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Synthesis, Docking Studies and Anticancer Activity of Some Pyrazole Derivatives

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ABSTRACT A series of pyrazole derivatives **(2a-m)** was synthesized by the reaction of pongamol with various hydrazines **(1a-m)** derivatives. All the synthesized pyrazoles (**2a-m**) were screened for their anticancer potential against breast carcinoma (MCF7, MDA-MB-231), ovarian carcinoma (SKOV3) HeLa cervical cancer cells, and HEK293 and MCF10A normal cells. Among 13 compounds, seven compounds **PONG**, **2j**, **2k**, **2e**, **2m**, **2h**, and **2g** were found to have more than 50% cell inhibition. Docking study of synthesized compounds was also performed for enzyme CYP1A1 using SWISS DOCK.

KEYWORDS CYP1A1, Doxorubicin, MTT, Pongamol, Pyrazole

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INTRODUCTION

Over 85% of FDA-approved drugs incorporate heterocycles, with numerous heterocyclic compounds demonstrating potential efficacy against various cancers. Their unique structural adaptability and dynamic core architecture have played a pivotal role in advancing cancer research.[1] Heterocyclic derivatives, which contain at least two distinct elements, are central to the development of pharmacologically active compounds and high-performance organic materials, accounting for more than 75% of clinically utilized substances. Given their wide-ranging biological and pharmacological uses, heterocycles with elements such as sulfur, nitrogen, and/or oxygen including structures like thiophene, pyrazole, and imines – continue to captivate medicinal chemists and researchers alike.[2] Cancer, an abysmal disease, is characterized by the uncontrolled division and proliferation of cells.[3] Cancer developed when the body's normal cells failed to respond to signals that regulate cell division. There are various types of cancer based on organ or tissue such as cancers of colon, breast, lung, cervical, ovarian, prostate, skin, and lymphoma. The symptoms of various types of cancer vary depending on their type.[4] It is anticipated that according to a report, 16.40 million cancer-related deaths by 2024 and 29.50 million new instances of cancer annually.[5] Naturally derived heterocyclic frameworks are essential components in the development of diverse therapeutics used in biomedical applications.[6] Natural products, a major source of novel "therapeutic drugs", have revealed encouraging results as cytotoxic agents because of their enormous molecular diversity and emerging bio-functionalities.[7] Over and above that, natural products can provide higher efficacy and safety due to their unique molecular properties, as they produce physiological and pharmacological effects within living cells.[8] Pongamol, a benzofuran derivative, contains hydroxyl and methoxy groups along with beta keto enol moiety, and is an active constituent of the seeds *Pongamia pinnata* and roots of *Tephrosia purpurea*.[9-12] CYP1A1 is part of the cytochrome P450 (CYP) enzyme family, playing a critical role in the metabolism of various therapeutic compounds, including anticancer medications.[13,14] In view of above observation, we synthesized 13 pyrazole

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derivatives starting from pongamol and evaluated them for anticancer properties using different cell lines. Docking studies of synthesized derivatives were performed using the target protein CYP1A1 (PDB ID: 4I8V) to identify the behavior of molecules and binding sites of the target protein.

RESULTS AND DISCUSSION

Chemistry

A series of 13 pyrazole derivatives **(2a-m)** was synthesized through the reaction of pongamol with various hydrazines **(1a-m) [Scheme 1].** Out of 13 pyrazole derivatives, two are already reported [**2l**, **2m** are known in lit.]. All the newly synthesized compounds **(2a-m)** were characterized thoroughly by their spectral data.

