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Benzophenone-*N*-ethyl piperidine ether analogues—Synthesis and efficacy as anti-inflammatory agent

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ABSTRACT

A sequence of substituted benzophenone-*N*-ethyl piperidine ether analogues has been synthesized and evaluated as orally active anti-inflammatory agents with reduced side effects. The anti-inflammatory and ulcerogenic activities of the compounds were compared with naproxen, indomethacin, and phenylbutazone. These analogues showed an interesting anti-inflammatory activity in carrageenan-induced foot pad edema assay. In the air-pouch test, some of the analogues reduced the total number of leukocytes of the exudate, which indicates inhibition of prostaglandin production. Side effects of the compounds were examined on gastric mucosa, in the liver and stomach. None of the compounds illustrated significant side effects compared with standard drugs like indomethacin and naproxen.

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Inflammation is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants.[1,2] Symptoms of inflammation include pain, swelling, red coloration to the area, and sometimes loss of movement or function.[3] The potent mediators of inflammation are derivatives of arachidonic acid a 20-carbon unsaturated fatty acid produced from membrane phospholipids.[4] The principal pathways of arachidonic acid metabolism are the 5-lipoxygenase pathway, which produce a collection of leukotrienes and cyclooxygenase (COX), the key enzyme required for the conversion of arachidonic acid to prostaglandins.[5] COX was first identified over 20 years ago and drugs that inhibit COX activity have been available to the public for about 100 years.[6] In the past decade, however, more progress has been made in understanding the role of COX enzymes in biology and disease than at any other time in history.[7,8] Pharmacological inhibition of COX can provide relief from the symptoms of inflammation and pain.[9] Two COX isoforms have been identified and are referred to as COX-1 and COX-2.[5] Both COX are constitutively expressed in most tissues, but COX-2, in contrast to COX-1, is the mitogen inducible isoform.[10,11] COX isoforms are almost identical in structure but have important differences in substrate and inhibitor selectivity and in their intracellular locations.[12] COX is the principal target of nonsteroidal anti-inflammatory drugs (NSAIDs) and metabolites of the COX pathway are widely accepted as mediators of the inflammatory response. NSAIDs blocks the formation of prostaglandins and have anti-inflammatory, analgesic, and antipyretic activity.[8]

The proficiency of piperidine analogues as chemotherapeutic agents, in particular anti-inflammatory agents are well documented.[13,14] Scientist has explored anti-proliferative and anti-inflammatory activities of phenylpiperidine analogues which is comparable or slightly inferior to that of standard drug.[15] For instance, piperidine ureas display an unprecedented combination of potency and selectivity for use as potential analgesic and anxiolytic agents.[16] Recently synthesis, anti-inflammatory activity and structure–activity relationship of a series of trialkyl-piperidine analogues were performed.[17]

Benzophenones, the precursor for the synthesis of the title compounds are essential due to their diverse biological and chemical properties. For instance, these analogues possess a high analgesic.[18] efficacy and also endowed with anti-inflammatory property.[7] Several attempts to derive COX-2 selective inhibitors from NSAIDs like benzophenone analogue[8] have been published and are indicated in the treatment of rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis. The literature investigation reveals that no endeavor was proposed toward the designing of benzophenone-*N*-ethyl piperidine ether analogues to verify the importance of title compounds on the pharmacological activity. Based on this information and in our search for new molecules with anti-inflammatory activity,[19,20] it was considered valuable to synthesize benzophenone-*N*-ethyl piperidine ether analogues (**5a–j**) as anti-inflammatory agents as explained below, for a rational study of the structure–activity relationships.

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Chemicals were purchased from Aldrich Chemical Co. TLC was performed on aluminium-backed silica plated with visualization by UV-light. Melting points were determined on a Thomas Hoover capillary melting point apparatus with a digital thermometer. IR spectra were recorded in Nujol on FT-IR Shimadzu 8300 spectrometer and ^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$. Chemical shifts were recorded in parts per million downfield from tetramethylsilane. Mass spectra were obtained with a VG70-70H mass spectrometer and elemental analysis results are within 0.4% of the calculated value.

