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A convenient preparation of novel benzophenone derivatives

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Abstract: A simple and high yielding method for the synthesis of novel benzophenone derivatives has been developed starting from ethyl(4-aroylaroxy)acetates. Confirmation for the structures of the newly synthesized compounds was proved by their physical, analytical and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and MS).

Keywords: aroylaryloxy esters; 2-oxazolines; *N*-arylacetamides; HIV reverse transcriptase (RT); antihaemostatic activity.

INTRODUCTION

In continuation of our ongoing project on synthetic studies of benzophenones,[1–3] the synthesis and spectral characterization of some benzophenone derivatives, *viz*., 2-(4-aroylaroxy)acetic acids (**2a**–**c**)[4–15], 2-[(4-aroylaroxy)methyl]--2-oxazolines (**3a**–**c**), 2-(4-aroylaroxy)acetyl chlorides (**4a**–**c**)[14,16,17] and 2-(4--aroylaroxy)-*N*-arylacetamides (**6d**–**i**),[18] is now reported. Benzophenone is an ultraviolet light (UV) absorbing agent that has been used in industry and medicine for more than 40 years.[19] The British India Biological Research Association (BIBRA) has published a toxicity profile of benzophenone on the basis of local effects (skin, eye and respiratory tract irritation), sensitization, intolerance, general systemic effects, reproductive toxicity, carcinogenicity and other genotoxicity.[20] Broitman[21] studied the toxicity of benzophenone derivatives on rabbits, rats and guinea pigs. These can penetrate intact skin and cause changes in the activity of the nervous system, along with changes in the kidneys and mucosa of the small intestine. Benzophenone derivatives have a local anesthetic effect and 2-hydroxy-4-propoxybenzophenone was found to be the least toxic. Benzophenone derivatives including garcinol and isogarcinol extracted from *Garcinia* plants are claimed to be inhibitors for Epstein–Barr virus early antigen induction and anti-tumor agents.[22]

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Wyatt *et al.*[23] synthesized some benzophenone derivatives, *i.e.*, (2-benzoylphenoxy)acetic acid and 2-(2-benzoylphenoxy)-*N*-[4-(2-diethylamino)ethoxy]phenylacetamide, to study their structure activity relationship. Benzophenone derivatives were initially tested for their ability to inhibit the poly(rA)-oligo(dT)[24–28] directed RT activity of HIV-I. Replacement of the methoxy group of ring A with fluorine resulted in a change in the activity, whereas removal of the substitution resulted in a modest increase in the inhibition of RT. Introduction of a methoxy group at the 4-position of ring B resulted in a slight loss of RT inhibition; however, introduction of a chlorine atom at the 5 position gave a 10-fold increase in activity in the RT assay but resulted in a compound toxic in the whole cell assay. SAR suggests that the major interaction is through the amide carbonyl.

Oxazolines have been known for many years[29–31] but only in recent years has the chemical literature shown considerable activity in this field.[32–35] Excellent review articles were published in 1949 and in 1971 covering the preparation, reactions and applications of oxazoline.[30,31] Substituted 2-oxazolines have been widely investigated for pharmaceutical uses. Substituted arylamino-2--oxazolines are useful in raising blood sugar levels and exhibit local anesthetic, sedative, vasoconstrictor, blood pressure depressant and gastric fluid secretion inhibitory effects.[36–38]

A survey of the literature on the structure–activity relationship among benzophenone derivatives revealed that no effort has been directed towards the study of the effect on antimicrobial activity of incorporation of the oxazoline ring system and amide group into the side chain of the benzophenone moiety and hence 2--oxazolines (**3a**–**c**) (Scheme 1) and the amide analogs (**6d**–**i**) were synthesized and their pharmacological activities studied.

