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Synthesis and anti-inflammatory activity of 2-aryloxy methyl oxazolines

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ABSTRACT

A series of potential biologically active 2-aryloxy methyl oxazolines **3a–n** have been synthesized from substituted hydroxybenzenes **1a–n** with good chemical yield. The compounds **3a–n** were screened for their anti-inflammatory, ulcerogenic, cyclooxygenase activities and also for their acute toxicity. The potency of the compounds was compared with that of the standard drugs, aspirin and phenyl butazone. The outcome indicates that compounds **3b** (48.2%), **3h** (48.5%) and **3l** (46.5%) offered significant anti-inflammatory activity with low ulcerogenic activity than the standard drugs.

Today design and study of new molecules potentially useful in the control of pain and particularly in the management of oncological pain is very important target. It is well known that the mechanism of pain transmission is very complex and involves numerous neuromodulators of pain response.[1] Inflammatory responses are considered to be mediated in part by the prostaglandins (PGs) derived from arachidonic acid by the action of prostaglandin H synthase, which is also referred as cyclooxygenase (COX).[2,3] Recent studies have shown that COX exists in two isoforms COX-1 and COX-2. Both COX are constitutively expressed in most tissues, but COX-2, in contrast to COX-1, is the mitogen inducible isoform. The inducing stimuli for COX-2 include pro-inflammatory cytokines and growth factors, implying a role for COX-2 in both inflammation and control of cell growth.[4–6] COX isoforms are almost identical in structure but have important differences in substrate and inhibitor selectivity and in their intracellular locations.[7] Non-steroidal anti-inflammatory drugs (NSAIDs) are therapeutic agents useful in the treatment of inflammation, pain and pyresis although they exhibit an undesirable gastrotoxicity profile.[8,9]

Oxazolines[10,11] are known as important heterocyclic compounds and have been investigated widely for pharmaceutical uses.[12] The efficiency of oxazoline analogues as chemotherapeutic agent especially as analgesic[13] and anti-inflammatory[14,15] agent is well documented. Besides, additional functionalities for targeting can readily be introduced into 2-oxazolines via functional monomer units, these compounds fulfil fundamental requirements for an application as carrier molecules in radionuclide therapy.[16] Recent studies have shown that highly active sugar oxazolines act as donor substrates for transglycosylation and exhibit potent anti-HIV activity.[17] Oxazoline analogues have been shown to induce cell growth inhibition, apoptosis, and microtubule disruption without alkylating beta-tubulin.[18] And polyoxazoline-based polymers have shown biological and biomedical application contexts which include nanoscalar systems such as membranes and nanoparticles, drug and gene delivery applications, as well as stimuli-responsive systems.[19] In addition to pharmaceutical uses it also possesses synthetic uses, for example it can catalyze the copper-catalyzed addition of indoles to benzylidene malonates up to 99%.[20] Nevertheless, substituted 2-oxazolines are found in several families of bioactive natural products and can be prepared in an efficient and general one-pot condensation.[21] For instance, new methodology for the synthesis of various substituted 2-oxazolines using aldehydes, amino alcohols, and *N*-bromosuccinimide as an oxidizing agent is reported.[22] Phenoxy acetic acid analogues, precursor of title compounds also exhibit anti-inflammatory activity.[23] Kunsch et al.[24] have investigated anti-inflammatory and anti-rheumatic activity of phenoxy acetic acid analogues and provided further support of inhibition of redox-sensitive inflammatory gene expression which is an attractive approach for the treatment of chronic inflammatory diseases,

In continuation of our[25] ongoing program to develop environmentally benign microwave irradiation in chemical reaction enhancement and the initial reports on microwave irradiation[26]

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has inspired us to synthesize some newer oxazoline analogues using microwave technique since these systems possess well documented anti-inflammatory activity.

The synthetic sequence is outlined in Scheme 1. A mixture of **1a–n**, chloro acetic acid in acetone and anhydrous potassium carbonate was refluxed for 8 h, cooled, and the solvent was removed under reduced pressure. The residual mass was triturated with ice water to remove potassium carbonate, extracted with ether and the ether layer was washed with 10% sodium hydroxide solution followed by distilled water. The ether layer was dried over anhydrous sodium sulfate and evaporated to dryness to get crude solid, which on recrystallization with ethanol gave pure substituted aryloxy ethanoic acids (**2a–n**).

