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Synthesis and Antimicrobial Evaluation of Some Chalcones and Their Derived Pyrazoles, Pyrazolines, Isoxazolines, and 5,6-Dihydropyrimidine-2-(1*H*)-thiones

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Summary. Chalcones were synthesized by a base catalyzed *Claisen-Schmidt* condensation reaction. Bromination of chalcones afforded the dibromo derivatives. Monobromo derivatives could be obtained by treating the corresponding dibromochalcones with dry benzene in the presence of triethylamine. Pyrazole derivatives were obtained by refluxing of dibromochalcones with phenylhydrazine or 2,4-dinitrophenylhydrazine in dry pyridine. Chalcones were treated with hydrazine hydrate or phenyl hydrazine in ethanol to afford Δ^2-pyrazolines and *N*-phenyl-Δ^2-pyrazolines. Condensation of chalcones with hydroxylamine hydrochloride or thiourea in ethanolic sodium hydroxide solution gave 4,5-dihydroisoxazoles and 5,6-dihydropyrimidine-2-(1*H*)-thiones. The prepared compounds were tested for antimicrobial activity against four different bacterial species displaying different degrees of antibacterial activities or inhibitory actions.

Keywords. Chalcones; Pyrazoles; Pyrazolines; Isoxazolines; 2-Thioxopyrimidines.

Introduction

For a structurally simple group of compounds, chalcones have displayed an impressive array of biological activities, among which anti-malarial [1], anti-protozoal [2], anti-inflammatory [3], immunomodulatory [4], nitric oxide inhibition [5], tyronase inhibition [6], cytotoxic [7], and anticancer [8] activities have been cited in literature. These compounds obtained by convenient synthesis methods strongly inhibit the polymerization of tubulin by binding to the colchicine-binding site [9]. The relatively simple structure and high affinity of chalcones for the colchicine-binding site because of similarity of the two-aryl group placements in the two molecules has led to the synthesis and subsequent evaluation of a large number of chalcones [10]. The synthesis of arylpyrazoles is of major interest [11]. Indeed these constitute an important class of heterocyclic compounds because this ring system is present in numerous compounds of therapeutic importance including a number of marketed drugs, such as Celecoxib (Celebrex®) or Deracoxib (Fig. 1) [12]. Due to the importance of these pharmacological properties, significant efforts toward the synthesis of this kind of compounds have been carried out in the last years [13]. Functionalized isoxazoline and isoxazole derivatives are active pharmacophores in several pharmacologically important molecules [14], and are also useful intermediates for the synthesis of a wide variety of bioactive natural products [15]. Thioxopyrimidine is an essential structural unit of several heterocycles, which display a wide range of interesting biological and pharmacological properties, such as anticancer and antimicrobial activities [16]. Despite these characteristics there are few synthesis methodologies for this class of heterocycles [17].

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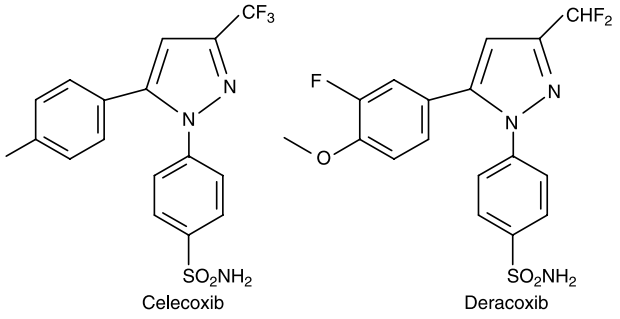


Fig. 1. Structures of Celecoxib and Deracoxib

Our interest in the synthesis of such compounds was to shed some light on their biological study as antimicrobial agents as a part of our program aimed at the development of new heterocyclic compounds with potential biological activities [18].