Anticancer activity

Pongamol **(PONG)** and all pyrazole derivatives **(2a-m)** were screened for anticancer activity at 50 μM concentrations against different cell lines. The compounds that showed more than 50% cell inhibition in the primary screening were selected for further study. Among the tested compounds, compound **PONG**, **2j**, **2k**, **2e**, **2m**, **2h,** and **2g** were found to have more than 50% cell inhibition **[Figure 1].** These compounds were further tested against HeLa, MCF7, MDAMB231, and SKOV3 and normal cells (HEK293 and MCF10A) at concentration ranging from 3.125 to 100 μM **[Figure 2a]** depicts the cell viability using HeLa cell line in which compounds **2k** (81.75%, IC_{50} = 40.60μM), **2j** (70.66%, IC_{50} = 21.42 μM), and **2b** (55.04%, IC_{50} = 51.37 μM) showed a more prominent anticancer response than the **PONG** (52.59%, IC_{50} = 45.88 μM). When these compounds were tested using the MCF7 cell line, a similar type of response was shown by all these compounds as in HELA cell line **[Figure 2b]**. In the MDAMB231 cell line, the **2e** (54.79%, IC_{50} = 52.16 μM) showed a more prominent anticancer response than **PONG** (69.37%, IC_{50} = 125.59 μM) **[Figure 2c]**. Against the SKOV3 cell line, **2k** (78.82%, IC_{50} = 60.85 μM) and **2j** (85.17%, IC_{50} = 42.15 μM) showed better anticancer responses than their parent compound, **PONG** (44.35%, IC_{50} = 125.59 μM) **[Figure 2d]**. Doxorubicin showed cell inhibition ranging from 60% to 85% for four different cancer cell lines. The docking study of synthesized derivatives of **PONG** on enzyme CYP1A1 suggests that **2j**, **2k**, **2e**, **2m**, **2h**, and **2g** have good binding score.

Molecular docking

PONG and pyrazole derivatives **(2a-m)** were docked with CYP1A1 (PDB ID: 4I8V) enzyme using SWISS DOCK. The interaction of **PONG** and its pyrazoles **(2a-m)** to the active site residues of CYP1A1 exhibit a good docking score is shown in **Table 1**.

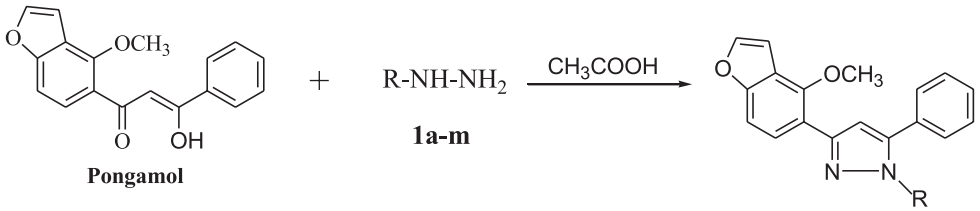
EXPERIMENTAL

The Nicolet 740 spectrometer was employed to record infrared spectra (IR) using KBr pellets. The ^{1}H and ^{13}C NMR experiments were conducted on a Bruker Advance-III 800 MHz NMR spectrometer, using $CDCl_3$ as an internal standard. The LC-MSD-Trap SL instrument was employed to measure mass spectra. Melting points were recorded in Thiel's tube using liquid paraffin.

Synthesis of pyrazoles (2a-m)

General procedure

To a solution of pongamol (1 mmol, 0.249 g) in glacial acetic acid (50 ml), added sodium acetate (0.328 g) and appropriate hydrazine derivative (1.2 mmol) with stirring. The solution was heated under reflux for 8–10 h (monitored by TLC). After refluxing the reaction mixture, the solvent removed by distillation. Then the residual material was suspended in water (50 mL) and transferred to the separating funnel and extracted with ethyl acetate (3 × 50 mL). The combined organic phase was concentrated under vacuum.



I	2	R	I	2	R
1a	**2a**	2-ClC_6H_4	**1h**	**2h**	4-CNC_6H_4
1b	**2b**	4-ClC_6H_4	**1i**	**2i**	4-$COOHC_6H_4$
1c	**2c**	2,4-$F_2C_6H_3$	**1j**	**2j**	$CSNH_2$,
1d	**2d**	4-C_5H_5N	**1k**	**2k**	$CONH_2$
1e	**2e**	2-$OCH_3C_6H_4$	**1l**	**2l**	C_6H_5
1f	**2f**	4-$OCH_3C_6H_4$	**1m**	**2m**	3-$OCH_3C_6H_4$
1g	**2g**	4-i $(CH_3)_2C_6H_4$			

Scheme 1: Synthesis of various pyrazole derivatives (2a-m)