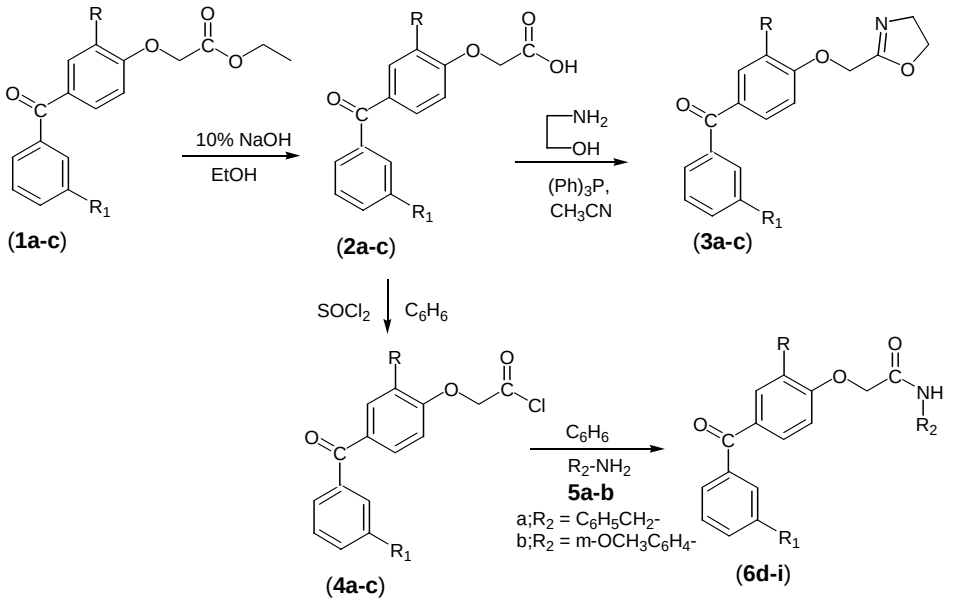
Normally the haemostatic process maintains a delicate balance between keeping blood in the fluid state to maintain flow and rapidly forming an occluding plug following vessel injury. Thrombosis occurs because of an alteration in this balance. Recent advances in understanding the haemostatic process have led to the design of novel antihaemostatic drugs. In the light of this observation, the title compounds were subjected to a preliminary determination of their antihaemostatic activity.

RESULTS AND DISCUSSION

The reaction scheme for the preparation of the title compounds is given in Scheme 1.

The analytic and spectral data for the acids **2a**–**c** are given below.

*Compound **2a***. Yield: 75 %; m.p. 130–132 °C. Anal. Calcd. for $C_{15}H_{12}O_4$: C, 70.31; H, 4.69. Found: C, 70.40; H, 4.60 %. IR (KBr, cm^{-1}): 3350 (−OH stretching of −COOH group), 1730 (−C=O stretching of −COOH group), 1645 (−C=O stretching of keto group); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 4.6 (2H, *s*, $-OCH_2$), 6.75 (2H, *d*, J = 7.3 Hz, aromatic), 6.8–7.8 (5H, *bm*, aromatic), 7.75 (2H, *d*, J = 7.3 Hz, aromatic), 9.2 (1H, *s*, COOH); MS (*m*/*z*, (relative abundance, %)): 226 (M^+, 55), 212 (BP, 100), 197 (70), 175 (46), 151 (21), 105 (9), 77 (14).



a: R=R_1=H , b: R=CH_3, R_1=H, c: R=H R_1= Cl, d: R = R_1= H, R_2=$C_6H_5CH_2$-, e: R=CH_3, R_1=H, R_2=$C_6H_5CH_2$-
f: R=H, R_1= Cl, R_2= $C_6H_5CH_2$-, g: R= R_1= H, R_2= m-$OCH_3C_6H_4$-, h:R=CH_3, R_1=H, R_2=m-$OCH_3C_6H_4$-,
i: R=H, R_1=Cl, R_2= m-$OCH_3C_6H_4$-

Scheme 1. The starting compounds (**1a**–**c**) and the products 2-(4-aroylaroxy)acetic acids (**2a**–**c**), 2-[(4-aroylaroxy)methyl]-2-oxazolines (**3a**–**c**), 2-(4-aroylaroxy)acetyl chlorides (**4a**–**c**) and 2-(4-aroylaroxy)-*N*-benzyl/*m*-methoxyphenyl/acetamides (**6d**–**i**).

