ISSN 1070-3632, Russian Journal of General Chemistry, 2019, Vol. 89, No. 7, pp. 1491–1495. © Pleiades Publishing, Ltd., 2019.

Synthesis and Biological Evaluation of Amide Derivatives of Imidazopyridine as Anticancer Agents

V. Ramesh[a]*, G. Purna Chander Rao[a], D. Ramachandran[a], and A. Kalyan Chakravarthy[b]

[a] *Department of Chemistry, Acharya Nagarjuna University, Guntur, Andhra Pradesh, India*

[b] *Dr. Reddy's Laboratories, Integrated Product Development, Bachupally, Hyderabad, India*
**e-mail: vramesh.chem1@gmail.com*

Received March 23, 2019; revised June 20, 2019; accepted June 20, 2019

Abstract—A series of new amide derivatives of imidazopyridine is synthesized and structures of the products are confirmed by ^{1}H and ^{13}C NMR, and mass spectral data. The synthesized derivatives are screened for their anticancer activity against four human cancer cell lines: lung cancer (A549), breast cancer (MCF-7), melanoma cancer (A375), and colon cancer (HT-29). Six synthesized compounds exhibit more potent activity than the control drug.

Keywords: Nocodazole, Celebrex, pyrazole and anticancer activity

DOI: 10.1134/S1070363219070193

INTRODUCTION

Benzimidazoles exhibit a range of biological activities including antitumor [1], antiviral [2], antimicrobial [3], antifungal [4], and more [5–7]. Nocodazole (Fig. 1a) is a benzimidazole nucleus containing anticancer agent that inhibits tubulin polymerization [8]. Similarly, imidazopyridines are fused heterocyclic compounds that demonstrate important biological activities including antitumor [9], antivirus [10], antibacterial [11], and anti-inflammatory [12].

Pyrazoles constitute another important class of heterocyclic compounds characterized by well known significant biological properties. For example, one of pyrazole core containing drugs is Celebrex (Fig. 1b) [13].

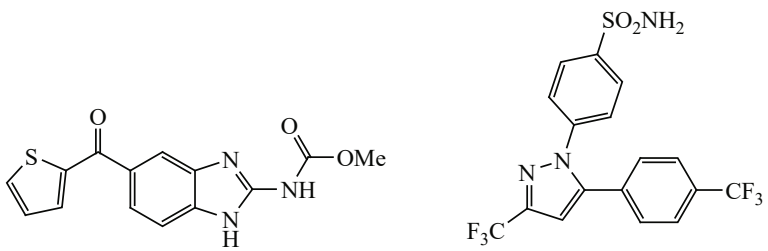
In view of the above information and in continua-tion of our earlier studies, we have designed and synthesized a series of amide derivatives of imidazopyridine. Structures of the products were confirmed by ^{1}H and ^{13}C NMR and mass spectral data. The compounds were screened for their anticancer activity against human cancer cell lines.

RESULTS AND DISCUSSION

Synthesis of the novel compounds **10a**–**10j** is outlined in Scheme 1. Compound **3** was cyclized with methyl-4-formylbenzoate **4** in presence of *p*-benzoquinone in ethanol medium upon refluxing to afford the compound **5**. Its following reaction with hydrazine hydrate in ethanol gave benzalhydrazide **6** in high yield. Reaction of the intermediate **6** with acetyl acetone in presence of acetic acid led to the product of cyclization **8**, which upon coupling with substituted acid chlorides **9a**–**9j** in presence of TEA gave the corresponding target compounds **10a**–**10j**.