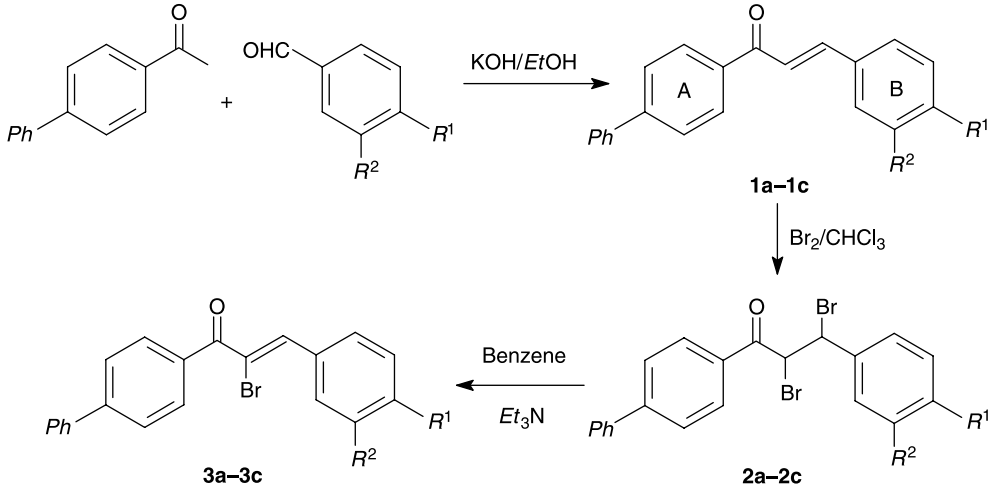
Results and Discussion

Synthesis

Chalcones **1a**–**1c** were synthesized by a base catalyzed *Claisen-Schmidt* condensation reaction [19] of appropriately substituted acetophenones and aldehydes. The method is attractive since it specifically generates the (*E*)-isomer. The IR spectra show the characteristic band for C=O at 1690–1695, C=C Ar at 1600 and 1475, while the vinyl CH=CH appeared at 1295–1300 cm^{-1}. From ^{1}H NMR spectra, all chalcones were geometrically pure and with *trans*-configuration ($J_{H_\alpha\text{-}H_\beta} = 15.50$–$15.60$ Hz). Saturation of the double bond or variation of the aliphatic part results in loss of the anti-inflammatory activity [20]. So, bromination of chalcones was carried out by adding bromine dropwise to the clear solution of **1a**–**1c** in chloroform to afford the corresponding 2,3-dibromochalcones **2a**–**2c**. Monobromo derivatives could be obtained from the corresponding dibromochalcones according to the method described by *Holla et al.* [21]. So, treatment of **2a**–**2c** with dry benzene in the presence of triethylamine afforded **3a**–**3c** (Scheme 1).