*Compound **2b***. Yield: 78 %; m. p. 140–142 °C. Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.11; H, 5.19. Found: C, 71.22; H, 5.15 %. IR (KBr, cm^{-1}): 3400 (−OH stretching of −COOH group), 1725 (−C=O stretching of −COOH group), 1638 (−C=O stretching of keto group); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.2 (3H, *s*, $-CH_3$), 4.5 (2H, *s*, $-OCH_2$), 6.9–8.0 (8H, *bm*, aromatic), 9.5 (1H, *s*, −COOH); MS (*m*/*z*, (relative abundance, %)): 270 (M^+, 54), 226 (BP, 100), 211 (70), 193 (48), 165 (43), 105 (9), 77 (14).

*Compound **2c***. Yield: 80 %, m. p. 128–130°C. Anal. Calcd. for $C_{15}H_{11}ClO_4$: C, 61.96; H, 3.79; Cl, 12.22. Found: C, 61.88; H, 3.70; Cl, 12.18 %. IR (KBr, cm^{-1}): 3400 (−OH stretching of −COOH group), 1732 (−C=O stretching of −COOH group), 1642 (−C=O stretching of keto group); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 4.5 (2H, *s*, $-OCH_2$), 6.95 (2H, *d*, J = 7.4 Hz, aromatic), 7.0–7.8 (4H, *bm*, aromatic), 7.95 (2H, *d*, J = 7.4 Hz, aromatic), 9.25 (1H, *s*, −COOH); MS (*m*/*z*, (relative abundance, %)): 290 (M^+, 56), 246 (BP, 100), 231 (72), 175 (42), 151 (20), 139 (9), 111(15).

The acid **2a** showed two strong IR absorptions at 1645 cm^{-1} and 1730 cm^{-1} due to aromatic carbonyl and acid carbonyl groups, respectively. The strong broad absorption at 3350 cm^{-1} is assigned to −OH groups. The ^{1}H-NMR spec-

trum of **2a** showed a singlet at δ 4.6, assigned to methylene protons, two doublets in the region δ 6.75 and δ 7.75, assigned to four aromatic protons, a broad multiplet at δ 6.8–7.8, assigned to the remaining five aromatic protons, and a singlet at δ 9.2, due to one proton of the acid hydroxyl group. All the compounds **2a**–**c** showed mass spectra with the molecular ion peaks at their respective mass numbers *m*/*z* 226, 270 and 290.

The analytic and spectral data for compounds **3a**–**c** are given below.

*Compound **3a***. Yield: 50 %; m. p. 117–118 °C. Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.60; H, 5.34; N, 4.98. Found: C, 72.56; H, 5.40; N, 4.90 %. IR (KBr, cm^{-1}): 1638 (−C=O stretching of keto group), 1600 (−C=N stretching of oxazoline ring); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 3.35 (2H, *t*, *J* = 6 Hz, N–CH_2), 4.2 (2H, *t*, *J* = 6 Hz, ring OCH_2), 4.65 (2H, *s*, −OCH_2), 6.8 (2H, *d*, *J* = 7.3 Hz, aromatic), 6.9–7.8 (5H, *bm*, aromatic), 7.85 (2H, *d*, *J* = 7.3 Hz, aromatic); MS (*m*/*z*, (relative abundance, %)): 281 (M^+, 58), 253 (54), 237 (42), 105 (BP, 100), 77 (16).