Biological evaluation. *In vitro cytotoxicity.* The newly synthesized compounds **10a**–**10j** were tested for their an-

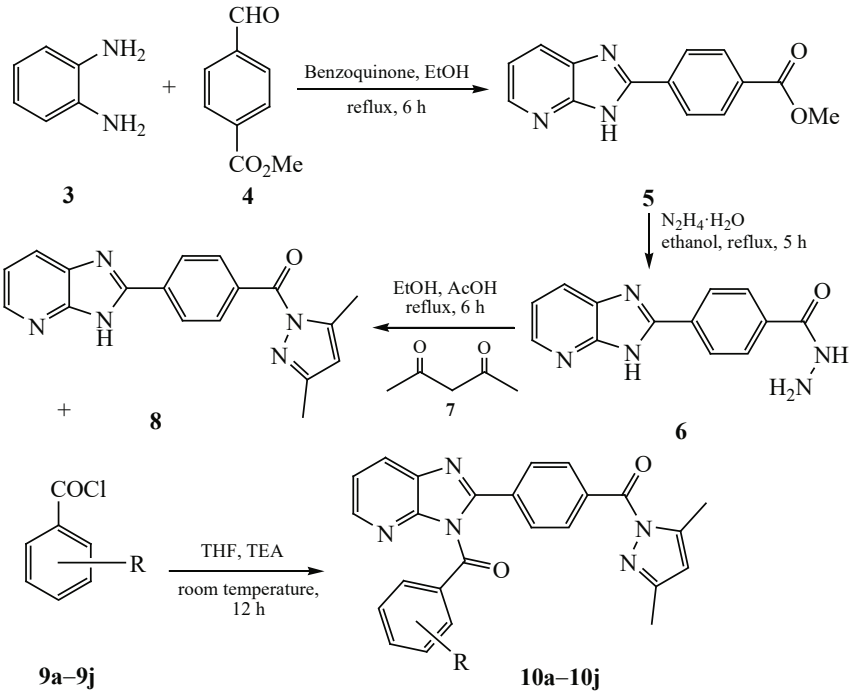
(a) (b)



1 **2**

Fig. 1. Structure of (a) Nocodazole and (b) Celebrex.

Scheme 1.



R = H (**9a**, **10a**), 3,4,5-trimethoxy (**9b**, **10b**), 4-methoxy (**9c**, **10c**), 4-chloro (**9d**, **10d**), 4-bromo (**9e**, **10e**), 4-fluoro (**9f**, **10f**), 4-nitro (**9g**, **10g**), 4-cyano (**9h**, **10h**), 4-methyl (**9i**, **10i**), 4-trifluoromethyl (**9j**, **10j**).

ticancer activity against four human cancer cell lines: lung cancer (A549), breast cancer (MCF-7), melanoma cancer (A375), and colon cancer (HT-29) by the MTT assay. Here CA4 was used as a positive control (see the table). All the compounds demonstrated high to moderate anticancer activity. The compounds **10b**, **10c**, **10d**, **10g**, **10h**, and **10j** exhibited more potent activity than the control drug. According to structure-activity relationship (SAR) study the compound **10b** with 3,4,5-trimethoxy substituents on the phenyl ring exhibited excellent anticancer activity. Compound **10c** containing 4-methoxy group, demonstrated lower activity than **10b.** The 4-chloro substituted product **10d** was characterized by the moderate activity. The compounds **10e** and **10f** with 4-bromo and 4-fluoro groups on the phenyl ring exhibited even lower activity. Interestingly, replacement of 4-fluoro substituent by the nitro group resulted in higher activity of compound **10g** than **10f.**

EXPERIMENTAL

All chemicals and reagents were obtained from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualized by UV light or iodine indicator. ^{1}H and ^{13}C NMR spectra were measured on a Gemini Varian-VXR-unity (300 MHz) instrument using TMS as an internal standard and DMSO-d_6 as a solvent. ESI spectra were measured on a Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined on an electrothermal melting point apparatus, and are uncorrected.