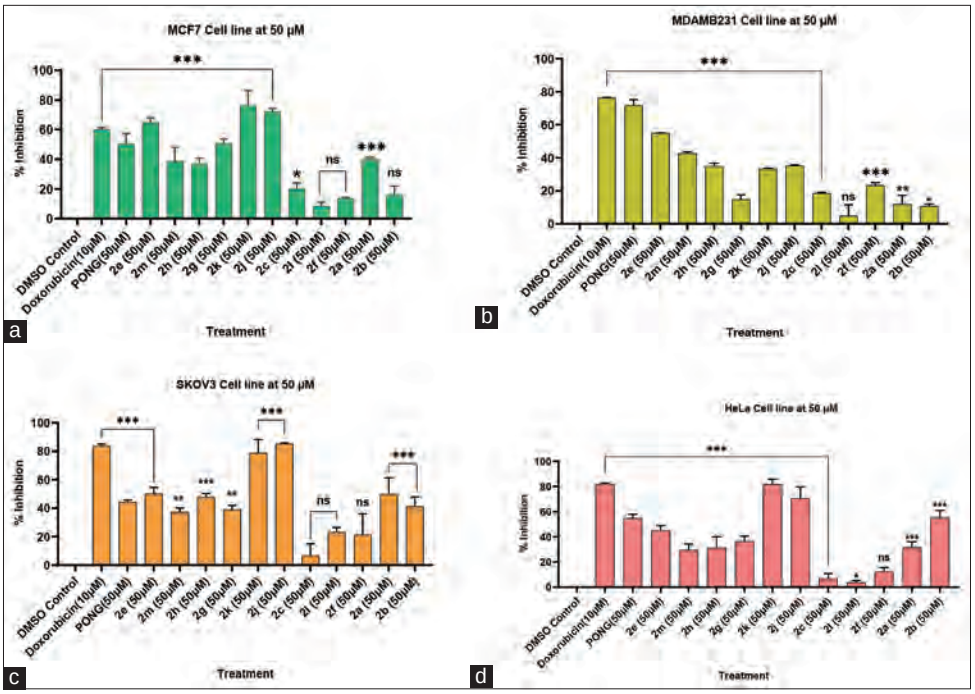


Figure 1: Antineoplastic activity of synthesized compounds targeting (a) breast cancer (MCF7), (b) breast cancer MDAMB231), (c) ovarian (SKOV3), (d) cervical (HeLa) cancer cell lines at 50 µM. One-way analysis of variance (ANOVA) was utilized for statistical analysis. Data are shown as means ± SD; *$P < 0.01$, **$P < 0.001$, ***$P < 0.0001$ compared to control (*significant, **highly significant, ***very highly significant)

