 157.02, 147.79, 136.56, 133.26, 132.80, 129.35, 129.03, 128.54, 127.98, 127.65, 122.68, 121.04, 69.81 ppm; MS (EI) *m/z* 238 (M^+); Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 79.98; H, 5.86. Compound **16**: yield, 35%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.62 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 16.0 Hz, 1H), 7.70 (d, J = 7.5, 1.2 Hz, 1H,), 7.37–7.65 (m, 5H), 7.23 (d, J = 7.2 Hz, 1H), 7.05 (dd, J = 7.5, 7.5 Hz, 1H), 6.82 (dd, J = 16.0, 7.8 Hz, 1H), 5.29 (s, 2H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ 194.82, 156.78, 147.58, 133.80, 133.32, 132.90, 130.38, 129.54, 129.32, 129.12, 127.48, 121.38, 120.13, 67.62 ppm; MS (EI) *m/z* 272 (M^+); Anal. Calcd for $C_{16}H_{13}O_2Cl$: C, 70.46; H, 4.80. Found: C, 70.32; H, 4.68. Compound **17**: yield, 31%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.62 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 16.0 Hz, 1H), 7.77 (dd, J = 7.5, 1.6 Hz, 1H), 7.25–7.56 (m, 5H), 6.99 (d, J = 8.4 Hz, 1H), 6.96 (dd, J = 7.5, 7.5 Hz, 1H,), 6.79 (dd, J = 16.0, 7.8 Hz, 1H), 5.13 (s, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 194.35, 156.93, 147.59, 138.31, 134.64, 132.62, 130.06, 129.13, 128.67, 128.40, 127.37, 125.31, 123.38, 121.45, 112.68, 69.71 ppm; MS (EI) *m/z* 272 (M^+); Anal. Calcd for: C, 70.46; H, 4.80. Found: C, 70.82; H, 5.04. Compound **18**: yield, 43%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.63 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 16.0 Hz, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.38–7.52(m, 5H), 7.16 (d, J = 8.4 Hz, 1H), 7.01 (dd, J = 7.5, 7.5 Hz, 1H), 6.83 (dd, J = 16.0, 7.8 Hz, 1H), 5.18 (s, 2H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ 194.73, 156.78, 147.63, 135.54, 132.76, 132.65, 129.46, 129.24, 129.01, 128.52, 122.69, 121.13, 113.19, 68.96 ppm; MS (EI) *m/z* 272 (M^+); Anal. Calcd for $C_{16}H_{13}O_2Cl$: C, 70.46; H, 4.80. Found: C, 69.88 ; H, 4.56. Compound **19**: yield, 33%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.60 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 16.0 Hz, 1H), 7.75 (dd, J = 7.6, 1.4 Hz, 1H), 7.59 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 7.41–7.47 (m, 2H), 7.21–7.32 (m, 3H), 7.04 (dd, J = 7.6, 7.6 Hz, 1H), 6.81 (dd, J = 16.0, 7.8 Hz, 1H), 5.28 (s, 2H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ 195.17, 160.72, 157.10, 148.02, 133.15, 130.97, 130.89, 129.56, 124.85, 123.52, 122.97, 121.61, 115.73, 113.54, 64.56 ppm; MS (EI) *m/z* 256 (M^+); Anal. Calcd for $C_{16}H_{13}O_2F$: C, 74.99; H, 5.11. Found: C, 73.56; H, 4.88. Compound **20**: yield, 34%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.70 (d, J = 7.8 Hz, 1H), 7.91 (d, J = 16.0 Hz, 1H), 7.06 (dd, J = 8.0, 1.6 Hz, 1H), 7.33–7.44 (m, 2H), 6.95–7.27 (m, 5H), 6.78 (dd, J = 16.0, 7.8 Hz, 1H), 5.17 (s, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 194.18, 156.78, 147.43, 138.54, 132.40, 130.15, 128.95, 128.49, 122.45, 122.31, 121.22, 114.95, 113.97, 112.47, 69.51 ppm; MS (EI) *m/z* 256 (M^+); Anal. Calcd for $C_{16}H_{13}O_2F$: C, 74.99; H, 5.11. Found: C, 75.65; H, 4.89. Compound **21**: yield, 31%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.67 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 16.0 Hz, 1H), 7.58 (dd, J = 8.0, 1.8 Hz, 1H), 7.20–7.43 (m, 4H), 6.97–7.05 (m,2H), 6.77 (dd, J = 16.0, 7.8 Hz, 1H), 5.13 (s, 2H), 2.38 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 