*Compound **3b***. Yield: 52 %; m. p. 115−116 °C. Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.22; H, 5.76; N, 4.75. Found: C, 73.28; H, 5.80; N, 4.82 %. IR (KBr, cm^{-1}): 1640 (−C=O stretching of keto group), 1605 (−C=N stretching of oxazoline ring); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.1 (3H, *s*, Ph−CH_3), 3.45 (2H, *t*, *J* = = 6 Hz, N−CH_2), 4.25 (2H, *t*, *J* = 6 Hz, ring OCH_2), 4.55 (2H, *s*, −OCH_2), 6.9––7.8 (8H, *bm*, aromatic); MS (*m*/*z*, (relative abundance, %)): 295 (M^+, 59), 267 (52), 251 (40), 105 (100), 77 (17).

*Compound **3c***. Yield: 50 %; m. p. 109–110 °C. Anal. Calcd. for $C_{17}H_{14}ClNO_3$: C, 64.66; H, 4.44; N, 4.44; Cl, 11.25. Found: C, 64.70; H, 4.52; N, 4.48; Cl, 11.20 %. IR (KBr, cm^{-1}): 1641 (−C=O stretching of keto group), 1603 (−C=N stretching of oxazoline ring); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 3.4 (2H, *t*, *J* = = 6 Hz, N−CH_2), 4.2 (2H, *t*, *J* = 6 Hz, ring OCH_2), 4.54 (2H, *s*, −OCH_2), 6.85 (2H, *d*, *J* = 7.4 Hz, aromatic), 6.9–7.75 (4H, *bm*, aromatic), 7.85 (2H, *d*, *J* = 7.4 Hz, aromatic); MS (*m*/*z*, (relative abundance, %)):315 (M^+, 55), 287 (53), 271 (40), 139 (BP, 100), 111 (15).

The IR spectrum of **3a** showed absorption peaks at 1600 and 1638 cm^{-1}, assigned to −C=N and aromatic carbonyl groups. The ^{1}H-NMR spectrum showed a triplet centered at δ 3.35, assigned to the two protons of −N−CH_2, with coupling constant *J* = 6 Hz, a triplet centered at δ 4.2, assigned to the two protons of the ring −OCH_2 group, a singlet at δ 4.65, assigned to the two protons of the −OCH_2 group, two doublets, one in the upfield region at δ 6.8 and the other in the downfield region at δ 7.85 with a coupling constant *J* = 7.3 Hz, due to four aromatic protons and a broad multiplet at δ 6.9–7.8, due to the remaining five aromatic protons. The mass spectra of **3a**–**c** showed molecular ion peaks at their respective mass numbers.

The analytic and spectral data for compounds **4a**–**c** are given below.

*Compound **4a***. Yield: 92 %. Anal. Calcd. for $C_{15}H_{11}ClO_3$: C, 65.58; H, 4.04; found C, 65.60; H, 4.05 %. IR (KBr, cm^{-1}): 1800 (−C=O stretching of −COCl group), 1642 (−C=O stretching of keto group); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 4.5 (2H, *s*, OCH_2), 6.95 (2H, *d*, *J* = 7.3 Hz, aromatic), 7.0–7.4 (5H, *bm*, aromatic), 7.5 (2H, *d*, *J* = 7.3 Hz, aromatic); MS 274 (M^+, 32), 243 (30), 227 (25), 95 (BP, 100).

*Compound **4b***. Yield: 80%. Anal. Calcd. for $C_{16}H_{13}ClO_3$: C, 66.56; H, 4.54. Found: C, 66.50; H, 4.50. IR (KBr, cm^{-1}): 1805 (−C=O stretching of −COCl group), 1638 (−C=O stretching of keto group); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.30 (3H, *s*, $-CH_3$), 4.3 (2H, *s*, $-OCH_2$), 7.0 (2H, *d*, *J* = 7.0 Hz, aromatic), 7.0–7.5 (4H, *bm*, aromatic), 7.6 (2H, *d*, *J* = 7.0 Hz, aromatic); MS (*m*/*z*, (relative abundance, %)): 288 (M^+, 45), 257 (43), 241 (20), 109 (100).