A mixture of **2a–n** and ethanolamine was subjected to microwave irradiation operating at its 20% power for 5–10 min. The reaction mixture was extracted into ether, washed with distilled water and dried over anhydrous sodium sulfate. After evaporation of ether layer, the crude solid was recrystallized with ethanol to afford, 2-aryloxy methyl oxazolines (**3a–n**). The compounds **2a–n**[27] and **3a–n**[28] were characterized by IR, ^{1}H NMR and mass spectrophotometer.

All the animal experiments with Albino rats were carried out at Farooqia College of Pharmacy, Mysore, and permission for conducting these animal experiments was obtained from institutional Animals Ethics Committee (1848/06–07).

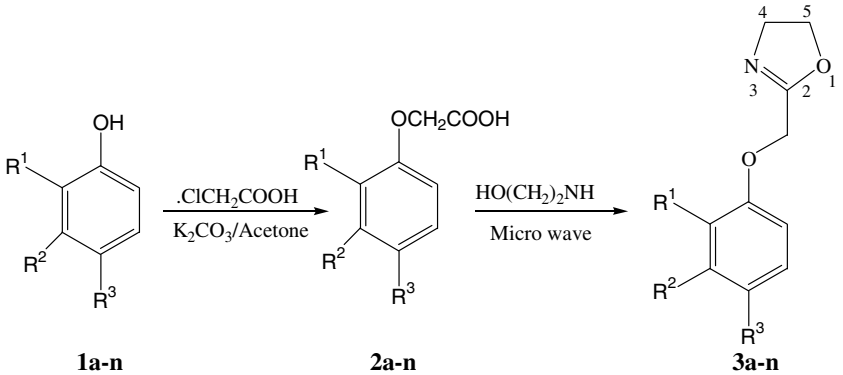
Anti-inflammatory activity. Anti-inflammatory activity was performed by paw oedema inhibition test adopting Winter et al., method.[29] Groups of five rats (body weight 200–230 g) were given a dose of a test compound. After 30 min, 0.2 ml of 1% carrageenan suspension in 0.9% sodium chloride solution was injected subcutaneously, into planter aponeurosis of the hind paw and the paw volume was measured by a water plethysmometer socrel and then measured again after a time span of 3 h. The mean increase of paw volume at each time interval was compared with that of control group (five rats treated with carrageenan, but not with test compounds) at the same time intervals. The percentage inhibition values were calculated using the formula:

% inhibition = $(1 - v_t/v_c) \times 100$, where v_t and v_c are the mean relative changes in the volume of paw oedema in the test compounds and control, respectively.

Ulcerogenic activity. Groups of 10 rats (body weight 200–230 g), fasted for 24 h were treated with an oral dose of test compounds, except control group. All animals were sacrificed 5 h after the completion of dosing. With the aid of a microscope the stomach and small intestine of the rats were examined to find incidence of hyperemia, shedding of epithelium, petechial, frank hemorrhages and erosion or discrete ulceration with or without perforation. The presence of any of these criteria was considered to be an evidence of ulcerogenic activity.[30]

Acute toxicity study. ALD_{50} of the compounds was determined in albino rats (body weight 200–230 g). The test compounds were injected intra peritoneally at different dose levels in groups of 10 animals. After 24 h of drug administration, percent mortality in each group was observed from the data obtained ALD_{50} was calculated by adopting previous method.[31]

Cyclooxygenase activity. The in vitro test on microsomal fraction of mucosal preparation of rabbit distal colon was carried out in order to search out the plausible mechanism of the compounds. By adopting previous procedure[32] the preparation was carried out. About 2–3 g of stripped, colonic mucosa was minced and homogenized in 3 volumes of tris buffer 0.1 M, pH 8.0, and the homogenized was centrifuged. The precipitate was suspended in tris buffer 0.1 M, pH 8.0, and recentrifuged. For enzyme assay cyclooxygenase activity, the microsomal pellet was used immediately. By measuring the rate of conversion of arachidonic acid to PGE_2, cyclooxygenase activity was assayed. About 50 ml of microsomal fractions was incubated with test agents for 10 min at 37 °C in 30 μl Tris–HCl, pH 8.0, containing 2 mM reduced glutathione, 5 mM L-tryptophan, 1 μM hematin. The substrate 20 μM arachidonic acid with tracer amount of [1-^{14}C] arachidonic acid was then added and the reaction proceeded for 5 min at 37 °C. The reaction was stopped by addition of 0.2 ml of ether/methanol/citric acid 0.2 M (30:4:1 v/v), which was precooled at −25 °C PGE_2, was extracted twice into the same mixture. The solvent was removed under nitrogen stream and radiolabelled arachidonic acid was separated and from this radiolabelled PGE_3 was separated by HPLC with 2 nmol unlabelled PGE_2as an interval standard. PG chromatographic profile was obtained by isocratic elution with 150 mM orthophosphoric acid in water, pH 3.5, containing 30% acetonitrile, a flow rate of 1 ml/min monitoring the UV absorption at 214 nm. Radioactivity that co-eluted with authentic PGE_2 was quantified by liquid scintillation spectrometry. Test samples were compared to paired control incubations. The percentage of inhibition was calculated as follows.