194.52, 157.45, 147.41, 138.09, 133.21, 132.61, 129.41, 128.98, 128.66, 127.54, 123.36, 121.09, 112.82, 70.54, 21.20 ppm; MS (EI) *m/z* 252 (M^+); Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 79.88; H, 6.54. Compound **22**: yield, 32%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.66 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 16.0 Hz, 1H), 7.58 (dd, J = 8.0, 1.8 Hz, 1H), 7.34–7.40 (m, 3H), 6.92–7.05 (m, 4H), 6.73 (dd, J = 16.0, 7.8 Hz, 1H), 5.10 (s, 2H), 3.83 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 194.54, 159.66, 157.49, 148.08, 132.62, 123.39, 121.11, 114.15, 112.87, 70.44, 55.33 ppm; MS (EI) *m/z* 268 (M^+); Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.58; H, 5.98. Compound **23**: yield, 22%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.64 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 16.0 Hz, 1H), 7.75–7.77 (m, 2H), 7.66 (d, J = 8.3 Hz, 1H), 7.41–7.50 (m, 2H), 7.17 (d, J = 8.4 Hz, 1H), 7.03 (dd, J = 7.5, 7.5 Hz, 1H), 6.83 (dd, J = 16.0, 7.8 Hz, 1H), 5.25 (s, 2H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ 194.92, 156.59, 147.65, 137.83, 132.89, 131.20, 130.84, 130.63, 129.68, 129.29, 129.13, 127.97, 122.76, 121.37, 113.30, 68.29 ppm; MS (EI) *m/z* 306 (M^+); Anal. Calcd for $C_{16}H_{12}O_2Cl_2$: C, 62.56; H, 3.94. Found: C, 63.51; H, 4.05. Compound **24**: yield, 24%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.71 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 16.0 Hz, 1H), 7.61 (dd, J = 7.5, 1.4Hz, 1H), 7.36–7.49 (m, 3H), 7.22–7.29 (*m*, 1H), 7.05 (d, J = 7.5, 7.5 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.78 (dd, J = 16.0, 7.8 Hz, 1H), 5.28 (s, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 194.31, 156.66, 147.50, 136.22, 133.31, 132.68, 130.75, 129.97, 129.10, 128.59, 127.56, 126.61, 123.35, 121.62, 112.72, 67.98 ppm; MS (EI) *m/z* 306 (M^+); Anal. Calcd

for $C_{16}H_{12}O_2Cl_2$: C, 62.56; H, 3.94. Found: C, 63.21; H, 4.01. Compound **25**: yield, 42%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.62 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 16.0 Hz, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.71 (d, 1H), 7.63 (m, 1H), 7.47–7.51 (m, 2H), 7.05 (d, J = 8.4 Hz, 1H), 6.95 (dd, J = 7.5, 7.5 Hz, 1H), 6.78 (dd, J = 16.0, 7.8 Hz, 1H), 5.27 (s, 2H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ 194.90, 156.63, 147.52, 133.87, 133.05, 132.95, 131.72, 129.29, 129.14, 127.70, 122.84, 121.53, 113.36, 67.06 ppm; MS (EI) m/z 306 (M^+); Anal. Calcd for $C_{16}H_{12}O_2Cl_2$: C, 62.56; H, 3.94. Found: C, 62.54; H, 3.88. Compound **26**: yield, 27%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.52 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 16.0 Hz, 1H), 7.72 (d, J = 1.2 Hz, 1H), 7.35–7.60 (m, 5H), 7.08 (dd, J = 7.5, 7.5 Hz, 1H), 6.73 (dd, J = 16.0, 7.8 Hz, 1H), 5.34 (s, 2H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ 194.92, 157.35, 147.65, 136.32, 133.18, 132.00, 131.45, 129.74, 129.41, 129.12, 123.14, 121.94, 113.83,66.11 ppm; MS (EI) m/z 306 (M^+); Anal. Calcd for $C_{16}H_{12}O_2Cl_2$: C, 62.56; H, 3.94. Found: C, 61.22; H, 4.02. Compound **28**: yield, 79%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 10.30 (s, 1H), 7.26–7.38 (m, 4H), 7.25 (d, J = 2.8Hz, 1H), 7.15 (d, J = 2.8Hz, 1H), 5.23 (s, 2H), 3.72 (s, 3H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ 189.14, 155.13, 153.78, 134.00, 132.87, 130.31, 129.67, 127.64, 