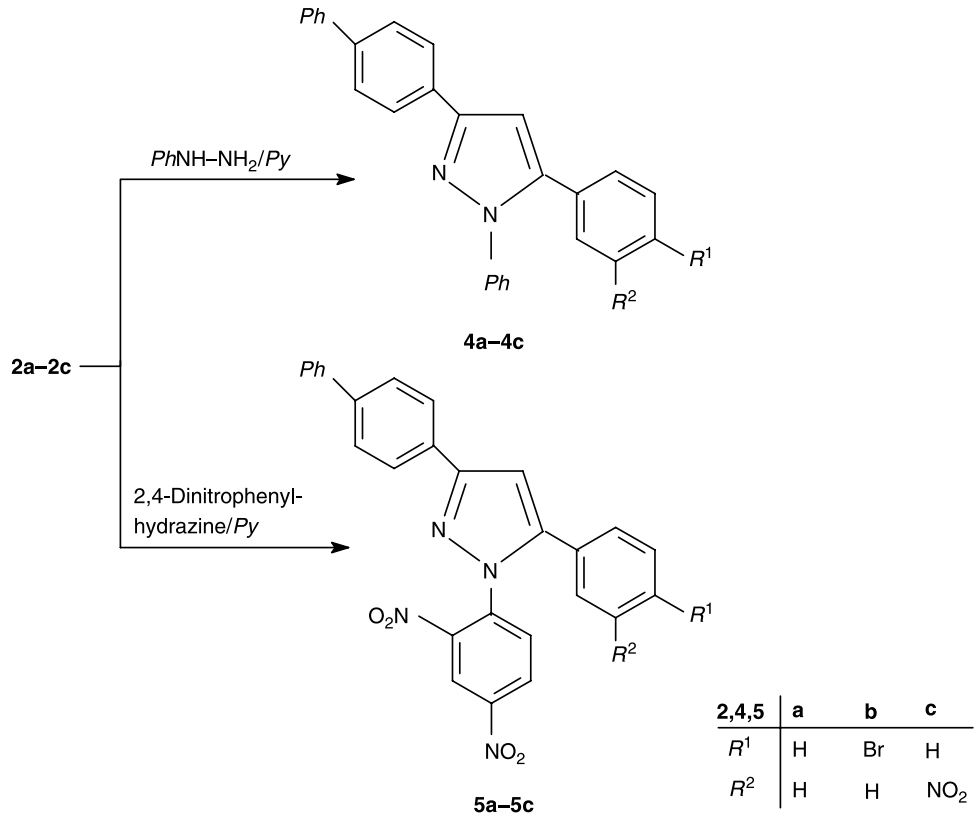
The pyrazole derivatives **4a**–**4c** or **5a**–**5c** were obtained by refluxing of dibromochalcones **2a**–**2c** with phenylhydrazine or 2,4-dinitrophenylhydrazine in dry pyridine. The IR spectra of **4a**–**4c** or **5a**–**5c** showed the characteristic band for C=N at 1673–1680 and C=C–Ar at 1598–1600 and 1450–1456 cm^{-1}, while the ^{1}H NMR spectra showed a singlet at $\delta =$ 6.84–6.99 ppm for the pyrazole-H-4 (Scheme 2).

It has been reported that, α,β-unsaturated ketones can react with hydrazine hydrate or phenylhydrazine to give the corresponding pyrazolines [22]. So, **1a**–**1c** were treated with hydrazine hydrate or phenyl hydrazine in ethanol to afford the Δ^2-pyrazolines