1a-n **2a-n** **3a-n**

a: R_1=R_2=H, R_3=OCH_3 b: R_1=R_2=H, R_3=Cl
c: R_1=Br, R_2=R_3=H d: R_1= CH_3, R_2=R_3=H
e: R_1=Cl, R_2=R_3=H f:: R_1=H, R_2=CH_3, R_3=Cl
g: R_1=R_3=H, R_2=CH_3 h: R_1=R_2=H, R_3=Br
i: R_1=R_2=H, R_3=F j: R_1=NO_2, R_2= R_3=H
k: R_1=R_2=H, R_3=NO_2 l: R_1=R_3=CH_3, R_3=H
m: R_1=F, R_2=R_3=H n: R_1=R_3=H, R_2=NO_2

Scheme 1.

cpm control − cpm test/cpm control × 100

The characteristic feature of the title compounds is the presence of oxazoline ring. All the compounds **3a–n** have shown good anti-inflammatory activity in the range 22.2–48.5% at a dose of 40 mg/kg po.

Among **3a–n**, the compound **3h** with a bromo group at para position in phenoxy moiety elicited maximum inhibition of oedema (48.5%), whereas compound **3e** with a chloro group at ortho position in phenoxy moiety elicited minimum inhibition of oedema (22.2%). Compound **3b** with chloro group at para position in phenoxy moiety has shown second highest anti-inflammatory activity (48.2%). Besides compounds **3g** (44.6%) with a methyl group at meta position, **3f** (45.4%) with a methyl group at meta and a chloro group at para position and **3l** (46.5%), with two methyl group at ortho and para position in phenoxy moiety have exhibited nearest anti-inflammatory activity. Compounds **3i** with a fluoro group at para position, **3k** with a nitro group at para position, **3m** a fluoro group at ortho position, **3a** with a methoxy group at para position and **3j**, with a nitro group at ortho position, in phenoxy moiety has elicited oedema inhibition in the range 30.2–35.5%. The remaining compounds **3c** with a bromo group at ortho position, **3n** a nitro group at meta position and **3d**, with a methyl group at ortho position in phenoxy moiety have exhibited oedema inhibition in the range 29.1–29.5%.

Compounds **3h**, **3b** and **3l** were studied in detail at three graded doses and have shown dose dependent activity. Anti-inflammatory activity of compounds **3a–n** and their comparison with standard drugs, aspirin and phenylbutazone are given in Table 1.

Table 1
Antiinflammatroy, ulcerogenic, cyclooxygenase and toxicity data of compounds **3a–n**