125.36, 123.24, 116.53, 110.57, 68.69, 55.75 ppm; MS (EI) m/z 276(M^+); Anal. Calcd for $C_{15}H_{13}O_3Cl$: C, 65.11; H, 4.74. Found: C, 64.99; H, 5.02. Compound **29**: yield, 73%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 10.37 (s, 1H), 7.52 (s, 1H), 7.35–7.41 (m, 3H), 7.18 (m, 3H), 5.17 (s, 2H), 3.17 (s, 3H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ 188.91, 155.03, 153.63, 139.33, 133.50, 130.49, 128.04, 127.40, 126.15, 125.15, 122.96, 115.91, 110.65, 69.74, 55.60 ppm; MS (EI) m/z 276(M^+); Anal. Calcd for $C_{15}H_{13}O_3Cl$: C, 65.11; H, 4.74. Found: C, 65.32; H, 4.74. Compound **30**: yield, 63%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 10.36, (s, 1H), 7.39–7.51 (m, 4H), 7.16–7.21 (m, 3H), 5.19 (s, 2H), 3.72 (s, 3H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ 188.79, 154.89, 153.38, 135.62, 132.54, 129.37, 128.45, 124.94, 122.88, 115.98, 110.30, 69.63, 55.47 ppm; MS (EI) m/z 276 (M^+); Anal. Calcd for $C_{15}H_{13}O_3Cl$: C, 65.11; H, 4.74. Found: C, 65.21; H, 4.69. Compound **31**: yield, 35%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.64 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 16.0 Hz, 1H), 7.31–7.48 (m, 6H), 7.13 (d, J = 9.1 Hz, 1H), 7.01 (dd, J = 9.1, 3.0 Hz, 1H), 6.90 (dd, J = 16.0, 7.8 Hz, 1H), 5.16 (s, 2H), 3.74 (s, 3H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ 194.89, 153.39, 151.30, 147.47, 136.81, 129.24, 128.52, 127.94, 127.66, 123.43, 118.83, 114.93, 112.97, 70.41, 55.59 ppm; MS (EI) m/z 268 (M^+); Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.01; H, 6.11. Compound **32**: yield, 55%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.62 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 16.0 Hz, 1H), 7.35–7.61 (m, 4H), 7.31 (d, J = 3.0 Hz, 1H), 7.16 (d, J = 9.1 Hz, 1H), 7.03 (dd, J = 9.1, 3.0 Hz, 1H), 6.88 (dd, J = 16.0, 7.8 Hz, 1H), 5.21 (s, 2H), 3.75 (s, 3H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ 194.73, 153.63, 151.02, 147.20, 134.01, 132.73, 130.284, 129.99, 129.46, 129.23, 127.40, 123.65, 118.83, 115.04, 112.81, 68.26, 55.57 ppm; MS (EI) m/z 276 (M^+); Anal. Calcd for $C_{17}H_{15}O_3Cl$: C, 67.44; H, 4.99. Found: C, 66.99; H, 5.01. Compound **33**: yield, 39%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.65 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 16.0 Hz, 1H), 7.52 (s, 1H), 7.31–7.44 (m, 3H),7.31 (d, J = 2.7 Hz, 1H), 7.12 (d, J = 9.1 Hz, 1H), 7.03 (dd, J = 9.1, 2.7 Hz, 1H), 6.89 (dd, J = 16.0, 7.8 Hz, 1H), 5.19 (s, 2H), 3.74 (s, 3H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ 194.95, 153.54, 151.00, 147.38, 139.44, 133.18, 130.51, 129.33, 127.92, 127.44, 126.27, 123.53, 118.86, 114.97, 112.93, 69.51, 55.61 ppm; MS (EI) m/z 302 (M^+); Anal. Calcd for$C_{17}H_{15}O_3Cl$: C, 67.44; H, 4.99. Found: C, 66.99; H, 5.01. Compound **34**: yield, 32%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.60 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 16.0 Hz, 1H), 7.42–7.52 (m, 4H), 7.31 (d, J = 2.9 Hz, 1H), 7.13 (d, J = 9.1 Hz, 1H), 7.02 (dd, J = 9.1, 2.9 Hz, 1H), 6.88 (dd, J = 16.0, 7.8 Hz, 1H), 5.18 (s, 2H), 3.74 (s, 3H) ppm; ^{13}C NMR (50 MHz, DMSO-d_6):δ 194.93, 153.50, 151.08, 147.36, 135.88, 132.55, 129.57, 129.28, 128.54, 123.49, 118.85, 114.96, 112.93, 69.58, 55.61 ppm; MS (EI) m/z 302 (M^+); Anal. Calcd for-$C_{17}H_{15}O_3Cl$: C, 67.44; H, 4.99. Found: C, 67.32; H, 5.02.

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