Methyl 4-(3*H*-imidazo[4,5-*b*]pyridin-2-yl)benzoate (5). The mixture of pyridine-2,3-diamine (**3**) (17 g, 155.7 mmol) with methyl 4-formylbenzoate **4** (25.5 g, 155.7 mmol) and *p*-benzoquinone (33.6 g, 311.4 mmol) in 100 mL of absolute ethanol was refluxed for 4 h. Upon completion the reaction, the mixture was cooled down to room temperature and diethyl ether was added. The crude product was filtered off, suspended in the mixture ethanol–diethyl ether several times until the powder was an analytically pure compound **5**, yield 70%. ^{1}H NMR spectrum, δ, ppm: 3.87 s (3H), 7.52 t (1H), 7.72–7.75 m (3H), 8.30 d (2H, J = 8.17 Hz), 8.65 d (1H, J = 8.10 Hz), 10.67 br.s (1H). MS (ESI): 254 $[M + H]^+$.

4-(3*H*-Imidazo[4,5-*b*]pyridin-2-yl)benzohydrazide (6). A mixture of methyl-4-(3*H*-imidazo[4,5-*b*]pyridin-

2-yl)benzoate **5** (26 g, 102.7 mmol) with hydrazine hydrate (149 mL, 308.3 mmol) in ethanol was refluxed for 5 h. The crude product was isolated after distilling off the excess ethanol, filtering off and washing with a small volume of cold water. The product **6** was introduced in the next step without further purification. Yield 83%. ^{1}H NMR spectrum, δ, ppm: 7.37 br.s (2H), 7.50 t (1H), 7.76 d (1H, J = 8.10 Hz), 8.20 d (2H, J = 8.18 Hz), 8.48 d (2H, J = 8.18 Hz), 8.62 d (1H, J = 8.10 Hz), 8.74 t (1H), 10.66 br.s (1H). MS (ESI): 254 [M + H]$^+$.

(3,5-Dimethyl-1*H*-1-pyrazolyl)[4-(3*H*-imidazo[4,5-*b*]pyridin-2-yl)phenyl]methanone (8). A mixture of 4-(3*H*-imidazo[4,5-*b*]pyridin-2-yl)benzohydrazide **6** (10 g, 39.5 mmol) with acetylacetone (11.3 mL, 39.5 mmol) and few drops of glacial acetic acid in absolute ethanol (40 mL) was refluxed for 6 h. Upon completion of the process the solvent was evaporated under reduced pressure and the residual solid was crystallized from $CHCl_3$/pet ether to afford the pure compound **8**, yield 85%. ^{1}H NMR spectrum, δ, ppm: 2.39 s (3H), 3.41 s (3H), 6.23 s (1H), 7.49 t (1H), 7.75 d (1H, J = 8.11 Hz), 8.56–8.60 m (3H), 8.69 d (2H, J = 8.19 Hz), 10.67 br.s (1H). MS (ESI): 318 [M + H]$^+$.

[4-(3-Benzoyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)phenyl-(3,5-dimethyl-1*H*-1-pyrazolyl)methanone (10a). To a solution of (3,5-dimethyl-1*H*-1-pyrazolyl)[4-(3*H*-imidazo[4,5-*b*]-pyridin-2-yl)phenyl]methanone **8** (500 mg, 1.57 mmol) in 30 mL of dry THF, benzoyl chloride **9a** (1.8 mL, 1.57 mmol) and Et_3N (6 mL, 4.71 mmol) were added. The reaction mixture was stirred at room temperature for 12 h upon TLC monitoring, washed with water, extracted with dichloromethane, dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography using ethyl acetate–hexane (6 : 4) as an eluent to obtain pure compound **10a**. Yield 81%, mp 298–300°C. ^{1}H NMR spectrum, δ, ppm: 2.38 s (3H), 3.40 s (3H), 6.22 s (1H), 7.49–7.55 m (3H), 7.67 t (1H), 7.74 d (1H, J = 8.10 Hz), 7.95 d (2H, J = 7.37 Hz), 8.78 d (1H, J = 8.20 Hz), 8.83 d (2H, J = 8.14 Hz), 8.98 d (2H, J = 8.14 Hz). ^{13}C NMR spectrum, δ, ppm: 13.7, 16.7, 110.5, 121.4, 129.5, 129.8, 130.4, 131.4, 131.9, 132.5, 133.4, 134.5, 134.9, 135.2, 136.7, 145.4, 152.3, 153.8, 154.7, 161.3, 164.9. MS (ESI): 422 [M + H]$^+$.