Compound	Dose (mg/kg po)	Anti-inflammatory activity % oedema inhibition relative to control	Dose (mg/kg po)	Ulcerogenic	Activity	Cyclooxygenase activity assay inhibitory action of some selected compound % inhibition 10 μM	ED_{50} (mg/kg po)	ALD_{50} (mg/kg po)
				% of animal with hyperemia	% of anima with ulcer			
3a	20	16.6	100	50	05	70	77.2	>1000
	40	33.2	200	70	10			
	80	64.1	400	90	15			
3b	20	30.3	100	30	10	ni	51.2	>1000
	40	48.2	200	60	20			
	80	94.1	400	90	12			
3c	20	20.1	100	70	10	40	62.5	>1000
	40	29.1	200	90	20			
	80	62.8	400	100	40			
3d	20	3.1	100	40	10	20	78.3	>1000
	40	29.5	200	60	20			
	80	55.3	400	100	40			
3e	20	13.7	100	20	40	ni	77.5	>1000
	40	22.2	200	40	30			
	80	45.5	400	60	80			
3f	20	22.2	100	50	20	87	60.2	>1000
	40	45.4	200	70	30			
	80	77.1	400	100	40			
3g	20	16.6	100	50	15	70	76.2	>1000
	40	44.6	200	70	20			
	80	64.1	400	90	25			
3h	20	35.5	100	60	05	60	65.5	>1000
	40	48.5	200	80	10			
	80	60.1	400	100	15			
3i	20	18.5	100	25	50	ni	75.5	>1000
	40	30.2	200	40	25			
	80	40.5	400	50	75			
3j	20	20.5	100	30	20	30	70.1	>1000
	40	35.5	200	55	25			
	80	50.5	400	90	45			
3k	20	29.2	100	50	10	85	60.5	>1000
	40	30.4	200	70	15			
	80	77.1	400	100	20			
3l	20	31.4	100	25	15	ni	57.3	>1000
	40	46.5	200	50	25			
	80	85.5	400	75	18			
3m	20	20.6	100	40	10	65	76.2	>1000
	40	30.5	200	60	15			
	80	60.1	400	80	20			
3n	20	15.5	100	20	45	ni	75.5	>1000
	40	29.4	200	35	30			
	80	46.5	400	55	80			
Aspirin	20	30.4	100	30	80	65	98.3	—
	40	35.5	200	60	90			
	80	59.6	400	90	90			
Phenyl butazone	20	31.3	100	30	30	60	—	—
	40	35.5	200	60	60			
	80	57.2	400	90	90			
Control	20	—	30	—	—	ni	—	—
	40		60					
	80		90					

ni[a], no inhibition.

Ulcerogenic activity. Compounds **3a–n** exhibited low ulcer production activity compared to standard drug, aspirin and phenylbutazone (10–30%) at 200 mg/kg po. Compounds **3a** and **3h** with a methoxy and a bromo group, respectively, at para position in phenoxy moiety have shown low ulcer production activity at 200 mg/kg po. Compounds **3e** with ortho chloro group, **3f** with meta methyl and para chloro groups and **3n** with meta nitro group in phenoxy moiety elicited maximum ulcer production activity.

Cyclooxygenase activity. Compounds **3a**, **3c**, **3d**, **3f**, **3g**, **3h**, **3j**, **3k** and **3m** showed good cyclooxygenase activity indicating that these compounds reduce inflammatory response by inhibition of Prostaglandins. The other compounds which did not inhibit the cyclooxygenase activity, therefore, seems to act through some other mechanism rather than inhibiting prostaglandin synthesis.

ALD50 studies. The toxicity study of these compounds indicates their good safety margin.

From the result of pharmacological activity, we can conclude that integration of oxazoline ring into the phenoxy moiety is fruitful as the compounds **3h** and **3b** were found to show potent anti-inflammatory activity. In addition compound **3h** also show decreased ulcer production activity. Compounds **3b**, **3e**, **3i**, **3l** and **3n** were found to have no suppressive effect on cyclooxygenase, which is the prime mechanism of anti-inflammatory activity.