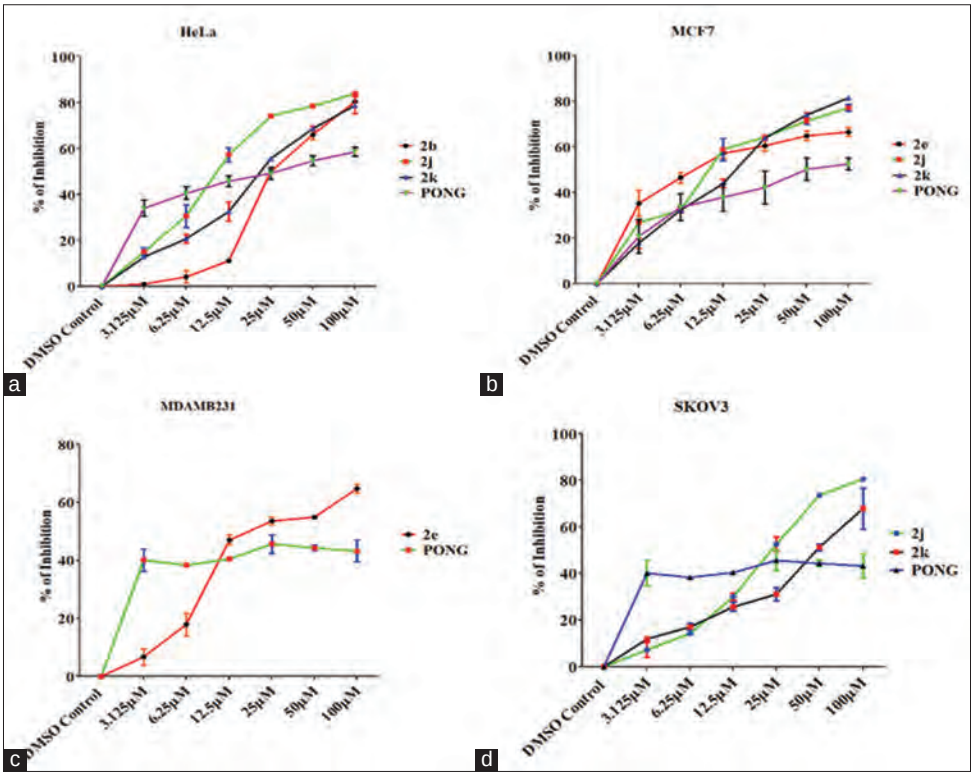


Figure 2: Concentrations dependent anticancer activity of compounds against (a) HeLa, (b) MCF7, (c) MDAMB231and (d) SKOV3 cell lines

The crude product was purified by column chromatography using silica gel 60–120 # as the stationary phase and a mobile phase composed of n-hexane and ethyl acetate in a 95: 5 ratio.

1-(2-Chlorophenyl)-3-(4-methoxybenzofuran-5-yl)-5-phenyl-1H-pyrazole (2a)

Yellow viscous liquid: IR ν (cm^{-1}): 1060.90, 1241.22, 1076.73, 1345.60, 1076 cm^{-1}; ^{1}HNMR (800 MHz, $CDCl_3$):

Table 1: The binding affinity of pyrazole derivatives with CYP1A1 enzyme

S. No.	Compounds	Binding energy	Hydrogen bond
1	**2e**	−7.51	GLY 231
2	**2g**	−8.17	-
3	**2h**	−8.42	MET 52, GLY 56
4	**2j**	−8.69	-
5	**2k**	−8.76	LEU 312
6	**2m**	−8.41	GLU 226, GLY 229

δ 7.31 (4-H, 1H), 7.56 (2'-H d, *J* = 2.4 Hz, 1H), 6.88 (3'-H, d, *J* = 0.8 Hz, 1H), 7.97 (6'-H, d, *J* = 1.6 Hz, 1H), 6.90 (7'-H, d, *J* = 1.6 Hz, 1H), 7.42–7.47 (2"-H, 3"-H, 4"-H, 5"-H, 6"-H, m, 5H), 7.16–7.31 (3"'-H, 4"'-H, 5"'-H, 6"'H m, 4H), 3.89 (OCH_3, s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): *δ* 157.26, 156.50, 152.13, 144.25, 143.11, 138.41, 129.59, 129.65, 128.63, 127.56, 125.92, 118.00, 114.86, 107.03, 105.77, 104.93, 59.67; ESI–MS: found 401.22 [M], 403.21 [M+2], $C_{24}H_{17}ClN_2O_2$ calculated 400.86.

1-(4-Chlorophenyl)-3-(4-methoxybenzofuran-5-yl)-5-phenyl-1H-pyrazole (2b)

Yellow viscous liquid: IR ν (cm^{-1}): 1240.73, 1065.51, 1014.62, 1698.26, 1339.46, 1091.61, 1557.63, 2922.17 cm^{-1}; ^{1}HNMR (800 MHz, $CDCl_3$): *δ* 7.31 (4-H, 1H), 7.56 (2'-H, d, *J* = 2.4 Hz, 1H), 6.88 (3'-H, d, *J* = 8.0 Hz, 1H), 7.97 (6'-H, d, *J* = 1.6 Hz, 1H), 6.90 (7'-H, d, *J* = 1.6 Hz, 1H), 7.42–7.47 (2"-H, 3"-H, 4"-H, 5"-H, 6"-H m, 5H), 7.16–7.31 (3"'-H, 4"'-H, 5"'-H, 6"'-H m, 4H), 3.89 (OCH_3, s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) *δ* 129.02, 128.85, 128.79, 125.80, 124.75, 106.96, 104.93; ESI–MS: found 401.19 [M], 403.17 [M+2] $C_{24}H_{17}ClN_2O_2$ calculated 400.86.