The compounds **10b**–**10j** were synthesized according to the above method from the intermediate **8** and the corresponding substituted benzoyl chlorides **9b**–**9j**, and the products were purified by column chromatography using ethyl acetate/hexane in the ratio 6 : 4 or 7 : 3 as an eluent.

In vitro cytotoxicity data for compounds **10a**–**10j**[a]

Comp. no.	IC_{50}, μM			
	A549[b]	MCF-7[c]	A375[d]	HT-29[e]
10a	2.33±1.950	4.78±2.340	2.10±1.450	2.30±1.460
10b	0.90±0.028	0.10±0.028	1.23±0.260	0.19±0.030
10c	0.28±0.030	0.89±0.035	0.33±0.031	Not active
10d	1.90±0.210	0.67±0.034	1.09±0.170	1.45±0.180
10e	3.89±2.140	4.74±2.320	Not active	Not active
10f	5.67±2.490	3.10±2.090	2.88±1.970	7.20±3.650
10g	0.13±0.030	0.15±0.031	0.76±0.033	2.50±1.480
10h	1.33±0.440	0.66±0.028	Not active	Not active
10i	2.19±1.550	8.56±4.560	9.40±4.620	10.34±4.78
10j	0.45±0.024	1.11±0.220	1.67±0.190	2.78±1.770
CA4[f]	0.11±0.020	0.18±0.021	0.21±0.029	0.93±0.034

[a] Each data is presented as mean ±S.D value of three different experiments performed in triplicates. [b] (A549) human lung cancer cell line. [c] (MCF-7) human breast cancer cell line. [d] (A375) human melanoma cancer cell line. [e] (HT-29) human colon cancer cell line. [f] (CA4) Combretastatin-A4.

(3,5-Dimethyl-1*H*-1-pyrazolyl)4-[3-(3,4,5-trimethoxybenzoyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]-phenylmethanone (10b). Yield 83%, mp 354–356°C. ^{1}H NMR spectrum, δ , ppm: 2.37 s (3H), 3.39 s (3H), 3.84 s (3H), 3.91 s (6H), 6.21 s (1H), 7.54 s (2H), 7.68 t (1H), 7.76 d (1H, J = 8.12 Hz), 8.69 d (1H, J = 8.12 Hz), 8.86 d (2H, J = 8.22 Hz), 8.95 d (2H, J = 8.22 Hz). ^{13}C NMR spectrum, δ, ppm: 13.7, 16.7, 57.4, 61.3, 106.5, 110.5, 121.4, 129.5, 130.4, 131.3, 133.4, 134.5, 135.6, 136.8, 144.6, 145.9, 152.4, 153.7, 154.8, 157.5, 161.8, 164.9. MS (ESI): 512 [M + H]$^+$.

(3,5-Dimethyl-1*H*-1-pyrazolyl)4-[3-(4-methoxybenzoyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]phenyl-methanone (10c). Yield 86%, mp 350–352°C. ^{1}H NMR spectrum, δ, ppm: 2.38 s (3H), 3.40 s (3H), 3.87 s (3H), 6.23 s (1H), 7.68 t (1H), 7.78–7.83 m (3H), 7.88 d (2H, J = 8.18 Hz), 8.68 d (1H, J = 8.12 Hz), 8.85 d (2H, J = 8.21 Hz), 8.94 d (2H, J = 8.21 Hz). ^{13}C NMR spectrum, δ, ppm: 13.7, 16.7, 57.4, 110.8, 115.6, 121.5, 128.5, 129.6, 130.5, 130.8, 131.5, 133.5, 134.6, 135.9, 136.8, 145.3, 152.3, 153.8, 154.8, 156.5, 161.8, 164.9. MS (ESI): 452 [M + H]$^+$.

