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# Synthesis and cytotoxic activities of novel phenacylimidazolium bromides

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ABSTRACT

A series of novel phenacylimidazolium derivatives, bearing an aryl or alkyl substituent at position-1 and a phenacyl substituent at position-3 of the imidazole ring, has been prepared and evaluated in vitro against a panel of human tumor cell lines. Phenacylimidazolium bromides bearing a highly sterically hindered aryl group at position-1 and an electron-rich phenacyl or naphthylacyl substituent at position-3 of imidazole ring proved to be more active than imidazolium bromides with other substituted groups. In particular, compound **5j** was found to be the most potent compounds with $IC_{50}$ values lower than 5.0 μM against 8 strains human tumor cell lines and more active than cisplatin (DDP).



Imidazolium salts have attracted considerable interests in recent years for their versatile properties in chemistry and pharmacology. They are well-known as room-temperature ionic liquids that can be used as electrolytes or green solvents because of their low vapor pressure and wide chemical stability.[1] Imidazolium salts are also used as precursors for stable carbenes with many applications in organic synthesis.[2,3]

A number of biological activities of imidazolium salts have been reported including antimicrobial and antifungal (l,3-dialky imidazolium chlorides),[4] antitumor (l,3-dialky imidazolium iodides),[5] antimuscarinic (1,3-disubstituted imidazolium halides),[6] thromboxane synthetase inhibition (1,3-disubstituted imidazolium halides),[7] anti-inflammatory (enol betaines of phenacyl halides),[8] antiarrhythmic (1,3-disubstituted imidazolium halides),[9] and plasmid DNA cleavage (monometallic cyclen complexes containing 1,3-disubstituted imidazolium bromides group)[10] activity. In 1989, a series of phenacylimidazolium halides were synthesized and found to possess effective hypoglycemic activity by Dominianni.[11] Proglycosyn (LY177507, **1**, Fig. 1), a representative of these compounds, stimulates glycogen synthesis and inhibits glucose production from various substrates in rat hepatocytes.[12] Additionally, phenacylimidazolium salts have been used as intermediates in a regiospecific synthesis of 3-substituted L-histidines.[13] To the best of our knowledge, however, no reports concerning antitumor activity for phenacylimidazolium salt was reported.

The present investigation was stimulated by the discovery of two new imidazolium halides (Fig. 1), 1,3-dibenzyl-4,5-dimethylimidazolium chloride (**2**) and 1,3-dibenzyl-2,4,5-trimethylimidazolium chloride (**3**), isolated from the roots of *Lepidium meyenii*, which showed potent cytotoxic activity against the human cancer cell lines (UMUC3, PACA2, MDA231, and FDIGROV).[14]

In our efforts to discover effective ligands for catalytic organic transformation and active agents toward antitumor activity, we were particularly interested in the imidazole ring. Our long standing interest in imidazole has resulted in the synthesis of a number of imidazolium salts.[15] In the present research, we have designed and synthesized a series of novel imidazolium bromides, bearing an aryl or alkyl substituent at position-1 and a phenacyl substituent at position-3 of imidazole ring. The purpose of this study was to investigate effect of phenacylimidazolium bromides on the antitumor activity, with the ultimate aim of developing novel potent antitumor agents.

Based on the synthetic method described in our previous reports,[16,17] a number of 1-aryl and 1-alkyl substituted imidazoles **4a**–**4u** were prepared, including a few *N*-arylimidazoles and *N*-alkylimidazoles with highly electron-rich and highly sterically hindered substituted groups (method A and B, Scheme 1).[18] Twenty-one phenacylimidazolium salts were prepared as shown in Scheme 1. 1-Aryl/alkyl and 3-phenacyl substituted imidazolium bromides (compounds **5a**–**5u**) were prepared with highly yields by reaction of 1-aryl or 1-alkyl substituted imidazoles with the

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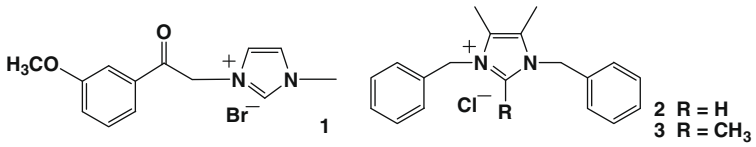