1–3	a	b	c
R^1	H	Br	H
R^2	H	H	NO_2

Scheme 1

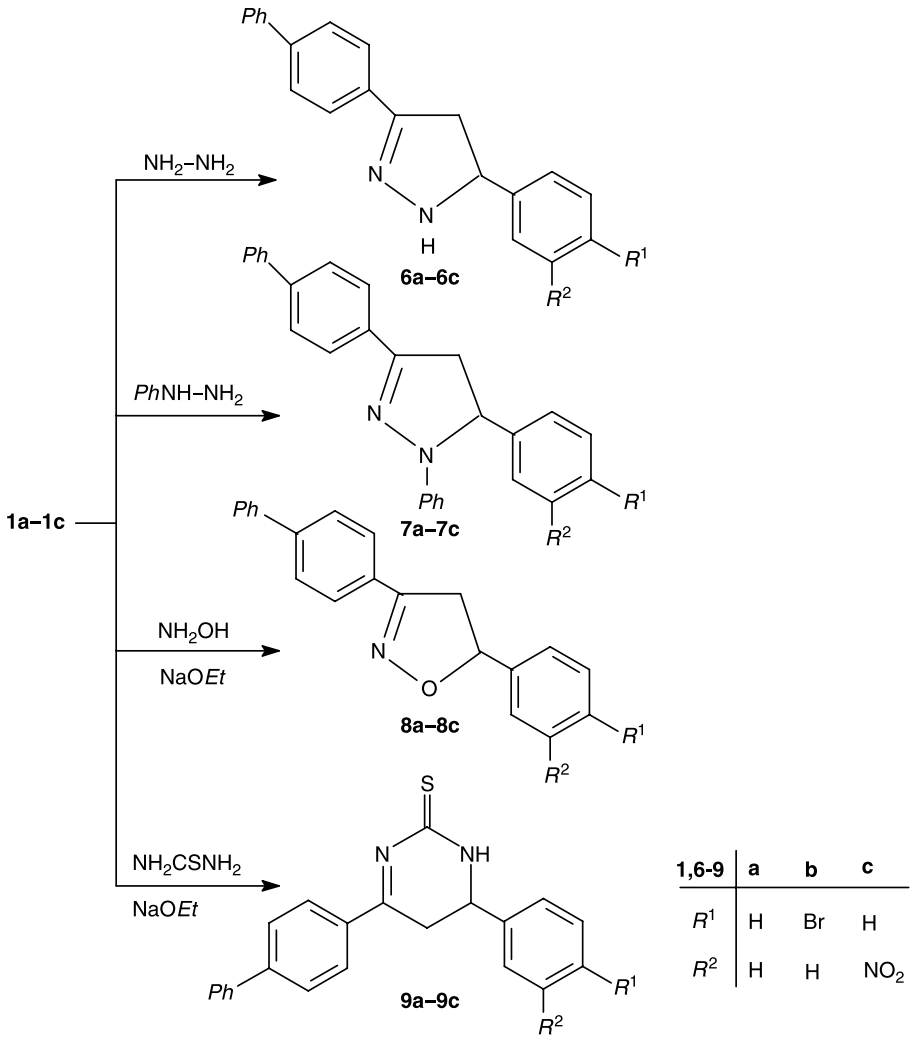


Scheme 2

6a–**6c** in 73–75% yields, and *N*-phenyl-Δ^2-pyrazolines **7a**–**7c** in 80–89% yields. The IR spectra of **6a**–**6c** showed the characteristic band for NH at 3370–3380 and C=N at 1690–1695 cm^{-1}. The ^1H NMR spectra showed two doublets at $\delta = 3.00$–3.03 and 3.50–3.57 ppm for the pyrazoline-H-4, while pyrazoline-H-5 appeared as a triplet at $\delta = 4.90$–4.98 ppm. The ^1H NMR spectra of **7a**–**7c** showed two doublets at $\delta = 3.15$–3.18 and 3.87–3.96 ppm for the pyrazoline-H-4 and a triplet at $\delta = 5.42$–5.50 ppm for the pyrazoline-H-5. Condensation of **1a**–**1c** with hydroxylamine hydrochloride or thiourea in ethanolic sodium hydroxide solution gave 4,5-dihydroisoxazoles **8a**–**8c** in 80–86% yields, and 5,6-dihydropyrimidine-2(1*H*)-thiones **9a**–**9c** in 75–80% yields. The ^1H NMR spectra of **8a**–**8c** showed two doublets at $\delta = 3.58$–3.62 and 3.86–3.90 ppm for the isoxazoline-H-4 and a triplet at $\delta = 5.91$–5.97 ppm for the isoxazoline-H-5. The IR bands of **9a**–**9c** showed the characteristic band for NH at 3320–3335, SH at 2450–2460, and C=N at 1690 cm^{-1}. The ^1H NMR spectra showed two doublets at $\delta = 5.06$–5.11 and 5.23–5.25 ppm for the dihydro-2-thioxopyrimidine-H-5, a triplet at $\delta = 5.45$–5.59 ppm for the dihydro-2-thioxopyrimidine-H-6, and a broad singlet at $\delta = 12.74$–12.80 ppm for the SH group (Scheme 3).

Antimicrobial Activity

The newly synthesized compounds were tested for their antimicrobial action [23] against four different bacterial species namely, *Pseudomonas sp.* (*Gram* negative bacterium), *Bacillus subtilis* (*Gram* positive bacterium), *Bacillus cereus* (*Gram* positive bacterium), and *Streptomyces sp.* (one of the important actinomycetes). All the tested compounds exhibited different degrees of antibacterial activities or inhibitory actions. The most susceptible organisms were the two *Gram* positive bacteria (*Bacillus subtilis* and *Bacillus cereus*) followed by *Streptomyces sp.*, while the lowest inhibitory effect was encountered in the case of *Pseudomonas sp.* The highest degrees of inhibition were recorded for compounds **4a**–**4c** and **5a**–**5c** followed by **1a**–**1c**, **3a**–**3c**, **6a**–**6c**, **7a**–**7c**, **8a**–**8c** and **9a**–**9c**, while the lowest degree of inhibition was recorded for the dibromochalcones **2a**–**2c** (Table 1). The results were compared to amoxicillin (penicillin) as a reference drug.