4-[3-(4-Chlorobenzoyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]phenyl(3,5-dimethyl-1*H*-1-pyrazolyl)methanone (10d). Yield 96%, mp 325–327°C. ^{1}H NMR spectrum, δ, ppm: 2.38 s (3H), 3.40 s (3H), 6.23 s (1H), 7.50 d (2H, *J* = 8.16 Hz), 7.68 t (1H), 7.80–7.85 m (3H), 8.67 d (1H, *J* = 8.12 Hz), 8.86 d (2H, *J* = 8.22 Hz), 8.95 d (2H, *J* = 8.22 Hz). ^{13}C NMR spectrum, δ, ppm: 13.7, 16.7, 110.6, 121.8, 129.5, 130.4, 130.6, 130.9, 131.5, 131.9, 133.5, 134.2, 135.6, 136.8, 138.4, 145.8, 152.3, 153.8, 154.7, 161.8, 165.6. MS (ESI): 456 $[M + H]^+$.

4-[3-(4-Bromobenzoyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]phenyl(3,5-dimethyl-1*H*-1-pyrazolyl)methanone (10e). Yield 82%, mp 320–322°C. ^{1}H NMR spectrum, δ, ppm: 2.38 s (3H), 3.40 s (3H), 6.23 s (1H), 7.68 t (1H), 7.81–7.87 m (3H), 7.89 d (2H, *J* = 8.19 Hz), 8.68 d (1H, *J* = 8.13 Hz), 8.86 d (2H, *J* = 8.23 Hz), 8.95 d (2H, *J* = 8.23 Hz). ^{13}C NMR spectrum, δ, ppm: 13.7, 16.7, 110.9, 121.7, 125.5, 129.7, 129.9, 130.5, 131.5, 133.6, 133.7, 134.6, 135.4, 135.8, 136.3, 145.8, 152.7, 153.8, 154.8, 162.3, 165.9. MS (ESI): 501 $[M + H]^+$.

(3,5-Dimethyl-1*H*-1-pyrazolyl)4-[3-(4-fluorobenzoyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]phenylmethanone (10f). Yield 82%, mp 310–312°C. ^{1}H NMR spectrum, δ, ppm: 2.38 s (3H), 3.40 s (3H), 6.23 s (1H), 7.66–7.70 m (3H), 7.83 d (1H, *J* = 8.14 Hz), 7.86 d (2H, *J* = 8.18 Hz), 8.67 d (1H, *J* = 8.12 Hz), 8.85 d (2H, *J* = 8.22 Hz), 8.94 d (2H, *J* = 8.22 Hz). ^{13}C NMR spectrum, δ, ppm: 13.7, 16.7, 110.8, 117.5, 121.4, 129.5, 129.8, 130.4, 131.5, 132.4, 133.5, 134.7, 135.2, 136.7, 145.7, 152.4, 153.7, 154.9, 158.7, 161.8, 164.9. MS (ESI): 440 $[M + H]^+$.

(3,5-Dimethyl-1*H*-1-pyrazolyl)4-[3-(4-nitrobenzoyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]phenylmethanone (10g). Yield 93%, mp 349–351°C. ^{1}H NMR spectrum, δ, ppm: 2.38 s (3H), 3.40 s (3H), 6.23 s (1H), 7.68 t (1H), 7.76 d (1H, *J* = 8.14 Hz), 8.10 d (2H, *J* = 8.24 Hz), 8.17 d (2H, *J* = 8.24 Hz), 8.67 d (1H, *J* = 8.12 Hz), 8.87 d (2H, *J* = 8.23 Hz), 8.96 d (2H, *J* = 8.23 Hz). ^{13}C NMR spectrum, δ, ppm: 13.7, 16.7, 110.9, 121.8, 125.7, 128.6, 129.7, 130.7, 131.4, 133.6, 134.7, 135.7, 136.6, 142.8, 145.9, 150.6, 152.4, 153.7, 154.8, 162.4, 165.9. MS (ESI): 467 $[M + H]^+$.