**Figure 1.** Chemical structure of proglycosyn and natural imidazolium chlorides.

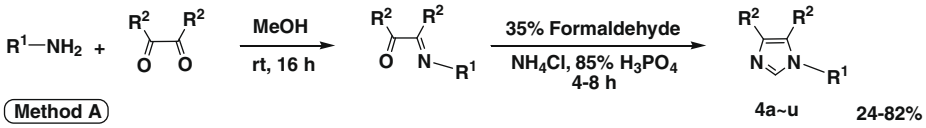
corresponding phenacyl bromides in refluxing toluene.[19] The structures and yields of imidazolium halides derivatives were shown in Scheme 1.

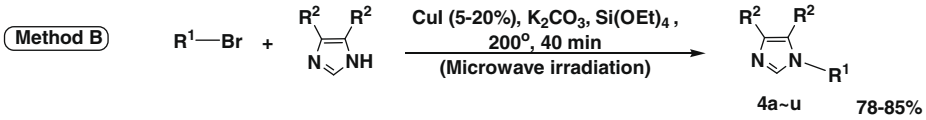
The cytotoxic potential of all newly synthesized phenacylimidazolium bromides was evaluated in vitro against a panel of human tumor cell lines according to procedures described in the literature.[20] The tumor cell line panel consisted of myeloid leukaemia (HL-60 and K562), epidermoid carcinoma (A431), ovarian carcinoma (Skov-3), gastric carcinoma (MKN-28), liver carcinoma (SMMC-7721), laryngeal carcinoma (Hep-2), and lung carcinoma (GLC-15). Cisplatin (DDP) was used as the reference drug. The results of the cytotoxicity studies were summarized in Table 1 ($IC_{50}$ value, defined as the concentrations corresponding to 50% growth inhibition).

As shown in Table 1, compounds **5a**–**5c** with a *tert*-butyl substituent at position-1 or a *tert*-butylacyl substituent at position-3 of imidazole ring were almost inactive to all tumor cell lines investigated at the concentration of 200 μM. However, compounds **5d**–**5h** with other alkyl substituents (adamantyl and phenethyl) at position-1 of imidazole ring exhibited moderate cytotoxic activities. Among them, compound **5f**, bearing a naphthylacyl substituent at position-3 of imidazole, was the most active.

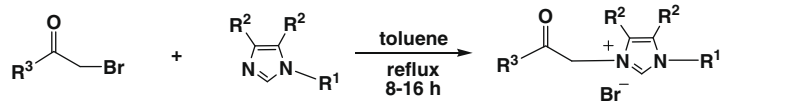
Compared with above alkyl substituted derivatives, 1- and 3-aromatic substituted imidazolium bromides **5e**–**5u** exhibited higher cytotoxic activities. Most of this kind of derivatives showed remarkable activities. Compounds **5j**, **5n, 5o**, and **5s**, bearing a highly sterically hindered alkyl substituted benzene (2,4,6-trimethylbenzene or 2,6-diisopropylbenzene) at position-1 and an elec-