*Compound **4c***. Yield: 75 %. Anal. Calcd. for $C_{15}H_{10}Cl_2O_3$: C, 58.28; H, 3.26. Found: C, 58.29; H, 3.25. IR (KBr, cm^{-1}): 1799 (−C=O stretching of −COCl group), 1630 (−C=O stretching of keto group); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 4.70 (2H, *s*, $-OCH_2$), 6.87 (2H, *d*, aromatic), 7.30–7.58 (4H, *m*, aromatic), 7.60 (2H, *d*, aromatic). MS (*m*/*z*, (relative abundance, %)): 312 (M+4, 5), 310 (M+2, 25), 308 (M^+, 28), 278 (45), 262 (11), 130 (BP, 98).

The IR spectrum of **4a** showed peaks in the region 1642 cm^{-1}, assigned to aromatic carbonyls, and in the region 1800 cm^{-1}, assigned to the acid chloride carbonyl group. The ^{1}H-NMR spectrum of **4a** showed a singlet at δ 4.5 due to two protons of OCH_2 group and two doublets at δ 6.95 and δ 7.5 with a coupling constant *J* = 7.3 Hz, assigned to four aromatic protons and a broad multiplet in the range δ 7.0–7.4, assigned to the remaining four aromatic protons. The IR and ^{1}H-NMR spectrum of **4b** was similar to that of **4a**, except for a singlet at δ 2.2 of the aromatic methyl group and all the aromatic protons appeared as a broad multiplet.

The analytic and spectral data of compounds **6d–i** are given below.

*Compound **6d***. Yield: 80 %, m. p. 115–116 °C. Anal. Calcd. for $C_{22}H_{19}NO_3$: C, 76.52; H, 5.50; N, 4.05. Found: C, 76.42; H, 5.40; N, 3.96. IR (KBr, cm^{-1}): 3275 (−NH stretching of $-CONH_2$ group), 1710 (−C=O stretching of $-CONH_2$ group), 1638 (−C=O stretching of keto group); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 4.25 (3H, *s*, CH_2), 4.6 (2H, *s*, $-OCH_2$), 6.8 (2H, *d*, *J* = 8.0 Hz, aromatic), 6.9–7.8 (10H, *bm*, aromatic), 7.9 (2H, *d*, *J* = 8.0 Hz, aromatic), 9.55 (1H, *bs*, NH, D_2O exchangeable); MS (*m*/*z*, (relative abundance, %)): 345 (M^+, 9), 328 (10), 294 (16), 252 (2), 157 (21), 129 (25), 101 (BP, 100).

*Compound **6e***. Yield: 85 %, m. p. 120–122 °C. Anal. Calcd. for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.82; H, 5.85; N, 3.92. IR (KBr, cm^{-1}): 3260 (−NH stretching of $-CONH_2$ group), 1720 (−C=O stretching of $-CONH_2$ group), 1641 (−C=O stretching of keto group); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.2 (3H, *s*, CH_3), 4.3 (2H, *s*, CH_2) 4.5 (2H, *s*, $-OCH_2$), 6.7–7.9 (13H, *bm*, aromatic), 9.6 (1H, *bs*, NH, D_2O exchangeable); MS (*m*/*z*, (relative abundance, %)): 359 (M^+, 8), 342 (10), 308 (16), 266 (16), 177 (14), 149 (2), 121 (BP, 100).