4-{(2-4-[(3,5-Dimethyl-1*H*-1-pyrazolyl)carbonyl]-phenyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)carbonyl}-benzonitrile (10h). Yield 94%, mp 356–358°C. ^{1}H NMR spectrum, δ, ppm: 2.38 s (3H), 3.40 s (3H), 6.23 s (1H), 7.69 t (1H), 7.76 d (1H, *J* = 8.15 Hz), 7.94 d (2H, *J* = 8.24 Hz), 8.09 d (2H, *J* = 8.24 Hz), 8.67 d (1H, *J* = 8.12 Hz), 8.87 d (2H, *J* = 8.23 Hz), 8.96 d (2H, *J* = 8.23 Hz). ^{13}C NMR spectrum, δ, ppm: 13.7, 16.7, 110.8, 115.6, 119.7, 121.7, 128.6, 129.7, 130.7, 131.4, 133.3, 134.5, 135.2, 135.8, 136.7, 136.9, 145.9, 152.4, 153.8, 154.9, 162.6, 165.9. MS (ESI): 447 $[M + H]^+$.

(3,5-Dimethyl-1*H*-1-pyrazolyl)4-[3-(4-methylbenzoyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]phenylmethanone (10i). Yield 78%, mp 309–311°C. ^{1}H NMR spectrum, δ, ppm: 2.30 s (3H), 2.38 s (3H), 3.40 s (3H), 6.23 s (1H), 7.49 d (2H, *J* = 8.18 Hz), 7.68 t (1H), 7.76–7.85 m (3H), 8.67 d (1H, *J* = 8.12 Hz), 8.85 d (2H, *J* = 8.20 Hz), 8.94 d (2H, *J* = 8.20 Hz). ^{13}C NMR spectrum, δ, ppm: 13.7, 16.7, 24.7, 110.7, 121.6, 127.5, 129.7, 130.5, 130.9, 131.5, 132.7, 133.4, 134.7, 135.7, 136.7, 141.8, 145.7, 152.4, 153.7, 154.7, 161.8, 164.7. MS (ESI): 436 $[M + H]^+$.

(3,5-Dimethyl-1*H*-1-pyrazolyl)(4-3-[4-(trifluoromethyl)benzoyl]-3*H*-imidazo[4,5-*b*]pyridin-2-ylphenyl)methanone (10j). Yield 79%, mp 314–316°C. ^{1}HNMR spectrum, δ, ppm: 2.38 s (3H), 3.40 s (3H), 6.23 s (1H), 7.69 t (1H), 7.78 d (1H, *J* = 8.16 Hz), 7.86 d (2H, *J* = 8.21 Hz), 8.30 d (2H, *J* = 8.21 Hz), 8.68 d (1H, *J* = 8.13 Hz), 8.85 d (2H, *J* = 8.22 Hz), 8.94 d (2H, *J* = 8.22 Hz). ^{13}C NMR spectrum, δ, ppm: 13.7, 16.7, 110.6, 114.8, 121.6, 127.6, 128.9, 129.6, 130.7, 131.7, 133.7, 134.8, 135.7, 135.9, 136.5, 136.8, 145.8, 152.7, 153.7, 154.8, 161.8, 164.9. MS (ESI): 490 $[M + H]^+$.

MTT assay. Cytotoxic activity of the compounds was determined using MTT assay. 1×10^4 Cells/well were seeded in 200 mL of DMEM, supplemented with 10% FBS in each well of 96-well microculture plates and incubated for 24 h at 37°C in a CO_2 incubator. Compounds, diluted to the desired concentrations in the culture medium, were added to the wells with the respective vehicle control. After 48 h of incubation, 10 mL MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] (5 mg/mL) was added to each well and the plates were further incubated for 4 h. The supernatant from each well was carefully removed, formazan crystals were dissolved in 100 mL of DMSO and absorbance at 540 nm wavelength was recorded.