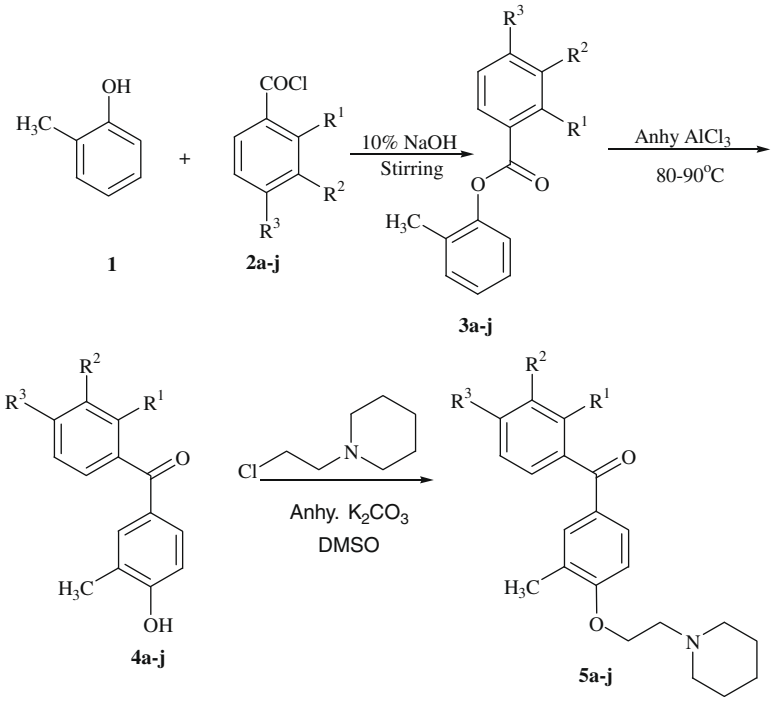
The synthetic sequence is outlined in Scheme 1. To 2-methylphenol (**1**, 13.9 mmol), corresponding benzoyl chlorides (**2a–j**, 13.9 mmol) were added with constant stirring. The reaction mixture was cooled to 0 °C, made alkaline by adding 10% sodium hydroxide solution and stirring was continued for about 1 h. The separated oil was extracted with ether (3 × 20 ml), the organic layer was washed with 10% sodium hydroxide solution (3 × 15 ml) and with distilled water (3 × 30 ml). Finally, the organic layer was dried over anhydrous sodium sulfate and ether was removed to afford substituted 2-methylphenyl benzoates (**3a–j**).

Substituted hydroxy benzophenones (**4a–j**) were synthesized by Fries rearrangement of **3a–j**. A mixture of anhydrous aluminum chloride (6.1 mmol) and **3a**–**j** (4.1 mmol) was heated over oil bath at 80–90 °C for 45 min. At the end of this period the solution was cooled and decomposed by ice-cold water. The residual solid was crushed into powder, dissolved in ether (40 ml) and extracted with 10% sodium hydroxide (3 × 30 ml). The basic aqueous solution was neutralized with 10% hydrochloric acid. The filtered solid was washed with distilled water (3 × 30 ml) and recrystallized from ethanol to afford **4a–j**.

A mixture of **4a–j** (2.06 mmol) and 1-(2-chloroethyl) piperidine hydrochloride (2.06 mmol) in presence of anhydrous potassium carbonate (5.15 mmol) and dimethyl sulfoxide (10 ml) was refluxed for 9 h then cooled. The residual mass was triturated with ice water to remove potassium carbonate and dimethyl sulfoxide and extracted with ethyl acetate (3 × 20 ml). The ethyl acetate layer was washed with saturated sodium chloride solution (3 × 20 ml), 10% sodium hydroxide solution (3 × 20 ml) followed by distilled water (3 × 30 ml) and then dried over anhydrous sodium sulfate. Finally the ether layer was evaporated to dryness to get crude product, which on recrystallization with ethanol gave pasty mass of the title compounds **5b**–**j**. The compounds **3a–j**,[21] **4a**–**j**,[22] and **5a–j**[23] were characterized by IR, ^{1}H NMR, and mass spectrophotometer.

Biological evaluation of compounds: All the animal experiments with Albino mice 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). The animals were housed in groups of six and acclimatized to room conditions for at least 2 days before the experiments, with food and water at libitum. The food was withdrawn on the day before the experiment, but free access to water was allowed. The compounds (100 mg/kg) and the reference NSAIDs, phenylbutazone (100 mg/kg), indomethacin (10 mg/kg), and naproxen (30 mg/kg), were suspended in 0.5% carboxymethylcellulose (CMC) and administered orally by animal feeding needle. The control groups received appropriate volumes of the vehicle (0.5% CMC, oral) only.