***Synthesis of 1-substituted imidazoles***




***Synthesis of phenacylimidazolium bromides***



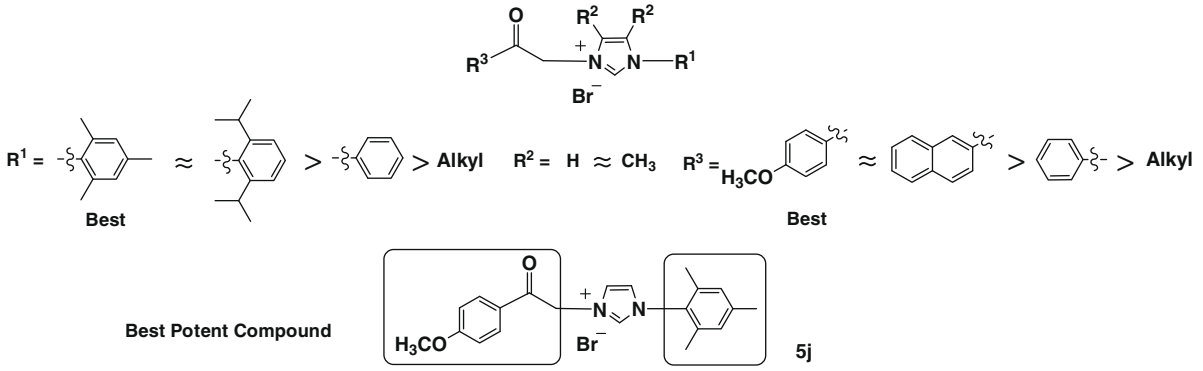

| | | | |
|---|---|---|---|
| 5a | $R^1$=*t*-$C_4H_9$ | $R^2$=H | $R^3$=$C_6H_5$ |
| 5b | $R_1$=*t*-$C_4H_9$ | $R^2$=H | $R^3$=$C_6H_4(OCH_3)$-4 |
| 5c | $R^1$=$C_6H_2(CH_3)_3$-2,4,6 | $R^2$=H | $R^3$=*t*-$C_4H_9$ |
| 5d | $R^1$=adamantyl | $R^2$=H | $R^3$=$C_6H_5$ |
| 5e | $R^1$=adamantyl | $R^2$=H | $R^3$=$C_6H_4(OCH_3)$-4 |
| 5f | $R^1$=adamantyl | $R^2$=H | $R^3$=2-naphthyl |
| 5g | $R^1$=$CH_2CH_2C_6H_2(OCH_3)_2$-3,4 | $R^2$=H | $R^3$=$C_6H_4(OCH_3)$-4 |
| 5h | $R^1$=$CH_2CH_2C_6H_3(OCH_3)_2$-3,4 | $R^2$=H | $R^3$=2-naphthyl |
| 5i | $R^1$=$C_6H_2(CH_3)_3$-2,4,6 | $R^2$=H | $R^3$=$C_6H_5$ |
| 5j | $R^1$=$C_6H_2(CH_3)_3$-2,4,6 | $R^2$=H | $R^3$=$C_6H_4(OCH_3)$-4 |
| 5k | $R^1$=$C_6H_4(CH_2COCH_3)$-4 | $R^2$=H | $R^3$=$C_6H_5$ |
| 5l | $R^1$=$C_6H_4(CH_2COCH_3)$-4 | $R^2$=H | $R^3$=$C_6H_4(OCH_3)$-4 |
| 5m | $R^1$=$C_6H_4(NO_2)$-4 | $R^2$=H | $R^3$=$C_6H_4(OCH_3)$-4 |
| 5n | $R^1$=$C_6H_2(CH_3)_3$-2,4,6 | $R^2$=H | $R^3$=2-naphthyl |
| 5o | $R^1$=$C_6H_3(i\text{-}C_3H_7)_2$-2,6 | $R^2$=H | $R^3$=$C_6H_4(OCH_3)$-4 |
| 5p | $R^1$=$C_6H_3(i\text{-}C_3H_7)_2$-2,6 | $R^2$=H | $R^3$=2-naphthyl |
| 5q | $R^1$=$C_6H_2(CH_3)_3$-2,4,6 | $R^2$=H | $R^3$=$C_6H_3(3\text{-}CH_2OCH_2\text{-}4)$ |
| 5r | $R^1$=$C_6H_3(i\text{-}C_3H_7)_2$-2,6 | $R^2$=H | $R^3$=$C_6H_3(3\text{-}CH_2OCH_2\text{-}4)$ |
| 5s | $R^1$=$C_6H_2(CH_3)_3$-2,4,6 | $R^2$=$CH_3$ | $R^3$=2-naphthyl |
| 5t | $R^1$=$C_6H_2(CH_3)_3$-2,4,6 | $R^2$=H | $R^3$=$C_6H_4$(Br)-4 |
| 5u | $R^1$=$C_6H_3(i\text{-}C_3H_7)_2$-2,6 | $R^2$=H | $R^3$=$C_6H_4$(Br)-4 |