Scheme 3

Conclusions

Chalcones and their derived analogues were assayed for antimicrobial activity against four different bacterial species. By comparing the antimicrobial activity of these compounds, the following conclusions were drawn: (a) presence of Br-atom on 4-position of ring B led to a higher antimicrobial activity than a nitro group in the 3-position as well as no substitution on the ring. (b) Converting α,β-unsaturated ketones **1a**–**1c** to the corresponding dibromochalcones **2a**–**2c** dramatically reduced the antimicrobial activity. This result demonstrated that the conformation of the two aryl rings in the molecule has an essential role to play for the activity of chalcones and the double bond seems to be a crucial moiety as reported earlier [24]. (c) Converting dibromochalcones **2a**–**2c** to the monobromo derivatives **3a**–**3c** resulted in the re-appearance of the activity comparable to **2a**–**2c**. (d) Converting **2a**–**2c** to the corresponding pyrazoles **4a**–**4c** and **5a**–**5c**, the antimicrobial activity was enhanced to its maximum, in fact higher than that of the chalcones **1a**–**1c**. This result demonstrated that the introduction of the pyrazole nucleus between two aryl rings enhanced the rigidity besides polarity and solubility in the molecule, which played an integral role for their increase in antimicrobial activity. (e) Pyrazolines **6a**–**6c** showed a higher antimicrobial activity than the *N*-phenylpyrazolines **7a**–**7c**. This result showed that the pyrazoline nucleus might be the active binding site, which becomes deactivated by arylation. (f) Isoxazolines **8a**–**8c** and 2-thioxopyrimidines **9a**–**9c** showed moderate antimicrobial activity.

Table 1. Antimicrobial activity of the newly synthesized compounds **1–9**

Compd no.	*Pseudomonas sp.*	*Bacillus subtilis*	*Bacillus cereus*	*Streptomyces sp.*
Amoxicillin (Penicillin)	−	++	+++	+
1a	−	+++	+++	++
1b	−	+++	+++	+
1c	−	+++	+++	+
2a	−	+	+	−
2b	+	+	+	+
2c	+	+	+	−
3a	+	++	++	+
3b	+	+++	+++	+
3c	+	++	++	+
4a	+	++++	++++	++
4b	+	++++	++++	++
4c	+	++++	++++	++
5a	+	++++	++++	+
5b	+	++++	+++	+
5c	+	++++	++++	+
6a	+	+++	+++	+
6b	+	+++	+++	++
6c	+	+++	+++	+
7a	+	++	++	+
7b	+	++	++	+
7c	+	++	++	+
8a	+	++	++	++
8b	+	++	++	+
8c	+	++	++	+
9a	+	++	++	+
9b	+	++	++	+
9c	+	++	++	+

− No antibacterial effect
+ Low antibacterial effect
++ Moderate antibacterial effect
+++ High antibacterial effect
++++ Complete antibacterial effect

Experimental

Melting points were determined using a *Kofler* block instrument. IR spectra were recorded with a Perkin-Elmer model 1720 FTIR (KBr), ^{1}H NMR spectra were recorded with a Bruker AC 250 FT NMR spectrometer at 250 MHz with *TMS* as an internal standard. MALDI-MS were measured with a KRATOS Analytical Compact, using 2,5-dihydroxybenzoic acid (*DHB*) as matrix. The $(M+Na)^+$ ions were peak-matched using ions derived from the 2,5-dihydroxybenzoic acid matrix. The microanalyses were performed at the micro-analytical unit, Cairo University, Egypt, and were found to agree favourably with the calculated values. Antimicrobial activity of the synthesized compounds was conducted at the Botany Department, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt.

*General Procedure for the Preparation of Chalcones **1a–1c***

To a solution of 1.96 g 4-phenylacetophenone (10 mmol) in ethanol, an aqueous solution of 10 cm^3 10% NaOH or 2 drops piperidine was added. The resulting solution was heated to 80°C and substituted benzaldehydes (10 mmol) were added with constant stirring. The reaction mixture was kept stirring at this temperature for 3–4 h, cooled to room temperature, and was allowed to stand overnight. The solid product separated was collected by filtration, dried, and recrystallized from ethanol to give **1a–1c** in 80–88% yields.