Anti-inflammatory activity–carrageenan paw edema test (CPE):[24,25] One hour after oral administration of the compounds, the thickness of right hind paw was measured by a peacok dial



a: R^1=R^2=H, R^3=Br b: R^1=R^3=H, R^2=Cl
c: R^1=CH_3, R^2=R^3=H d: R^1=R^2=H, R^3=F
e: R^1=R^2=H, R^3=CH_3 f: R^1=R^3=Cl. R^2=H
g: R^1=R^2=H, R^3=OCH_3 h: R^1=R^3=H, R^2=CH_3
i: R^1=Br, R^2=R^3=H j: R^1=R^2=R^3=H

Scheme 1.

thickness gauge and 0.1 ml 2% carrageenan was injected subcutaneously into the plantar surface of the right hind paw. After 2 h, the volume of the edema was measured again and the anti-edematic effects of the drugs were estimated in terms of percent inhibition using following equation:

$$\text{Anti-inflammatory activity } (\%) = \left[\frac{(m - m')}{m}\right] \times 100$$

where m and m' indicate the difference in thickness between the first and second measurements of hind paws in control and test groups, respectively.

Air-pouch test:[26–28] The carrageenan powder was dissolved in saline to a concentration of 10 mg/ml. The solution was sterilized and homogenized by placing it in an oven at 90 °C for about 1 h. It was then maintained at 37 °C. Air pouches were formed by subcutaneous (sc) injection of 1 ml of air for 3 days. On the third day, after the initial injection of air, carrageenan solution (1 ml) was injected into the air-pouch to induce inflammation. Compounds were administered orally 1 h before injection of the carrageenan into the pouch. After 4 h, mice were killed by ether exposure and pouches washed thoroughly with 3 ml of phosphate buffer solution (PBS) containing 50 μ/ml heparin. Lavage fluids were centrifuged at 2000 rpm for 15 min at 4 °C and the pellet was resuspended in 1 ml of PBS-heparin. The total number of polymorphonuclear leukocytes (PMNL) infiltration was measured using a Coulter Counter.

Histopathological examination: Mice were sacrificed 4 h after the paw edema experiments and their liver, stomach, and kidneys were removed and put into 10% formalin solution. The sections taken from these specimens were stained with hematoxilen eosine and examined under the light microscope.

The pharmacological results (Table 1) indicate that some of the compounds possess anti-inflammatory properties. In the CPE assay, compounds **5a**, **5b**, **5d**, **5f**, **5g**, and **5i** showed anti-inflammatory activity. The most effective compounds were **5a**, **5d**, and **5f** which have a bromo, chloro, and fluoro, respectively, group at *para* position in benzoyl moiety. Compound **5b** with chloro groups at *meta* position, **5g** with a methoxy group at *para* position and **5i** with a bromo group at *ortho* position, in benzoyl moiety, showed promising activity whereas compounds **5c** with a methyl group at *ortho* position, **5h** with a methyl group *meta* position and **5j** with no substituent in benzoyl moiety showed only weak activity compared to standard. In addition to the synthesis and identification of new anti-inflammatory compounds, it is desirable to search for a new series of compounds with low ulceration potential. Our results show that the newly synthesized compounds reduce leukocytes, which suggests inhibition of PG synthesis. COX-1, is constitutively expressed in most tissues and appears to be relevant for tissue homeostatic functions of PGs, whereas COX-2 is an inducible isozyme and plays a role in many inflammatory reactions.[11] The enzymes are the primary targets of aspirin and other NSAIDs and thus are of major interest in pharmacology, pharmacogenetics, and epidemiology. NSAIDs have several potential pharmacologic effects. However, their anti-inflammatory action depends primarily on their ability to inhibit the COX enzymes.[29] This results in the decreased production of pro-inflammatory PGs. Macrophages is known to produce PGE_2 via the COX-2 dependent pathway in response to pro-inflammatory cytokines. Furthermore, rat peritoneal macrophages have been recently found to have the capacity to metabolize exogenous arachidonic acid to thromboxane via COX-1 and to PGE_2 via COX-2.[30] This observation suggested that there is a preferential, phase-specific correlation between the two COX isoforms and the downstream respective terminal PG synthases.