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27. **2a**: Mp 140–142 °C; IR (Nujol): 1738 (acid C=O), 3470–3575 cm^{-1} (acid OH); ^1H NMR ($CDCl_3$): δ 3.8 (s, 3H, OCH_3), 4.88 (s, 2H, OCH_2), 6.7–7.1 (m, 4H, Ar–H), 9.1 (s, 1H, COOH, D_2O exchangeable); EI–MS: *m/z* 182 (M^+, 60), 138 (100), 123 (70), 107 (21). Anal. Calcd for $C_9H_{10}O_4$(182): C, 59.34; H, 5.53. Found: C, 59.25; H, 5.42%. **2b**: Mp 137–139 °C; IR (Nujol): 1730 (acid C=O), 3400–3500 cm^{-1} (acid OH); ^1H NMR ($CDCl_3$): δ 4.46 (s, 2H, OCH_2), 6.65–7.05 (m, 4H, Ar–H), 9.5 (s, 1H, COOH, D_2O exchangeable); EI–MS: *m/z* 186.5 (M^+, 60), 142.5 (100), 127.5 (71), 111.5 (18). Anal. Calcd for $C_8H_7ClO_3$ (186.5): C, 51.50; H, 3.78; Cl, 19.00. Found: C, 51.33; H, 3.61; Cl, 19.15%. **2c**: Mp 147–149 °C; IR (Nujol): 1735 (acid C=O), 3410–3510 cm^{-1} (acid OH); ^1H NMR ($CDCl_3$): δ 4.45 (s, 2H, OCH_2), 7.1–7.6 (m, 4H, Ar–H), 9.4 (s, 1H, COOH, D_2O exchangeable); EI–MS: *m/z* 231 (M^+, 58), 233 (M^+, 53), 187 (100), 189 (98), 172 (68), 174, (66), 156 (20), 158 (18). Anal. Calcd for $C_8H_7BrO_3$ (231): C, 41.59; H, 3.05; Br, 34.58. Found: C, 41.51; H, 3.17; Br, 34.50%. **2d**: Mp 155–157 °C; IR (Nujol): 1733 (acid C=O), 3450–3540 cm^{-1} (acid OH); ^1H NMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 4.44 (s, 2H, OCH_2), 6.9–7.55 (m, 4H, Ar–H), 9.2 (s, 1H, COOH, D_2O exchangeable); EI–MS: *m/z* 166 (M^+, 58), 122 (100), 107 (69), 91 (16). Anal. Calcd for $C_9H_{10}O_3$ (166): C, 65.05; H, 6.07. Found: C, 65.15; H, 6.16%. **2e**: Mp 151–153 °C; IR (Nujol): 1735 (acid C=O), 3410–3510 cm^{-1} (acid OH); ^1H NMR ($CDCl_3$): δ 4.42 (s, 2H, OCH_2), 6.8–7.6 (m, 4H, Ar–H), 9.3 (s, 1H, COOH, D_2O exchangeable); EI–MS: *m/z* 186.5 (M^+, 59), 142.5 (100), 127.5 (70), 111.5 (17). Anal. Calcd for $C_8H_7ClO_3$ (186.5): C, 51.50; H, 3.78; Cl, 19.00. Found: C, 51.58; H, 3.58; Cl, 19.18%. **2f**: Mp 158–160 °C; IR (Nujol): 1750 (acid C=O), 3430–3510 cm^{-1} (acid OH); ^1H NMR ($CDCl_3$): δ 2.5 (s, 3H, CH_3), 4.21 (s, 2H, OCH_2), 6.8–7.5 (m, 3H, Ar–H), 9.1 (s, 1H, COOH, D_2O exchangeable); EI–MS: *m/z* 200.5 (M^+, 59), 141.5 (100), 156.5 (68), 125.5 (15). Anal. Calcd for $C_9H_9ClO_3$ (200.5): C, 53.88; H, 4.52; Cl, 17.67. Found: C, 53.72; H, 4.42; Cl, 17.53%. **2g**: Mp 135–137 °C; IR (Nujol): 1715 (acid C=O), 3420–3530 cm^{-1} (acid OH); ^1H NMR ($CDCl_3$): δ 2.25 (s, 3H, CH_3), 4.35 (s, 2H, OCH_2), 6.95–7.6 (m, 4H, Ar–H), 9.3 (s, 1H, COOH, D_2O exchangeable); EI–MS: *m/z* 166 (M^+, 59), 122 (100), 107 (69), 91 (17). Anal. Calcd for $C_9H_{10}O_3$ (166): C, 65.05; H, 6.07. Found: C, 65.20; H, 6.25%. **2h**: Mp 141–143 °C; IR (Nujol): 1740 (acid C=O), 3420–3520 cm^{-1} (acid OH); ^1H NMR ($CDCl_3$): δ 4.3 (s, 2H, OCH_2), 6.7–6.9–7.3 (m, 4H, Ar–H), 9.5 (s, 1H, COOH, D_2O exchangeable); EI–MS: *m/z* 231 (M^+, 57), 233 (M^+, 52), 187 (100), 189 (98), 172 (67), 174, (66), 156 (19), 158 (18). Anal. Calcd for $C_8H_7BrO_3$ (231): C, 41.59; H, 3.05; Br, 34.58. Found: C, 41.14; H, 3.15; Br, 34.49%. **2i**: Mp 150–152 °C; IR (Nujol): 1755 (acid C=O), 3450–3540 cm^{-1} (acid OH); ^1H NMR ($CDCl_3$): δ 4.21 (s, 2H, OCH_2), 6.9 (m, 4H, Ar–H), 9.35 (s, 1H, COOH, D_2O exchangeable); EI–MS: *m/z* 170 (M^+, 60), 126 (100), 111 (67), 98 (19). Anal. Calcd for $C_8H_7FO_3$ (170): C, 56.14; H, 4.15; F, 11.17. Found: C, 56.32; H, 4.22; F, 11.23%. **2j**: Mp 125–127 °C; IR (Nujol): 1725 (acid C=O), 3435–3565 cm^{-1} (acid OH); ^1H NMR ($CDCl_3$): δ 4.15 (s, 2H, OCH_2), 6.9–7.5 (m, 4H, Ar–H), 9.35 (s, 1H, COOH, D_2O exchangeable); EI–MS: *m/z* 197 (M^+, 57), 153 (100), 138 (65), 122 (14). Anal. Calcd for $C_8H_7NO_5$ (197): C, 14.74; H, 3.58; N, 7.10. Found: C, 14.65; H, 3.45; N, 7.22%. **2k**: Mp 149–151 °C; IR (Nujol): 1745 (acid C=O), 3465–3560 cm^{-1} (acid OH); ^1H NMR ($CDCl_3$): δ 4.2 (s, 2H, OCH_2), 6.8–7.2 (m, 4H, Ar–H),, 9.4 (s, 1H, COOH, D_2O exchangeable); EI–MS: *m/z* 197 (M^+, 58), 153 (100), 138 (66), 122 (15). Anal. Calcd for $C_8H_7NO_5$ (197): C, 14.74; H, 3.58; N, 7.10. Found: C, 14.55; H, 3.42; N, 7.25%. **2l**: Mp 163–165 °C; IR (Nujol): 1743 (acid C=O), 3465–3550 cm^{-1} (acid OH); ^1H NMR ($CDCl_3$): δ 2.2 (s, 6H, $2CH_3$), 4.1 (s, 2H, OCH_2), 6.9–7.6 (m, 3H, Ar–H), 9.25 (s, 1H, COOH, D_2O exchangeable); EI–MS: *m/z* 180 (M^+, 59), 136 (100), 120 (68), 105 (17). Anal. Calcd for $C_{10}H_{12}O_3$ (180): C, 66.65; H, 6.71. Found: C, 66.73; H, 6.79%. **2m**: Mp 129–131 °C; IR (Nujol): 1725 (acid C=O), 3450–3545 cm^{-1} (acid OH); ^1H NMR ($CDCl_3$): δ 4.2 (s, 2H, OCH_2), 6.8–7.4 (m, 4H, Ar–H), 9.35 (s, 1H, COOH, D_2O exchangeable); EI–MS: *m/z* 170 (M^+, 60), 126 (100), 111 (68), 98 (18). Anal. Calcd for $C_8H_7FO_3$ (170): C, 56.14; H, 4.15; F, 11.17. Found: C, 56.37; H, 4.25; F, 11.25%. **2n**: Mp 168–170 °C; IR (Nujol): 1750 (acid C=O), 3465–3565 cm^{-1} (acid OH); ^1H NMR ($CDCl_3$): δ 4.32 (s, 2H, OCH_2), 6.9–7.55 (m, 4H, Ar–H), 9.42 (s, 1H, COOH, D_2O exchangeable); EI–MS: *m/z* 197 (M^+, 56), 153 (100), 138 (63), 122 (13). Anal. Calcd for $C_8H_7NO_5$ (197): C, 14.74; H, 3.58; N, 7.10. Found: C, 14.61; H, 3.47; N, 7.25%.