(E)-1-(Biphenyl-4-yl)-3-phenylprop-2-en-1-one
(**1a**, $C_{21}H_{16}O$)

Pale yellow powder (88%); $R_f = 0.33$ (petroleum ether: CH_2Cl_2, 2:1); mp 143–145°C; IR (KBr): $\bar{\nu} = 1695$ (C=O), 1600, 1475 (C=C Ar), 1295 (CH=CH) cm^{-1}; ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): $\delta = 7.33$–7.48 (m, Ar–H), 7.50–7.53 (m, Ar–H), 7.56 (d, $J = 15.5$ Hz, COC*H*=CH), 7.80–7.90 (m, Ar–H), 7.92 (d, $J = 15.5$ Hz, COCH=C*H*) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 307 [$(M+Na)^+$, 59].

(E)-1-(Biphenyl-4-yl)-3-(4-bromophenyl)prop-2-en-1-one
(**1b**, $C_{21}H_{15}BrO$)

Yellow powder (85%); $R_f = 0.38$ (petroleum ether:CH_2Cl_2, 2:1); mp 203–204°C; IR (KBr): $\bar{\nu} = 1690$ (C=O), 1600, 1475 (C=C Ar), 1295 (CH=CH) cm^{-1}; ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): $\delta = 7.46$–7.51 (m, Ar–H), 7.58 (d, $J = 15.6$ Hz, COC*H* = CH), 7.70–7.88 (m, Ar–H), 7.90 (d, $J = 15.6$ Hz, COCH=C*H*) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 385 [$(M+Na)^+$, 45].

(E)-1-(Biphenyl-4-yl)-3-(3-nitrophenyl)prop-2-en-1-one
(**1c**, $C_{21}H_{15}NO_3$)

Yellow powder (80%); $R_f = 0.32$ (petroleum ether:CH_2Cl_2, 2:1); mp 190–192°C; IR (KBr): $\bar{\nu} = 1693$ (C=O), 1600, 1475 (C=C Ar), 1300 (CH=CH) cm^{-1}; ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): $\delta = 7.33$–7.53 (m, Ar–H), 7.57–7.63 (m, Ar–H), 7.69–7.85 (m, Ar–H), 7.90–8.18 (m, Ar–H), 8.27 (d, $J =$ 15.6 Hz, COC*H*=CH), 8.54 (d, $J = 15.6$ Hz, COCH=C*H*) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 352 [$(M+Na)^+$, 33].

*General Procedure for the Preparation of 2,3-Dibromochalcones **2a–2c***

Bromine (1.6 g, 10 mmol) was added dropwise with vigorous stirring to a solution of **1a–1c** (10 mmol) in 10 cm^3 $CHCl_3$ over 30 min. After complete addition of Br_2, the reaction mixture was allowed to stand for 1 h. The dibromo derivatives were precipitated, filtered off, and washed with 3×10 cm^3 ether to remove the excess of Br_2. Recrystallization from ethanol afforded **2a–2c** in 85–90% yields.

1-(Biphenyl-4-yl)-2,3-dibromo-3-phenylpropan-1-one
(**2a**, $C_{21}H_{16}Br_2O$)

White powder (88%); $R_f = 0.68$ (petroleum ether:CH_2Cl_2, 2:1); mp 208–210°C; ^{1}H NMR (*DMSO*-d$_6$, 250 MHz): $\delta =$

5.65 (d, $J = 2.5$ Hz, CH), 5.77 (d, $J = 2.5$ Hz, CH), 7.12–7.26 (m, Ar–H), 7.48–7.52 (m, Ar–H), 7.75–7.82 (m, Ar–H), 7.90–8.03 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 464 [$(M + Na)^+$, 22].