1-(2,4-Difluorphenyl)-3-(4-methoxybenzofuran-5-yl)-5-phenyl-1H-pyrazole *(2c)*

Yellow solid, yield: 75%, mp 128–130°C. IR ν (cm-1): 1139.13, 1270.04, 1068.50, 1683.89, 1337.51, 1606.35, 1234.26 cm-1. 1 HNMR (800 MHz, $CDCl_3$): δ 7.13 (4-H, 1H), 7.62 (2'-H, d, *J* = 3.2 Hz, 1H), 6.98 (3'-H, d, *J* = 3.2, 1H), 8.01 (6'-H d, *J* = 8 Hz, 1H), 7.00 (7'-H d, *J* = 2.4 Hz, 1H), 7.61–7.57 (2"-H, 3"-H, 4"-H, 5"-H, 6"-H, 5H), 7.35–7.30 (3"-H, 5"-H, 6"-H, 3H), 3.96 (-OCH_3, s, 3H); 13C NMR (200 MHz, $CDCl_3$): δ 162.50, 158.90, 156.78, 151.27, 145.63, 144.20, 13.29, 130.18, 128.54, 128.42, 125.58, 125.42, 118.37, 111.97, 111.75, 106.94, 105.18, 104.91, 60.47; ESI–MS: found 403.28 [M], $C_{24}H_{16}FN_2O_2$ calculated 402.39

3-[3-(4-Methoxybenzofuran-5-yl)-5-phenylpyrazol-1-yl]-pyridine (2d)

White solid, yield 55%, mp 103–105°C: IR ν (cm^{-1}): 1139.4, 1237.68, 1033.72, 1642.53, 1360.07, 1589.04, 1459.49, 682.06, 1448.14, 748.70 cm^{-1}; ^{1}HNMR (800 MHz, $CDCl_3$): *δ* 6.99 (4-H, s, 1H), 7.29 (2'-H, d, *J* = 2.8 Hz, 1H), 7.12 (3"-H, d, *J* = 2.8 Hz, 1H), 7.33 (6'-H, d, *J* = 0.8 Hz, 1H), 7.34 (7'-H, d, *J* = 8.0 Hz, 1H), 7.79 (3"-H, 2"-H, 4"-H, 5"-H, 6"-H m, 5H), 8.40 (2"'-H, *J* = 1.8 Hz, 1H), 8.41 (3"'-H, *J* = 1.8 Hz, 1H), 8.09 (4"'-H, 6"'-H, s, 2H), 4.11 (OCH_3, s, 3H). ^{13}C NMR (200 MHz, $CDCl_3$) *δ* 156.78, 152.67, 151.41, 148.43, 144.28, 138.17, 131.33, 128.76, 128.22, 128.05, 125.58, 122.25, 118.92, 118.92, 118.55, 106.96, 104.88, 60.57; ESI–MS: found 368.40 [M+], $C_{23}H_{17}N_3O_2$ calculated 367.40.

3-(4-Methoxybenzofuran-5-yl)-1-(2-methoxyphenyl)-5-phenyl-1H-pyrazole *(2e)*

Colorless crystalline solid, yield: 38%, mp 126–129°C. IR ν (cm-1): 1234.26, 1270.04, 1068.50, 1683.89, 1337.51, 1076.73, 1606.35, 3565.87 cm-1; 1H NMR (800 MHz, $CDCl_3$): δ 3.81 (3H, s, 2"'-OCH_3), 3.47 (3H, s, 4'-OCH_3), 6.88 (1H, s, 4-H), 6.90 (1H, d, *J* = 8 Hz, 3'-H), 7.60 (1H, d, 2'-H), 7.79 (2H, d, *J* = 2 Hz 6'-H, 7'-H), 7.56–7.53 (m, 1"-5"(5H); 13CNMR (200 MHz, $CDCl_3$): δ 158.53, 156.96, 151.93, 144.27, 133.64, 129.02, 128.59, 127.78, 126.02, 121.93, 119.50, 117.32, 108.18, 104.37, 59.95; HRMS m/z found 397.4421 [M+], ($C_{25}H_{20}N_2O_3$ requires 396.44).