28. **3a**: Mp 120–122 °C; IR (Nujol): 1670 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 3.4 (t, J = 7 Hz, 2H, NCH_2), 3.78 (s, 3H, OCH_3), 4.35 (t, J = 7 Hz, 2H, OCH_2), 4.68 (s, 2H, OCH_2), 6.78–7.4 (m, 4H, Ar–H); EI–MS: *m/z* 207 (M^+, 72), 179 (52), 163 (35), 123 (100), 107 (25). Anal. Calcd for $C_{11}H_{13}NO_3$ (207): C, 63.76; H, 6.32; N, 6.76. Found C, 63.61; H, 6.22; N, 6.64%. **3b**: Mp 130–132 °C; IR (Nujol): 1680 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 3.45 (t, J = 7 Hz, 2H, NCH_2), 4.41 (t, J = 7 Hz, 2H, OCH_2), 4.7 (s, 2H, OCH_2), 6.9–7.4 (m, 4H, Ar–H); EI–MS: *m/z* 211.5 (M^+, 71), 183.5 (52), 167.5 (34), 127.5 (100), 111.5 (24). Anal. Calcd for $C_{10}H_{10}ClNO_2$ (211.5): C, 56.75; H, 4.76; Cl, 16.75; N, 6.62. Found: C, 56.81; H, 4.81; Cl, 16.85; N, 6.71%. **3c**: Mp 98–100 °C; IR (Nujol): 1690 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 3.5 (t, J = 7 Hz, 2H, NCH_2), 4.45 (t, J = 7 Hz, 2H, OCH_2), 4.72 (s, 2H, OCH_2), 6.9–7.5 (m, 7H, Ar–H); EI–MS: *m/z* 256 (M^+, 70), 258 (M^+, 68), 345 (55), 228 (52), 230 (50), 212 (34), 214 (32), 172 (100), 174 (97), 156 (26), 158 (25). Anal. Calcd for $C_{10}H_{10}BrNO_2$ (256): C, 46.90; H, 3.94; Br, 31.20; N, 5.47. Found: C, 46.83; H, 3.81; Br, 31.11; N, 5.39%. **3d**: Mp 104–106 °C; IR (Nujol): 1675 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.23 (s, 3H, CH_3), 3.4 (t, J = 7 Hz, 2H, NCH_2), 4.4 (t, J = 7 Hz, 2H, OCH_2), 4.65 (s, 2H, OCH_2), 6.8–7.5 (m, 4H, Ar–H); EI–MS: *m/z* 191 (M^+, 70), 163 (52), 147 (36), 107 (100), 91 (27). Anal. Calcd for $C_{11}H_{13}NO_2$ (191): C, 69.09; H, 6.85; N, 7.32. Found: C, 69.15; H, 6.93; N, 7.41%. **3e**: Mp 134–136 °C; IR (Nujol): 1680 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 3.45 (t, J = 7 Hz, 2H, NCH_2), 4.41 (t, J = 7 Hz, 2H, OCH_2), 4.7 (s, 2H, OCH_2), 6.9–7.5 (m, 4H, Ar–H), EI–MS: *m/z* 211.5 (M^+, 70), 183.5 (51), 167.5 (33), 127.5 (100), 111.5 (23). Anal. Calcd for $C_{10}H_{10}ClNO_2$ (211.5): C, 56.75; H, 4.76; Cl, 16.75; N, 6.62. Found: C, 56.77; H, 4.76; Cl, 16.79; N, 6.72%. **3f**: Mp 138–140 °C; IR (Nujol): 1680 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.25 (s, 3H, CH_3), 3.45 (t, J = 7 Hz, 2H, NCH_2), 4.41 (t, J = 7 Hz, 2H, OCH_2), 4.7 (s, 2H, OCH_2), 6.9–7.5 (m, 3H, Ar–H), EI–MS: *m/z* 225.5 (M^+, 69), 197.5 (51), 181.5 (33), 141.5 (100), 125.5 (22). Anal. Calcd for $C_{11}H_{12}ClNO_2$ (225.5): C, 58.54; H, 5.36; Cl, 15.71; N, 6.21. Found: C, 58.41; H, 5.26; Cl, 15.66; N, 6.15%. **3g**: Mp 108–110 °C; IR (Nujol): 1670 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.25 (s, 3H, CH_3), 3.45 (t, J = 7 Hz, 2H, NCH_2), 4.45 (t, J = 7 Hz, 2H, OCH_2), 4.6 (s, 2H, OCH_2), 6.9–7.6 (m, 4H, Ar–H); EI–MS: *m/z* 191 (M^+, 69), 163 (51), 147 (35),