1-(Biphenyl-4-yl)-2,3-dibromo-3-(4-bromophenyl)propan-1-one (**2b**, $C_{21}H_{15}Br_3O$)
White powder (90%); $R_f = 0.72$ (petroleum ether:CH_2Cl_2, 2:1); mp 240–242°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): δ = 5.62 (d, $J = 2.5$ Hz, CH), 5.73 (d, $J = 2.5$ Hz, CH), 7.02–7.17 (m, Ar–H), 7.48–7.59 (m, Ar–H), 7.72–7.79 (m, Ar–H), 7.97–8.00 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 542 [$(M + Na)^+$, 14].

1-(Biphenyl-4-yl)-2,3-dibromo-3-(3-nitrophenyl)propan-1-one (**2c**, $C_{21}H_{15}Br_2NO_3$)
White powder (85%); $R_f = 0.72$ (petroleum ether:CH_2Cl_2, 2:1); mp 130–131°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): δ = 5.66 (d, $J = 2.5$ Hz, CH), 5.77 (d, $J = 2.5$ Hz, CH), 7.40–7.57 (m, Ar–H), 7.72–7.82 (m, Ar–H), 8.00–8.07 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 509 [$(M + Na)^+$, 17].

General Procedure for the Preparation of 2-Bromochalcones ***3a–3c***
Triethylamine (4.04 g, 40 mmol) in 30 cm^3 dry benzene was added to a solution of **2a–2c** (10 mmol) in 100 cm^3 dry benzene with stirring. The reaction mixture was stirred at room temperature for 24 h. After removal of the separated triethylamine hydrobromide, the filtrate was concentrated under reduced pressure. The residue was recrystallized from ethanol to give **3a–3c** in 86–90% yields.

(Z)-1-(Biphenyl-4-yl)-2-bromo-3-phenylprop-2-en-1-one (**3a**, $C_{21}H_{15}BrO$)
Brown powder (87%); $R_f = 0.16$ (petroleum ether:CH_2Cl_2, 2:1); mp 100–102°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): δ = 7.30–7.43 (m, Ar–H), 7.75–7.83 (m, Ar–H), 8.44 (s, CH) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 385 [$(M + Na)^+$, 76].

(Z)-1-(Biphenyl-4-yl)-2-bromo-3-(4-bromophenyl)prop-2-en-1-one (**3b**, $C_{21}H_{14}Br_2O$)
Pale brown powder (90%); $R_f = 0.18$ (petroleum ether:CH_2Cl_2, 2:1); mp 109–111°C; ^{1}H NMR (*DMSO*-d_6, 250 MHz): δ = 7.19–7.33 (m, Ar–H), 7.45–7.49 (m, Ar–H), 7.75–7.89 (m, Ar–H), 8.47 (s, CH) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 462 [$(M + Na)^+$, 43].

(Z)-1-(Biphenyl-4-yl)-2-bromo-3-(3-nitrophenyl)prop-2-en-1-one (**3c**, $C_{21}H_{14}BrNO_3$)
Pale brown gum (86%); $R_f = 0.12$ (petroleum ether:CH_2Cl_2, 2:1); ^{1}H NMR (*DMSO*-d_6, 250 MHz): δ = 7.40–7.46–7.33 (m, Ar–H), 7.69–7.88 (m, Ar–H), 8.15–8.28 (m, Ar–H), 8.58 (s, CH) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 430 [$(M + Na)^+$, 53].

General Procedure for the Preparation of Pyrazoles ***4a–4c*** and ***5a–5c***
A mixture of **2a–2c** (10 mmol), phenylhydrazine or 2,4-dinitrophenylhydrazine (20 mmol) in 20 cm^3 dry pyridine was refluxed in an oil bath for 14 h (TLC). The reaction mixture was poured onto crushed ice and the residual oil was extracted with 3×100 cm^3 $CHCl_3$. The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using 5% $CHCl_3$ in petroleum ether to give **4a–4c** in 72–80% and **5a–5c** in 70–75% yields.

3-(Biphenyl-4-yl)-1,5-diphenyl-1H-pyrazole (**4a**, $C_{27}H_{20}N_2$)
Pale yellow crystals (80%); $R_f = 0.34$ (petroleum ether: CH_2Cl_2, 2:1); mp 121–123°C; IR (KBr): $\bar{\nu} = 1677$ (C=N), 1598, 1456 (C=C Ar) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 6.88$ (s, pyrazole-H-4), 7.33–7.46 (m, Ar–H), 7.47–7.77 (m, Ar–H), 7.95–8.04 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 395 [$(M + Na)^+$, 32].