Compound ***6f***. Yield: 82 %; m. p. 155–156 °C. Anal. Calcd. for $C_{22}H_{18}ClNO_3$: C, 69.57; H, 4.78; N, 3.69; Cl, 9.33. Found: C, 69.50; H, 4.72; N, 3.65; Cl, 9.30. IR (KBr, cm^{-1}): 3300 (−NH stretching of $-CONH_2$ group), 1700 (−C=O stretching of $-CONH_2$ group), 1630 (−C=O stretching of keto group); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 4.0 (2H, *s,* CH_2), 4.5 (2H, s, $-OCH_2$), 6.8 (2H, *d*, J = 8.2 Hz, aromatic), 6.85–7.8 (9H, *bm*, aromatic), 7.85 (2H, *d*, aromatic, J = 8.2 Hz), 9.55 (1H, *bs,* NH, D_2O exchangeable); MS (*m*/*z*, (relative abundance, %)): 381 (M+2, 10), 379 (M^+, 32), 362 (10), 268 (5), 215 (18), 148 (BP, 100), 123 (24).

Compound ***6g***. Yield: 76 %, m. p. 132–133 °C. Anal. Calcd. for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.08; H, 5.25; N, 3.85. IR (KBr, cm^{-1}): 3425 (−NH stretching of $-CONH_2$ group), 1714 (−C=O stretching of $-CONH_2$ group), 1619 (−C=O stretching of keto group); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 3.73 (3H, *s*, $-OCH_3$), 4.88 (2H, *s*, $-OCH_2$), 6.75 (2H, *d*, J = 8.0 Hz, aromatic), 6.87 (2H, *d*, J = 8.0 Hz, aromatic), 7.0–7.59 (9H, *bm*, aromatic), 10.05 (1H, *bs,* NH, D_2O exchangeable); MS (*m*/*z*, (relative abundance, %)): 361 (M^+, 9), 344 (7), 310 (15), 268 (100).

Compound ***6h***. Yield: 88 %, m. p. 176–178 °C. Anal. Calcd. for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.52; H, 5.65; N, 3.72. IR (KBr, cm^{-1}): 3410 (−NH stretching of $-CONH_2$ group), 1720 (−C=O stretching of $-CONH_2$ group), 1625 (−C=O stretching of keto group); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.2 (3H, *s*, $-CH_3$), 3.80 (3H, *s*, $-OCH_3$), 4.80 (2H, *s*, $-OCH_2$), 6.75 (2H, *d*, J = 6.0 Hz, aromatic), 6.82 (2H, *d*, J = 6.0 Hz, aromatic), 7.36–7.82 (8H, *bm*, aromatic), 9.70 (1H, *bs*, NH, D_2O exchangeable); MS (*m*/*z*, (relative abundance, %)): 375 (M^+, 11), 358 (9), 322 (17), 269 (BP, 100).

Compound ***6i***. Yield: 82 %, m. p. 167–168 °C. Anal. Calcd. for $C_{22}H_{18}ClNO_4$: C, 66.75; H, 4.55; N, 3.54; Cl, 8.98. Found: C, 66.82; H, 4.60; N, 3.62; Cl, 8.90. IR (KBr, cm^{-1}): 3290 (−NH stretching of $-CONH_2$ group), 1710 (−C=O stretching of $-CONH_2$ group), 1640 (−C=O stretching of keto group); ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 4.12 (3H, *s*, $-OCH_3$), 4.63 (2H, *s*, $-OCH_2$), 6.8 (2H, *d*, J = = 8.2 Hz, aromatic), 6.85–7.8 (78H, *bm*, aromatic), 7.85 (2H, *d*, J = 8.2 Hz, aromatic), 9.86 (1H, *bs*, NH, D_2O exchangeable); MS (*m*/*z*, (relative abundance, %)): 395 (M^+, 10), 378 (10), 284 (3), 231 (16), 164 (BP, 100), 139 (21), 111 (25), 107 (24).