Previous work has shown that the inflammatory effect of carrageenan is due to an influx of predominantly neutrophilic leukocytes (predominantly PMNL) from blood circulation into the cavity. In addition, leukocyte migration is induced locally in the inflammatory process and leukocytes also intensify inflammation by releasing several inflammatory mediators. The method is used for measuring the edema induced by injection of carrageenan into the pouches in mice back. Air-pouches were highly reactive to inflammatory stimulus. The enhanced inflammatory reactions in the sites correlated with formation of lining tissue, the type of cells, and/or the reactivity of newly formed blood cells.[26,27,31,32] Mean leukocyte numbers per milliliter of exudates for each drug compared with control values obtained from similar group of animals receiving vehicle alone and the degree of inflammatory response produced in the air pouch cavity was assessed by measuring total cell number of the exudates. Compounds **5a**, **5d**, and **5f** reduced total number of leukocytes of the exudates. The reduction of leukocytes suggests inhibition of PG production. Compounds **5a**, **5d**, and **5f** were inhibited PMNL production compared with control and reference compounds 4–4.5 and 1–1.4-fold greater, respectively (Table 1).

The ulcerogenic potential of anti-inflammatory compounds can be demonstrated in animal models using positive (naproxen, idomethacin) and negative (phenylbutazone) controls. Upon microscopic examination, lesions seen in the stomach, kidney and liver tissues are graded according to their severity. The grade of the scale is designed as (+) for mild (++) for moderate and (+++) for severe changes. Stomachs of the mice are thoroughly sectioned and both corpus and antrum are evaluated. Surface epithelium and the lamina propria of the gastric mucosa are all examined. Acute gastritis may exist in an earlier or milder non-erosive form with merely mucosal congestion, edema and histological evidence of inflammation. These earlier changes are known to be transient and completely reversible within few days, but the development of erosions and hemorrhages is more serious and related to an increased risk of major upper gastrointestinal bleeding. In our study, the animals were sacrificed 4 h after ingestion of the drugs. None of the sections displayed the morphology of the ulceration, but the non-erosive form of acute gastritis was observed in various degrees of severity with compounds **5b**, **5c**, **5e**, **5h**, and **5j** (Table 2). Upon microscopic examination of the kidney sections, the morphologic mononuclear cell infiltrations were characteristic for tubulointerstitial nephritis. The presence of some scattered eosinophil leukocytes also provided evidence for the drug effect. Focal areas displaying variable but generally mild degree of tubular regeneration were also present. Acute pyelonephritis should be considered

Table 1
Anti-inflammatory activity of compounds **5a–j**

Compd 100 mg/kg	CPE (% inhibition SE)[a]	PMNL (10^5/cm^3) (n = 6, after 4 h)[b]
Control	–	122.40 4.06
5a	67.51 9.26[c]	31.75 0.75
5b	51.42 3.97[c]	56.26 0.37
5c	35.62 1.21[d]	69.51 0.96
5d	60.60 8.54[c]	32.41 3.14
5e	n.a	n.t
5f	68.70 9.55[c]	30.15 0.77
5g	51.42 3.97[c]	56.26 0.37
5h	15.45 1.67[d]	104.76 1.56
5i	51.41 3.98[c]	56.25 0.38
5j	22.44 3.08[d]	95.25 0.80
Naproxen (30 mg/kg)	66.90 1.70[c]	49.20 1.30
Phenylbutazone (100 mg/kg)	53.28 1.84[c]	53.28 1.71
Indomethacin (10 mg/kg)	32.11 1.39[c]	68.81 1.80

PMNL, polymorphonuclear leucocytes; n.a.: no activity; n.t: not tested.
[a] Results are expressed as their mean values (n = 6).
[b] Mean SEM (n = 6).
[c] $p < 0.01$.
[d] $p < 0.05$.

Table 2
Histopathological examination results of compounds **5a–j**

Compd (100 mg/kg) p.o.	Kidney		Stomach	Liver		
	Edema	Infected cell (MNL)	Gastritis	Fatty change	Acute hepatitis/spotty necrosis	Cholestasis
5a	–	–	–	–	–	–
5b	–	+	–	++	+	–
5c	–	–	–	++	++	++
5d	–	–	–	–	–	–
5e	–	–	–	–	++	–
5f	–	–	–	–	+	–
5g	–	–	+	–	+	–
5h	–	++	++	+	–	–
5i	–	–	+	–	–	–
5j	–	–	++	+	+	+
Indomethacin (10 mg/kg)	++	+	+++	++	++	–
Naproxen (30 mg/kg)	+	+	+	+	+++	–
Phenylbutazone (100 mg/kg)	–	–	–	–	–	–