3-(4-Methoxybenzofuran-5-yl)-1-(4-methoxyphenyl)5-phenyl-1H-pyrazole (2f)

White solid, yield: 40%, mp 99–101°C. IR ν (cm^{-1}): 1240.33, 1027.98 1217.47, 1058, 1646.90, 1363.34, 1461.47 cm^{-1}; ^{1}HNMR (800 MHz, $CDCl_3$): *δ* 3.76 (4'-OCH_3, s, 3H), 3.69 (3"'-OCH_3 s, 3H), 8.06 (2'-H, d, 1H), 6.78 (3'-H, d, 1H), 7.28 (7'-H, d, 1H), 7.29 (6'-H, d, 1H), 7.08 (4-H, s, 1H), 7.95–7.94 (2"'-H, 3"'-H, 5"'-H, 6"'-H, dd, *J* = 6 Hz, *J* = 2 Hz, 4H), 7.59–7.57 (1"-5"-H, m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 158.81, 157.39, 151.48, 144.42, 144.24, 134.33, 133.48, 128.88, 128.72, 128.57, 127.87, 127.57, 125.36, 119.68, 118.90, 115.66, 114.17, 113.91, 106.10,105.10, 105.26, 56.6, 55.5; HRMS m/z found 397.4423 [M+], ($C_{25}H_{20}N_2O_3$ requires 396.44).

1-(4-Isopropylphenyl)-3-(4-methoxybenzofuran-5-yl)5-phenyl-1H-pyrazole (2g)

White solid, yield 70%, mp 72–74°C: IR ν (cm^{-1}): 1237, 1053, 1592, 1342, 2958, 1004 cm^{-1}; ^{1}HNMR (800 MHz, $CDCl_3$): *δ* 7.57 (2'-H, 1H), 7.30 (6'-H, 1H), 7.44 (2"-H, 1H), 7.43 (6"-H, 1H), 7.32 (3"-H, 1H), 7.32 (5"-H, 1H), 7.22 (4"-H, 1H), 7.13 (3"'-H, 1H), 7.14 (4"'-H, 1H), 7.09 (4H, 1H), 7.13 (7'-H, 1H), 6.79 (3'-H, 1H)}, 3.64 (OCH_3, 3H), 3.60 (2'"-H, 1H), 1.26 (2"'-H, 1H), 1.25 (3"'-H, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) *δ* 157.46, 156.76, 151.61, 147.78, 144.40, 138.18, 128.95, 128.54, 127.03, 123.85, 118.35, 115.73, 106.37, 105.32, 59.42, 33.92, 24.12; HRMS m/z found 409.4914 [M+] ($C_{27}H_{24}N_2O_2$ requires 408.49).

4-[3-(4-Methoxybenzofuran-5-yl)-5-phenylpyrazol-1-yl] benzonitrile (2h)

Colorless crystalline solid, yield 75%, mp 157–159°C: IR ν (cm^{-1}): 1234.26, 1270.04, 1068.50, 1683.89, 1337.51, 1076.73, 1606.35, and 3565.87. ^{1}H NMR (800 MHz, $CDCl_3$): *δ* 3.65 (4'-OCH_3, 3H, s), 8.02 (2'-H, 1H, d), 6.89 (3'-H, 1H, d), 7.94 (6'-H, 1H, d), 6.99 (7'H, 1H, d), 7.09 (4-H), 7.40–7.36 (2"', 3"', 5"', 6"'-H, 4H, m), 7.33–7.36 (2"6"-H, 5H, m); ^{13}C NMR (200 MHz, $CDCl_3$): *δ* 157.83, 157.05, 152.95, 144.42, 133.01, 132.71, 129.01, 128.50, 127.06, 124.89, 119.53, 118.02, 114.81, 110.19, 106.47, 105.09, 59.36; HRMS m/z: found 392.4217 [M+], ($C_{25}H_{17}N_3O_2$ requires 391.42.

4-[3-(4-Methoxybenzofuran-5-yl)-5-phenylpyrazol-1-yl] benzoic acid (2i)

White solid, yield 78%, mp 186–188°C: IR ν (cm^{-1}): 1287.46, 1238, 1060.02, 1683.44, 1338.63, 1604.53,