**Scheme 1.** Synthesis of phenacylimidazolium bromides **5a–5u**.

**Table 1**
Cytotoxic activities of phenacylimidazolium bromides in vitro[b] ($IC_{50}$, μM[a])

| Compound | HL-60 | A431 | Skov-3 | MKN-28 | K562 | SMMC-7721 | Hep-2 | GLC-15 |
|---|---|---|---|---|---|---|---|---|
| **5a** | >200 | >200 | >200 | >200 | >200 | >200 | >200 | >200 |
| **5b** | >200 | 66.2 | >200 | >200 | >200 | >200 | 116.8 | 178.8 |
| **5c** | 112.6 | >200 | 191.8 | >200 | >200 | 154.4 | 132.0 | >200 |
| **5d** | 39.0 | 13.3 | 59.3 | 197.5 | >200 | 107.9 | 93.4 | 108.0 |
| **5e** | 14.7 | 6.3 | 5.6 | 158.1 | 1.5 | 27.9 | 7.1 | 59.3 |
| **5f** | 4.2 | 6.4 | 4.0 | 12.8 | 3.4 | 7.7 | 0.8 | 0.8 |
| **5g** | 50.4 | 187.6 | 37.4 | >200 | >200 | 62.3 | 62.3 | 33.4 |
| **5h** | 54.2 | 75.0 | 11.0 | 85.4 | 168.8 | 34.4 | 77.2 | 50.2 |
| **5i** | 31.3 | 15.6 | 29.9 | >200 | >200 | 16.8 | 97.6 | >200 |
| **5j** | 3.1 | 1.7 | 1.6 | 5.0 | 2.4 | 4.7 | 1.5 | 2.2 |
| **5k** | 25.8 | 7.0 | >200 | >200 | >200 | 53.4 | >200 | 53.5 |
| **5l** | 44.4 | 14.5 | 61.1 | 140.1 | 16.7 | 91.6 | 84.8 | 26.5 |
| **5m** | 8.6 | 75.5 | 26.6 | 112.7 | 112.6 | >200 | 41.6 | 97.6 |
| **5n** | 2.8 | 4.4 | 2.1 | 8.7 | 2.7 | 6.8 | 0.7 | 0.4 |
| **5o** | 1.1 | 4.2 | 5.0 | 10.0 | 2.6 | 9.9 | 2.8 | 5.1 |
| **5p** | 1.5 | 14.7 | 1.9 | 9.6 | 0.4 | 10.5 | 3.5 | 6.2 |
| **5q** | 6.1 | 18.2 | 31.5 | 85.3 | 70.1 | 33.5 | 12.3 | 23.5 |
| **5r** | 4.5 | 5.1 | 25.5 | 59.6 | 12.1 | 44.3 | 11.6 | 36.9 |
| **5s** | 4.1 | 3.9 | 3.7 | 1.7 | 0.2 | 9.8 | 1.9 | 4.3 |
| **5t** | 13.4 | 5.4 | 33.1 | 76.6 | 21.4 | 23.8 | 22.1 | 36.9 |
| **5u** | 3.8 | 4.6 | 11.3 | 35.3 | 2.8 | 10.9 | 9.2 | 18.4 |
| DDP | 4.7 | 2.0 | 1.7 | 4.3 | 4.7 | 9.2 | 1.5 | 5.7 |

[a] Cytotoxicity as $IC_{50}$ for each cell line, is the concentration of compound which reduced by 50% the optical density of treated cells with respect to untreated cells using the MTT assay.
[b] Data represent the mean values of three independent determinations.




**Scheme 2.** Structure–activity relationship of phenacylimidazolium bromides.

tron-rich phenacyl or naphthylacyl substituent at position-3 of imidazole ring, displayed potent or similar cytotoxic activity in vitro compared with DDP. The $IC_{50}$ values of these compounds were lower than 10.0 μM against all of human tumor cell lines investigated. Interestingly, compound **5j**, with a 2,4,6-trimethylbenzene at position-1 and a 4-mehtoxyphenacyl substituent at position-3 of imidazole ring, was found to be the most potent derivative with $IC_{50}$ values lower than 5.0 μM against 8 strains human tumor cell lines and more active than DDP (except against MKN-28 cell). These results suggested that substitution of the position-1 with a highly sterically hindered alkyl substituted benzene and substitution of the position-3 with an electron-rich phenacyl substituent played a vital role in the modulation of the cytotoxic activities (Scheme 2).