107 (100), 91 (25). Anal. Calcd for $C_{11}H_{13}NO_2$ (191): C, 69.09; H, 6.85; N, 7.32. Found: C, 69.19; H, 6.96; N, 7.45%. **3h**: Mp 91–93 °C; IR (Nujol): 1670 cm^{-1} (C═N); ^1H NMR ($CDCl_3$): δ 3.4 (t, J = 7 Hz, 2H, NCH_2), 4.3 (t, J = 7 Hz, 2H, OCH_2), 4.65 (s, 2H, OCH_2), 6.8–7.3 (m, 4H, Ar–H); EI–MS: m/z 256 (M^+, 69), 258 (M^+, 67), 345 (54), 228 (51), 230 (50), 212 (33), 214 (31), 172 (100), 174 (98), 156 (25), 158 (23). Anal. Calcd for $C_{10}H_{10}BrNO_2$ (256): C, 46.90; H, 3.94; Br, 31.20; N, 5.47. Found: C, 46.80; H, 3.82; Br, 31.15; N, 5.36%. **3i**: Mp 126–128 °C; IR (Nujol): 1675 cm^{-1} (C═N); ^1H NMR ($CDCl_3$): δ 3.5 (t, J = 7 Hz, 2H, NCH_2), 4.5 (t, J = 7 Hz, 2H, OCH_2), 4.8 (s, 2H, OCH_2), 6.9–7.45 (m, 4H, Ar–H), EI–MS: m/z 195 (M^+, 66), 167 (49), 151(31), 111 (100), 95 (20). Anal. Calcd for $C_{10}H_{10}FNO_2$ (195): C, 61.53; H, 5.16; F, 9.73; N, 7.18. Found: C, 61.61; H, 5.26; F, 9.71; N, 7.25%. **3j** Mp 135–137 °C; IR (Nujol): 1675 cm^{-1} (C═N); ^1H NMR ($CDCl_3$): δ 3.6 (t, J = 7 Hz, 2H, NCH_2), 4.55 (t, J = 7 Hz, 2H, OCH_2), 4.75 (s, 2H, OCH_2), 6.9–7.45 (m, 4H, Ar–H); EI–MS: m/z 222 (M^+, 67), 194 (49), 178 (30), 138 (100), 122 (20). Anal. Calcd for $C_{10}H_{10}N_2O_4$ (222): C,54.05; H, 4.54; N, 12.61. Found: C, 54.18; H, 4.63; N, 12.69%. **3k**: Mp 115–117 °C; IR (Nujol): 1680 cm^{-1} (C═N); ^1H NMR ($CDCl_3$): δ 3.45 (t, J = 7 Hz, 2H, NCH_2), 4.75 (t, J = 7 Hz, 2H, OCH_2), 4.85 (s, 2H, OCH_2), 6.85–7.4 (m, 4H, Ar–H); EI–MS: m/z 222 (M^+, 68), 194 (50), 178 (31), 138 (100), 122 (21). Anal. Calcd for $C_{10}H_{10}N_2O_4$ (222): C, 54.05; H, 4.54; N, 12.61. Found: C, 54.19; H, 4.65; N, 12.67%. **3l**: Mp 121–123 °C; IR (Nujol): 1690 cm^{-1} (C═N); ^1H NMR ($CDCl_3$): δ 2.23 (s, 6H, $2CH_3$), 3.35 (t, J = 7 Hz, 2H, NCH_2), 4.45 (t, J = 7 Hz, 2H, OCH_2), 4.7 (s, 2H, OCH_2), 6.8–7.5 (m, 3H, Ar–H); EI–MS: m/z 205 (M^+, 68), 177 (51), 161 (34), 121 (100), 105 (25). Anal. Calcd for $C_{12}H_{15}NO_2$ (205): C, 70.22; H, 7.37; N, 6.82. Found: C, 70.15; H, 7.26; N, 6.77%. **3m**: Mp 129–131 °C; IR (Nujol): 1635 cm^{-1} (C═N); ^1H NMR ($CDCl_3$): δ 3.52 (t, J = 7 Hz, 2H, NCH_2), 4.52 (t, J = 7 Hz, 2H, OCH_2), 4.75 (s, 2H, OCH_2), 6.8–7.45 (m, 4H, Ar–H), EI–MS: m/z 195 (M^+, 67), 167 (14), 151(32), 111 (100), 95 (21). Anal. Calcd for $C_{10}H_{10}FNO_2$ (195): C, 61.53; H, 5.16; F, 9.73; N, 7.18. Found: C, 61.65; H, 5.24; F, 9.73; N, 7.27%. **3n**: Mp 139–141 °C; IR (Nujol): 1625 cm^{-1} (C═N); ^1H NMR ($CDCl_3$): δ 3.4 (t, J = 7 Hz, 2H, NCH_2), 4.5 (t, J = 7 Hz, 2H, OCH_2), 4.7 (s, 2H, OCH_2), 6.8–7.4 (m, 4H, Ar–H), EI–MS: m/z 222 (M^+, 68), 194 (14), 178 (31), 138 (100), 122 (19). Anal. Calcd for $C_{10}H_{10}N_2O_4$ (222): C, 54.05; H, 4.54; N, 12.61. Found: C, 54.19; H, 4.64; N, 12.67%.

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