1470.52, 694.69, 1741.56, 2952.93, 1312.56 cm^{-1}; ^{1}HNMR (800 MHz, $CDCl_3$): δ 4.1023 (4-OCH_3, s, 3H,), 8.05 (5"'-H, 3"'-H, d, *J* = 8.4 Hz, 2H), 7.51(6"'-H, 2'"-H, 6"-H, 2"-H, d, *J* = 8.8 Hz, 4H), 7.38 (3"-H, 4"-H, 5"-H, m, 3H), 7.32 (3"-H, 4"-H, 5"-H, s, 3H), 7.61 (2'-H, d, *J* = 2 Hz, 1H), 7.01 (3'-H, d, *J* = 2 Hz, 1H}, 7.26 (6'-H d, *J* = 2 Hz, 1H), 7.13 (7'-H, d, *J* = 2 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 172.05, 157.01, 151.50, 144.51, 131.14, 130.79, 129.07, 127.48, 124.51, 119.66, 118.38, 110.10, 107.16, 105.10, 60.67; ESI–MS: found 411.20 [M+], $C_{25}H_{18}N_2O_4$ calculated 410.42.

3-(4-Methoxybenzofuran-5-yl)-5-phenylpyrazole-1-carboxylic acid amide (2j)

Brown solid, yield: 45%, mp 95–98°C. IR ν (cm^{-1}): 1234.45, 1249.24, 1004.83, 1683.78, 1345.75, 1456.83, 3119.30, 1635.72 cm^{-1}. ^{1}HNMR (800 MHz, $CDCl_3$): δ 6.95 (NH_2, s, 2H), 4.16 (OCH_3, s, 3H), 7.02 (4H, s, 1H), 7.68 (2'-H d, *J* = 8.8 Hz, 1H), 7.34 (3'-H, d, *J* = 8.0 Hz, 1H), 7.91 (6'-H, d, *J* = 7.2 Hz 1H), 7.01 (7'-H d, *J* = 7.2 Hz, 1H), 7.35–7.47 (1"-H, 2"-H, 3"-H, 4"-H, 5"-H, 6"-H, m, 6H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 165.00, 156.56, 153.13, 150.13, 144.74, 132.19, 128.69, 128.66, 127.79, 124.55, 118.94, 107.31, 105.30, 105.00, 60.56; ESI–MS: found 334.44 [M+], $C_{19}H_{15}N_3O_3$ calculated 333.34.

3-(4-Methoxybenzofuran-5-yl)-5-phenylpyrazole-1-carbothioic acid amide (2k)

White crystalline solid, yield: 55%, mp 162–164°C. IR ν (cm^{-1}): 1339.07, 1647.35, 1339.07, 1623.69, 3525.58, 1636 cm^{-1}. ^{1}HNMR (800 MHz, $CDCl_3$): δ 7.26 (4-H, 1H), 3.80 (OCH_3, 3H, s), 6.92 (CS-NH_2, 2H, s), 7.62 (2H, d, *J* = 2 Hz, 2'H), 6.99 (3'-H, d, *J* = 2 Hz, (1H), 7.88 (6'-H, d, *J* = 8 Hz, 1H), 7.66 (7'-H, d, *J* = 8 Hz, 1H), 7.31–7.34 (2"-H, 6"H, 2H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 156.55, 150.12, 144.72, 133.35, 128.68, 127.79, 124.53, 118.91, 107.29, 105.00, 100.00, 60.50; ESI–MS: found 350.41 [M+], $C_{25}H_{17}N_3O_2$ calculated 349.41.

3-(4-Methoxybenzofuran-5-yl)-1,5-diphenyl1H-pyrazole (2l)

mp 155–156°C, lit. mp 156–157°C.[15]

3-(4-Methoxybenzofuran-5-yl)-1-(3-methoxyphenyl)-5-phenyl-1H-pyrazole (2m)

mp 127–130°C.[15]

Anticancer activity

MTT assay

The cytotoxic effects of the synthesized compounds were assessed using an MTT cell viability assay.[16-19] Graphs were generated using GraphPad Prism 5.0.

CONCLUSION

A series of some new pyrazole-based heterocyclic compounds was synthesized using a common scaffold in this study. The 13 synthesized derivatives were obtained in significant yields and characterized through FTIR, proton (1H), and C13 NMR, as well as mass spectrometry and assessed their *in vitro* anticancer activities using breast cancer (MCF7 and MDA-MB-231), ovarian cancer (SKOV3), and cervical cancer (HeLa) cell lines. Docking analysis further suggested that these derivatives exhibit potential anticancer activity. These derivatives would significantly accelerate the drug development process by reducing the risk of harmful effects on healthy tissues and organs.

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