–, no; +, mild; ++, moderate; +++, severe side effects.

in the differential diagnosis of the tubulointerstitial nephritis, but none of our samples showed interstitial suppurative (inflammation with polymorphonuclear leukocytes) inflammation with microabscesses. Therefore, the renal morphologic findings reflect the effects of the compounds. Liver tissues were also examined thoroughly and the integrity of the basic structure, degree of lobular and portal inflammation and the presence or absence of necrosis, fatty change or cholestasis were evaluated. NSAIDs such as phenylbutazone[33] and naproxen[34] are known to cause acute or chronic hepatitis, confluent or spotty necrosis, cholestatic hepatitis and/or fatty change. This shows the importance of examining the liver tissues to better assess the safety of NSAIDs. In compounds **5b**, **5c**, **5h**, and **5j** (moderate, ++) showed macro and microvesicular fatty change and several scattered mild (+) focal spotty necrosis. Multiple foci of spotty necrosis (moderate ++) was seen with compounds **5c** and **5e**. Cholestatic hepatitis was observed for compounds **5c** and **5j** (Table 2).

In conclusion, a new sequence of benzophenone *N*-ethyl piperidine ether analogues exhibiting anti-inflammatory activity was synthesized. Halo compounds, with a bromo group (**5a**), fluoro group (**5d**), and chloro group (**5f**), at para position showed significant anti-inflammatory profile with low gastric ulceration incidence as compared with similar toxic profiles for reference non NSAIDs in the liver.