The IR and ^{1}H-NMR spectra of **6d**–**i** showed almost similar type of absorptions except for the substituents. The IR absorption of **6d** in the region 1638 cm^{-1} was assigned to aromatic carbonyl, the absorption at 1710 cm^{-1} to amide carbonyl stretching and the absorption at 3275cm^{-1} due to −NH stretching. The ^{1}H-NMR spectrum of **6d** exhibits a singlet at δ 4.25 due to two benzylic protons, a singlet at δ 4.6 due to the $-OCH_2$ group, two doublets in the region δ 6.8 and 7.9, with a coupling constant J = 8.0 Hz, assigned to four aromatic protons and a broad multiplet at δ 6.9–7.8 due to the remaining ten aromatic protons and a broad

singlet at δ 9.55, assigned to the −NH proton. For the compound **6e**, a singlet appeared at δ 2.2 from the aromatic $-CH_3$ group and a broad multiplet appeared in the region δ 6.7–7.9 due to all the aromatic protons. The IR and ^{1}H-NMR spectra of **6e**–**f** are similar to that of **6d**. The IR absorptions in the region 1630––1640 cm^{-1}, 1700–1710 cm^{-1} and 3290–3300 cm^{-1} were assigned to aromatic carbonyl, amide carbonyl and −NH stretching, respectively. The ^{1}H-NMR spectral signals of **6g**–**i** were the same as those of **6d**–**f**, except for the absence of benzylic protons. A singlet appeared at δ 3.7–4.1 due to the three protons of the methoxy group and the aromatic protons appeared as a broad multiplet. The mass spectra of **6d**–**i** showed molecular ion peaks at their respective mass numbers *m*/*z*.

The antihaemostasis results (Fig. 1) revealed that the compounds **3a**–**c**, containing the 2-oxazoline ring exhibited considerable antihaemostatic activity. The compound **3c**, containing an electronegative chlorine atom, had an activity (487) almost equal to that of the standard indomethacin. However, the remaining compounds **4a**–**c** and **6d**–**i** exhibited poor antihaemostatic activities. The compound **6g** did not show the significant activity.

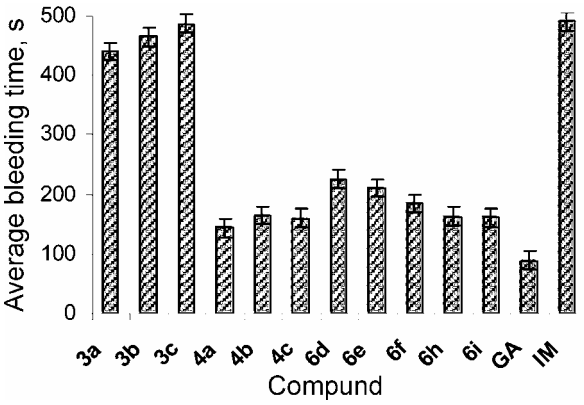


Fig. 1. The average bleeding time exhibited by the compounds **3a–c**, **4a–c** and **6d–i**. (GA – gum acacia, IM – indomethacin). Dose 100 mg/kg for all.

EXPERIMENTAL

Materials

TLC was run on silica gel G plates using acetone-benzene (1:3) as the mobile phase. Melting points were determined in open capillaries and are uncorrected. IR (KBr) spectra were recorded on a Nicolet Impact-410 FTIR spectrometer and the NMR spectra in $CDCl_3$ (δ, ppm downfield from TMS) were recorded on a Bruker Varian-300 MHz FT-NMR spectrometer. Elemental analyses were performed on a CEST 1106 elemental analyzer. Mass spectra were recorded on EI-70 eV and FR ver. 1on UIC 002002 spectrometers. The ethyl(4-aroylaroxy)acetates (**1a**–**c**) were prepared according to the reported literature.[39]

Methods

*General preparation procedure for 2-(4-aroylaroxy)acetic acids (**2a**–**c**)*: Ethyl(2-(4-benzoylphenoxy)acetate) (**1a**) (8.0 g, 0.028 mol) was dissolved in ethanol (25 ml) and sodium hydroxide (2.256 g, 0.056 mol) in water (20 ml) was added and the mixture refluxed for 1 h. The reaction mixture was cooled and acidified with hydrochloric acid (4M). The precipitate

was extracted with dichloromethane (25×3 ml), washed with water (15×3 ml). For further purification, the product was extracted into 10 % sodium bicarbonate solution (25×3 ml) and acidified with hydrochloric acid (4M). The white solid which separated was filtered, dried and on recrystallization from hexane gave pure crystals of **2a**.