CONCLUSIONS

A novel series of amide derivatives of imidazopyridine **10a**–**10j** is synthesized and their structures are confirmed by ^{1}H and ^{13}C NMR, and mass spectral data. The products are tested for their anticancer activity against four human cancer cell lines: lung cancer (A549), breast cancer (MCF-7), melanoma cancer (A375), and colon cancer

(HT-29). Among these, the compounds **10b**, **10c**, **10d**, **10g**, **10h**, and **10j** exhibit more potent activity than the control drug.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Charlson, A., *J. Carbohydr. Res., 19*73, vol. 29, p. 89. doi 10.1016/S0008-6215(00)82072-8
2. Cheng, J., Xie, J., and Luo, X., *Bioorg. Med. Chem. Lett*., 2005, vol. 15, p. 267. doi 10.1016/j.bmcl.2004.10.087
3. Sheng, J., Nguyen, T., Baldeck, J., Olsson, J., and Marquis, R., *Arch. Oral Biol*., 2006, vol. 51, p. 1015. doi 10.1016/j.archoralbio.2006.05.002
4. Walker, K., Braemer, A.C., Hitt, S., Jones, R.E., and Mathews, T R., *Med. Chem*., 1978, vol. 21, p. 840. doi 10.1021/jm00206a028
5. Deshpane, S.M., Datta, K.C., Sanyal, A.K., and Raina, M.K., *J. Med. Chem*., 1970, vol. 13, p. 143. doi 10.1021/jm00295a040
6. Mavrova, A.T., Anichina, K.K., Vuchev, D.I., Tsenov, J.A., Denkova, P.S., Kondeva, M.S., and Micheva, M.K., *Eur. J. Med. Chem*., 2006, vol. 41, p. 1412. doi 10.1016/j.ejmech.2006.07.005
7. Nakano, H., Inoue, T., Kawasaki, N., Miyataka, H., Matsumoto, H., Taguchi, T., and Inagaki, N., *Bioorg. Med. Chem*., 2000, vol. 8, p. 373. doi 10.1016/S0968-0896(99)00291-6
8. Tishler, R., Lamppu, D.M., Park, S., and Price, B.D., *Cancer Res.,* I995, vol. 55, p. 6021.
9. Bavetsias, V., Faisal, A., Crumpler, S., Brown, N., Kosmopoulou, M., Joshi, A., Atrash, B., Pérez-Fuertes, Y., Schmitt, J.A., Boxall, K.J., Burke, R., Sun, C., Avery, S., Bush, K., Henley, A., Raynaud, F.I., Workman, P., Bayliss, R., Linardopoulos, S., and Blagg, J., *J. Med. Chem*., 2013, vol. 56, p. 9122. doi 10.1021/jm401115g
10. Liu, C., Chen, Q., Yang, M., and Schneller, S.W., *Bioorg. Med. Chem*., 2013, vol. 21, p. 359. doi 10.1016/j.bmc.2012.09.051
11. Jose, G., Kumara, T.H.S., Nagendrappa, G., Sowmya, H.B.V., Jasinski, J.P., Millikan, S.P., Chandrika, N., More, S.S., and Harish, B.G., *Eur. J. Med. Chem*., 2014, vol. 77, p. 288. doi 10.1016/j.ejmech.2014.03.019
12. Grädler, U., Fuch, T., Ulrich, W.-R., Boer, R., Strub, A., Hesslinger, C., Anézo, C., Diederichs, K., and Zaliani, A., *Bioorg. Med. Chem. Lett*., 2011, vol. 21, p. 4228. doi 10.1016/j.bmcl.2011.05.073
13. Penning, T.D., Talley, J.J., Bertenshaw, S.R., Carter, J.S., Collins, P.W., Docter, S., Graneto, M.J., Lee, L.F., Malecha, J.W., Miyashiro, J.M., Rogers, R.S., Rogier, D.J., Yu, S.S., Anderson, G.D., Burton, E.G., Cogburn, J.N., Gregory, S.A., Koboldt, C.M., Perkins, W.E., Seibert, K., Veenhuizen, A.W., and Zhang, Y.Y., Isakson, P.C., *J. Med. Chem*., 1997, vol. 40, p. 1347. doi 10.1021/jm960803q