In conclusion, a number of novel phenacylimidazolium halides derivatives prepared in this paper proved to be remarkably potent antitumor activities. Phenacylimidazolium bromides **5j**, **5n, 5o**, and **5s**, bearing a highly sterically hindered alkyl substituted benzene at position-1 and an electron-rich phenacyl or naphthylacyl substituent at position-3 of imidazole ring, were found to be the most potent compounds with $IC_{50}$ values lower than 10.0 μM against a panel of human tumor cell lines. Therefore, imidazolium bromides **5j**, **5n, 5o**, and **5s** can be considered promising leads for further structural modifications guided by the valuable information derivable from our detailed SARs.

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18. *General procedure for the preparation of N-arylimidazoles* **4a–4u**. Method A: see Ref. 16, yield **4g** 80%, **4i** 85% and **4n** 78%. Method B: see Ref. 17, yield **4a** 82%, **4c** 60%, **4e** 43% and **4m** 24%.
19. *General procedure for the preparation of phenacylimidazolium bromides* **5a–5u**. A mixture of *N*-arylimidazoles **4a–4u** (1 mmol) and phenacyl bromides (1.2 mmol) was stirred in toluene (10 ml) at reflux for 8–16 h. A white solid was formed. After completion of the reaction as indicated by TLC, the precipitate was filtered through a small pad of Celite, and washed with toluene (3 × 10 ml), then dried to afford **5a–5u** in 75–99% yields. Pure samples were obtained after recrystallization from appropriate solvent (acetone or methanol). *Compound* **5j**: white powder, yield 90%, mp 312–314 °C. ESI-MS *m*/*e* 336 $[M+1-Br]^+$ (69), 335 $[M-Br]^+$ (100). IR (KBr) 3423, 3156, 3119, 2954, 2916, 2838, 1693, 1600, 1571, 1512, 1462, 1422, 1244, 1214, 1177, 1113, 1065, 1015, 983, 839, 813, 745, 670 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.36 (s, 1H, $H_{imidazole}$-2), 8.08 (d, 2H, $J$ = 8.7 Hz, Ph*H*), 7.99 (d, 2H, $J$ = 6.5 Hz, $H_{imidazole}$-4,5), 7.18–7.16 (m, 4H, Ph*H*), 6.09 (s, 2H, PhCOC$H_2$), 3.89 (s, 3H, OC$H_3$), 2.35 (s, 3H, C$H_3$), 2.08 (s, 6H, 2 × C$H_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$ 189.27, 164.17, 140.30, 138.92, 134.27, 131.13, 130.65, 129.26, 126.40, 124.68, 123.38, 114.40, 55.78, 55.41, 20.57, 16.82. HR-ESI-MS *m*/*z* Calcd for $C_{21}H_{23}BrN_2O_2$ 414.0943, found 414.0912. *Compound* **5n**: white powder, yield 99%, mp 294–296 °C. ESI-MS *m*/*e* 356 $[M+1-Br]^+$ (85), 355 $[M-Br]^+$ (100). IR (KBr) 3418, 3156, 3119, 2954, 2916, 2838, 1693, 1600, 1571, 1512, 1462, 1422, 1364, 1244, 1214, 1177, 1113, 1065, 1015, 983, 861, 839, 812, 745, 670 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.42 (s, 1H, $H_{imidazole}$-2), 8.86 (s, 1H, $H_{imidazole}$-5), 8.23–8.03 (m, 6H, Ph*H* and $H_{imidazole}$-4), 7.79–7.69 (m, 2H, Ph*H*), 7.19 (s, 2H, Ph*H*), 6.29 (s, 2H, PhCOC$H_2$), 2.36 (s, 3H, C$H_3$), 2.11 (s, 6H, 2 × C$H_3$). $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$ 191.44, 140.71, 139.40, 135.95, 134.68, 132.43, 131.54, 131.28, 131.07, 129.68, 129.21, 128.26, 127.77, 125.12, 123.87, 123.59, 56.29, 20.99, 17.27. HR-ESI-MS *m*/*z* Calcd for $C_{24}H_{23}BrN_2O$ 434.0994, found 434.0992.
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