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21. *Compound* **3a**: IR (Nujol): 1725 cm^{-1} (ester, C=O); ^1H NMR ($CDCl_3$): δ 2.0 (s, 3H, CH_3), 6.9–7.3 (m, 8H, Ar-H). Anal. Calcd for $C_{14}H_{11}BrO_2$ (291): C, 57.76; H, 3.81; Br, 27.45. Found: C, 57.61; H, 3.89; Br, 27.32. *Compound* **3b**: IR (Nujol): 1718 cm^{-1} (ester, C=O); ^1H NMR ($CDCl_3$): δ 2.1 (s, 3H, CH_3), 6.5–7.3 (m, 8H, Ar-H). Anal. Calcd for $C_{14}H_{11}ClO_2$ (246.5): C, 68.16; H, 4.49; Cl, 14.37. Found: C, 68.22; H, 4.58; Cl, 14.45. *Compound* **3c**: IR (Nujol): 1760 cm^{-1} (ester, C=O); ^1H NMR ($CDCl_3$): δ 2.25 (s, 6H, $2CH_3$), 6.9–7.4 (m, 8H, Ar-H). Anal. Calcd for $C_{15}H_{14}O_2$ (226): C, 79.62; H, 6.24. Found: C, 79.49; H, 6.15. *Compound* **3d**: Yield 27.74 g (92%). IR (Nujol): 1770 cm^{-1} (ester, C=O); ^1H NMR ($CDCl_3$): δ 2.3 (s, 3H, CH_3), 6.95–7.45 (m, 8H, Ar-H). Anal. Calcd for $C_{14}H_{11}FO_2$ (230): C, 73.03; H, 4.82; F, 8.25. Found: C, 73.13; H, 4.75; F, 8.12. *Compound* **3e**: IR (Nujol): 1760 cm^{-1} (ester, C=O); ^1H NMR ($CDCl_3$): δ 2.2–2.5 (d, 6H, $2CH_3$), 6.95–7.43 (m, 8H, Ar-H). Anal. Calcd for $C_{15}H_{14}O_2$ (226): C, 79.62; H, 6.24. Found: C, 79.51; H, 6.16. *Compound* **3f**: IR (Nujol): 1735 cm^{-1} (ester, C=O); ^1H NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3), 6.9–7.5 (m, 7H, Ar-H). Anal. Calcd for $C_{14}H_{10}Cl_2O_2$ (281): C, 59.81; H, 3.59; Cl, 25.22. Found: C, 59.72; H, 3.66; Cl, 25.15. *Compound* **3g**: IR (Nujol): 1750 cm^{-1} (ester, C=O); ^1H NMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 6.8–7.65 (m, 8H, Ar-H). Anal. Calcd for $C_{15}H_{14}O_3$ (242): C, 74.38; H, 5.78. Found: C, 74.34; H, 5.75. *Compound* **3h**: IR (Nujol): 1720 cm^{-1} (ester, C=O); ^1H NMR ($CDCl_3$): δ 2.2–2.4 (d, 6H, $2CH_3$), 6.85–7.5 (m, 8H, Ar-H). Anal. Calcd for $C_{15}H_{14}O_2$ (226): C, 79.62; H, 6.24. Found: C, 79.44; H, 6.10. *Compound* **3i**: IR (Nujol): 1710 cm^{-1} (ester, C=O); ^1H NMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 6.95–7.4 (m, 8H, Ar-H). Anal. Calcd for $C_{14}H_{11}BrO_2$ (291): C, 57.76; H, 3.81; Br, 27.45. Found: C, 57.59; H, 3.81; Br, 27.29. *Compound* **3j**: IR (Nujol): 1765 cm^{-1} (ester, C=O); ^1H NMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 6.75–7.55 (m, 9H, Ar-H). Anal. Calcd for $C_{14}H_{12}O_2$ (212): C, 79.22; H, 5.70. Found: C, 79.05; H, 5.79.
22. *Compound* **4a**: mp 166–168 °C; IR (Nujol): 1640 (C=O), 3515–3630 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 2.1 (s, 3H, CH_3), 6.9–7.4 (m, 7H, Ar-H), 9.0 (br s, 1H, OH); EI-MS: *m*/*z* 290 (M^+, 84), 292 (M^+, 81), 289 (100), 291 (94), 135 (56), 107 (51). Anal. Calcd for $C_{14}H_{11}BrO_2$ (291): C, 57.73; H, 3.78; Br, 27.49. Found: C, 57.67; H, 3.88; Br, 27.39. *Compound* **4b**: mp 158–160 °C; IR (Nujol): 1660 (C=O), 3515–3625 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 6.9–7.35 (m, 7H, Ar-H), 9.3 (br s, 1H, OH); EI-MS: *m*/*z* 246.5 (M^+, 86), 245.5 (100), 135 (57), 107 (52). Anal. Calcd for $C_{14}H_{11}ClO_2$ (246.5): C, 68.15; H, 4.46; Cl, 14.40. Found: C, 68.11; H, 4.42; Cl, 14.36. *Compound* **4c**: mp 156–158 °C; IR (Nujol): 1660 (C=O), 3520–3610 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 2.3 (s, 6H, $2CH_3$), 6.95–7.65 (m, 7H, Ar-H), 9.25 (br s, 1H, OH); EI-MS: *m*/*z* 226 (M^+, 87), 225 (100), 135 (56), 107 (51). Anal. Calcd for $C_{15}H_{14}O_2$ (226): C, 79.62; H, 6.24. Found: C, 79.75; H, 6.38. *Compound* **4d**: mp 130–132 °C; IR (Nujol): 1670 (C=O), 3570–3665 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 2.0 (s, 3H, CH_3), 6.8–7.55 (m, 7H, Ar-H), 9.3 (br s, 1H, OH); EI-MS: *m*/*z* 230 (M^+, 79), 229 (100), 135 (60), 107 (47). Anal. Calcd for $C_{14}H_{11}FO_2$ (230): C, 73.03; H, 4.82; F, 8.25. Found: C, 73.13; H, 4.75; F, 8.32. *Compound* **4e**: mp 160–162 °C; IR (Nujol): 1673 (C=O), 3550–3640 cm^{-1} (OH);^1H NMR ($CDCl_3$): δ 2.2–2.45 (d, 6H, $2CH_3$), 6.95–7.65 (m, 7H, Ar-H), 9.1 (br s, 1H, OH); EI-MS: *m*/*z* 226 (M^+, 88), 225 (100), 135 (55), 107 (50). Anal. Calcd for $C_{15}H_{14}O_2$ (226): C, 79.62; H, 6.24. Found: C, 79.70; H, 6.35. *Compound* **4f**:

mp 128–130 °C; IR (Nujol): 1675 (C=O), 3515–3655 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 6.9–7.5 (m, 7H, Ar-H), 9.1 (br s, 1H, OH); EI-MS: *m/z* 281 (M^+, 80), 280 (100), 135 (57), 107 (51). Anal. Calcd for $C_{14}H_{10}Cl_2O_2$ (281): C, 59.81; H, 3.59; Cl, 25.22. Found: C, 59.73; H, 3.45; Cl, 25.12. *Compound* **4g**: mp 150–152 °C; IR (Nujol): 1665 (C=O), 3520–3640 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 2.3 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 6.8–7.5 (m, 7H, Ar-H), 9.5 (br s, 1H, OH); EI-MS: *m/z* 242 (M^+, 83), 241 (100), 135 (56), 107 (52). Anal. Calcd for $C_{15}H_{14}O_3$ (242): C, 74.38; H, 5.78. Found: C, 74.31; H, 5.71. *Compound* **4h**: mp 168–170 °C; IR (Nujol): 1620 (C=O), 3560–3650 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 2.1–2.4 (d, 6H, $2CH_3$), 6.9–7.6 (m, 7H, Ar-H), 9.0 (br s, 1H, OH); EI-MS: *m/z* 226 (M^+, 85), 225 (100), 135 (53), 107 (50). Anal. Calcd for $C_{15}H_{14}O_2$ (226): C, 79.62; H, 6.24. Found: C, 79.61; H, 6.28. *Compound* **4i**: mp 164–166 °C; IR (Nujol): 1650 (C=O), 3510–3610 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 2.3 (s, 3H, CH_3), 6.8–7.75 (m, 7H, Ar-H), 12.0 (br s, 1H, OH); EI-MS: *m/z* 290 (M^+, 85), 292 (M^+, 80), 289 (100), 291 (95), 135 (55), 107 (50). Anal. Calcd for $C_{14}H_{11}BrO_2$ (291): C, 57.73; H, 3.78; Br, 27.49. Found: C, 57.80; H, 3.69; Br, 27.41. *Compound* **4j**: mp 138–140 °C; IR (Nujol): 1670 (C=O), 3545–3649 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 2.3 (s, 3H, CH_3), 6.85–7.75 (m, 8H, Ar-H), 9.05 (br s, 1H, OH); MS: *m/z* 212 (M^+, 87), 211 (100), 135 (60), 107 (55). Anal. Calcd for $C_{14}H_{12}O_2$ (212): C, 79.24; H, 5.66. Found: C, 79.33; H, 5.58.