*General preparation procedure for 2-[(4-aroylaroxy)methyl]-2-oxazolines (**3a**–**c**)*: A mixture of 2-(4-benzoylphenoxy)acetic acid (**2a**) (1 g, 4 mmol), acetonitrile (27 ml), ethanolamine (1.16 g, 19 mmol) and carbon tetrachloride (2.44 g, 0.02 mol) was stirred at 2 °C for 2 h. Triethylamine (2.02 g, 0.02 mol) in 25 ml acetonitrile was added slowly followed by the addition of triphenylphosphine (2.62 g, 0.01 mol) at 2–3 °C. Then the temperature was raised to 29 °C and the stirring continued for 1 h. The precipitate of $Et_3N{\cdot}HCl$ was removed by filtration and the filtrate was concentrated to 50 ml and cooled to 0 °C. The contents were filtered to remove the precipitated triphenylphosphine oxide and washed with acetonitrile. The filtrate was extracted with hexane (25×3 ml). The hexane layer was cooled to obtain solid oxazoline **3a**.

*General procedure for 2-(4-aroylaroxy)acetyl chlorides (**4a**–**c**)*: A mixture of 2-(4-benzoylphenoxy)acetic acid (**2a**) (4 g, 0.014 mmol), thionyl chloride (28 g, 0.235 mol) and benzene (28 ml) was heated at reflux for 30 min and then evaporated. The residue was dissolved in benzene (8 ml) and on re-evaporation gave **4a** as a pale yellow oily liquid.

General procedure for 2-(4-(aroylaroxy)-N-*benzyl/*m-*methoxyphenyl/acetamides (**6d**–**i**)*: A mixture of 2-(4-benzoylphenoxy)acetyl chloride (**4a**) (1 g, 3.24 mmol) in benzene (20 ml) was stirred at room temperature for 30 min and then benzylamine (**5a**) (0.466 g, 4.35 mmol) in benzene (10 ml) was added dropwise. The mixture was stirred at room temperature for 3 h and then water (20 ml) was added, extracted with diethyl ether (3×10 ml). The ether layer was washed with dilute aqueous sodium hydroxide (3×5 ml), dried over anhydrous sodium sulfate and evaporated to give **6d** as colorless crystals.

Antihaemostatic screening

All protocols of animal experiments were approved by the Institutional Animal Ethics Committee (IAEC). The tail bleeding time in conscious mice was used to determine the antihaemostatic activity of the title compounds.[40] Mice of either sex weighing 20–25 g were divided into 13 groups each being comprised of five mice. The control group received 0.4 ml of 2 % gum acacia. The test compounds were administered in 2 % gum acacia to the remaining 12 groups. Thirty minutes after administration of the test compounds, the tail bleeding time was measured.

CONCLUSIONS

In the present study, a highly efficient and simple procedure for the synthesis of novel benzophenone derivatives was developed. The method is simple, inexpensive, gave good yields and could be useful in for the construction of pharmacologically important molecules. Antihaemostatic analysis of the newly synthesized compounds showed that the compounds having the 2-oxazoline moiety, *viz*., **3a**–**c**, exhibited promising activity.

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И З В О Д

ПОГОДНА СИНТЕЗА НОВИХ БЕНЗОФЕНОНСКИХ ДЕРИВАТА

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Развијен је једноставан поступак синтезе нових бензофенонских деривата у високом приносу полазећи од етил-(4-ароиларокси)ацетата. Структуре новосинтетисаних једињења потврђене су физичким, аналитичким и спектралним (ИЦ, ^{1}H-NMR, ^{13}C-NMR и MS) подацима.

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