23. *Compound* **5a**: IR (Nujol): 1650 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.2–1.5 (m, 6H, ring-$3CH_2$), 2.0 (s, 3H, CH_3), 2.35 (t, 4H, ring-$2NCH_2$), 2.78 (t, 2H, NCH_2), 4.1 (t, 2H, OCH_2), 6.8–7.4 (m, 7H, Ar-H); EI-MS: *m/z* 403 (M^+, 65) and 401 (M^+, 62). Anal. Calcd for $C_{21}H_{24}BrNO_2$ (402): C, 62.69; H, 6.01; Br, 19.86; N, 3.48. Found: C, 62.54; H, 6.21; Br, 19.69; N, 3.32. *Compound* **5b**: IR (Nujol): 1655 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.25–1.52 (m, 6H, ring-$3CH_2$), 2.2 (s, 3H, CH_3), 2.4 (t, 4H, ring-$2NCH_2$), 2.8 (t, 2H, NCH_2), 4.15 (t, 2H, OCH_2), 6.8–7.55 (m, 7H, Ar-H); EI-MS: *m/z* 357.5 (M^+, 63). Anal. Calcd for $C_{21}H_{24}ClNO_2$ (357.5): C, 70.48; H, 6.76; Cl, 9.91; N, 3.91. Found: C, 70.37; H, 6.65; Cl, 9.82; N, 3.81. *Compound* **5c**: IR (Nujol): 1605 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.22–1.51 (m, 6H, ring-$3CH_2$), 2.3 (s, 6H, $2CH_3$), 2.55 (t, 4H, ring-$2NCH_2$), 2.81 (t, 2H, NCH_2), 4.15 (t, 2H, OCH_2), 6.8–7.65 (m, 7H, Ar-H); EI-MS: *m/z* 337 (M^+, 60). Anal. Calcd for $C_{22}H_{27}NO_2$ (337): C, 78.30; H, 8.06; N, 4.15. Found: C, 78.39; H, 8.16; N, 4.25. *Compound* **5d**:IR (Nujol): 1655 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.2–1.5 (m, 6H, ring-$3CH_2$), 2.0–2.3 (d, 6H, $2CH_3$), 2.56 (t, 4H, ring-$2NCH_2$), 2.85 (t, 2H, NCH_2), 4.2 (t, 2H, OCH_2), 6.9–7.7 (m, 7H, Ar-H); EI-MS: *m/z* 230 (M^+, 61). Anal. Calcd for $C_{21}H_{24}FNO_2$ (341): C, 73.88; H, 7.09; F, 5.56; N, 4.10. Found: C, 73.77; H, 7.18; F, 5.42; N, 4.22. *Compound* **5e**: IR (Nujol): 1615 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.23–1.53 (m, 6H, ring-$3CH_2$), 2.0–2.2 (d, 6H, $2CH_3$), 2.5 (t, 4H, ring-$2NCH_2$), 2.8 (t, 2H, NCH_2), 4.1 (t, 2H, OCH_2), 6.9–7.6 (m, 7H, Ar-H); EI-MS: *m/z* 337 (M^+, 61). Anal. Calcd for $C_{22}H_{27}NO_2$ (337): C, 78.30; H, 8.06; N, 4.15. Found: C, 78.38; H, 8.18; N, 4.26. *Compound* **5f**: IR (Nujol): 1675 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.24–1.53 (m, 6H, ring-$3CH_2$), 2.1 (s, 3H, CH_3), 2.42 (t, 4H, ring-$2NCH_2$), 2.85 (t, 2H, NCH_2), 4.2 (t, 2H, OCH_2), 6.9–7.8 (m, 6H, Ar-H); EI-MS: *m/z* 392 (M^+, 63). Anal. Calcd for $C_{21}H_{23}Cl_2NO_2$ (392): C, 64.29; H, 5.91; Cl, 18.07; N, 3.57. Found: C, 64.15; H, 5.62; Cl, 18.16; N, 3.44. *Compound* **5g**: IR (Nujol): 1605 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.21–1.52 (m, 6H, ring-$3CH_2$), 2.1 (d, 6H, $2CH_3$), 2.45 (t, 4H, ring-$2NCH_2$), 2.75 (t, 2H, NCH_2), 3.8 (s, 3H, OCH_3), 4.2 (t, 2H, OCH_2), 6.95–7.75 (m, 7H, Ar-H); EI-MS: *m/z* 353 (M^+, 59). Anal. Calcd for $C_{22}H_{27}NO_3$ (353): C, 74.76; H, 7.70; N, 3.96. Found: C, 74.82; H, 7.61; N, 3.83. *Compound* **5h**: IR (Nujol): 1610 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.24–1.54 (m, 6H, ring-$3CH_2$), 2.1–2.25 (d, 6H, $2CH_3$), 2.6 (t, 4H, ring-$2NCH_2$), 2.85 (t, 2H, NCH_2), 4.2 (t, 2H, OCH_2), 6.9–7.65 (m, 7H, Ar-H); EI-MS: *m/z* 337 (M^+, 60). Anal. Calcd for $C_{22}H_{27}NO_2$ (337): C, 78.30; H, 8.06; N, 4.15. Found: C, 78.35; H, 8.11; N, 4.21. *Compound* **5i**: IR (Nujol): 1620 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.25–1.55 (m, 6H, ring-$3CH_2$), 2.1 (s, 3H, CH_3), 2.36 (t, 4H, ring-$2NCH_2$), 2.8 (t, 2H, NCH_2), 4.2 (t, 2H, OCH_2), 6.9–7.3 (m, 7H, Ar-H); EI-MS: *m/z* 403 (M^+, 64) and 401 (M^+, 60). Anal. Calcd for $C_{21}H_{24}BrNO_2$ (402): C, 62.69; H, 6.01; Br, 19.86; N, 3.48. Found: C, 62.76; H, 6.15; Br, 19.63; N, 3.58. *Compound* **5j**: IR (Nujol): 1620 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.21–1.5 (m, 6H, ring-$3CH_2$), 2.1 (s, 3H, CH_3), 2.55 (t, 4H, ring-$2NCH_2$), 2.8 (t, 2H, NCH_2), 4.2 (t, 2H, OCH_2), 6.9–7.7 (m, 8H, Ar-H); EI-MS: *m/z* 337 (M^+, 60). Anal. Calcd for $C_{21}H_{25}NO_2$ (323): C, 77.98; H, 7.79; N, 4.33. Found: C, 77.82; H, 7.64; N, 4.26.

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