3-(Biphenyl-4-yl)-5-(4-bromophenyl)-1-phenyl-1H-pyrazole (**4b**, $C_{27}H_{19}BrN_2$)
Pale brown crystals (78%); $R_f = 0.39$ (petroleum ether: CH_2Cl_2, 2:1); mp 145–147°C; IR (KBr): $\bar{\nu} = 1680$ (C=N), 1600, 1456 (C=C Ar) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 6.85$ (s, pyrazole-H-4), 7.40–7.50 (m, Ar–H), 7.60–7.80 (m, Ar–H), 7.90–8.07 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 473 [$(M + Na)^+$, 30].

3-(Biphenyl-4-yl)-5-(3-nitrophenyl)-1-phenyl-1H-pyrazole (**4c**, $C_{27}H_{19}N_3O_2$)
Pale yellow crystals (72%); $R_f = 0.38$ (petroleum ether: CH_2Cl_2, 2:1); mp 153–155°C; IR (KBr): $\bar{\nu} = 1679$ (C=N), 1600, 1450 (C=C Ar) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 6.84$ (s, pyrazole-H-4), 7.43–7.59 (m, Ar–H), 7.88–8.03 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 440 [$(M + Na)^+$, 19].

3-(Biphenyl-4-yl)-1-(2,4-dinitrophenyl)-5-phenyl-1H-pyrazole (**5a**, $C_{27}H_{18}N_4O_4$)
Yellow crystals (75%); $R_f = 0.34$ (petroleum ether:CH_2Cl_2, 2:1); mp 175–177°C; IR (KBr): $\bar{\nu} = 1675$ (C=N), 1600, 1450 (C=C Ar) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 6.94$ (s, pyrazole-H-4), 7.33–7.69 (m, Ar–H), 7.85–7.93 (m, Ar–H), 8.35–8.44 (m, Ar–H), 8.74–8.79 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 485 [$(M + Na)^+$, 29].

3-(Biphenyl-4-yl)-5-(4-bromophenyl)-1-(2,4-dinitrophenyl)-1H-pyrazole (**5b**, $C_{27}H_{17}BrN_4O_4$)
Yellow crystals (74%); $R_f = 0.38$ (petroleum ether:CH_2Cl_2, 2:1); mp 166–168°C; IR (KBr): $\bar{\nu} = 1679$ (C=N), 1600, 1450 (C=C Ar) cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 250 MHz): $\delta = 6.99$ (s, pyrazole-H-4), 7.30–7.65 (m, Ar–H), 7.85–7.90 (m, Ar–H), 8.30–8.40 (m, Ar–H), 8.70–8.80 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 563 [$(M + Na)^+$, 29].

3-(Biphenyl-4-yl)-1-(2,4-dinitrophenyl)-5-(3-nitrophenyl)-1H-pyrazole (**5c**, $C_{27}H_{17}N_5O_6$)
Yellow crystals (70%); $R_f = 0.41$ (petroleum ether:CH_2Cl_2, 2:1); mp 155–157°C; IR (KBr): $\bar{\nu} = 1673$ (C=N), 1600, 1450 (C=C Ar) cm^{-1}; ^1H NMR (*DMSO*-d_6, 250 MHz): $\delta = 6.92$ (s, pyrazole-H-4), 7.30–7.60 (m, Ar–H), 7.80–7.94 (m, Ar–H), 8.42–8.65 (m, Ar–H), 8.73–8.86 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 530 [$(M + Na)^+$, 25].

*General Procedure for the Preparation of Pyrazolines **6a–6c** and N-Phenylpyrazolines **7a–7c***
A mixture of **1a–1c** (5 mmol), 0.13 cm^3 $N_2H_4 \cdot H_2O$ (5 mmol) and/or 0.27 cm^3 phenylhydrazine (5 mmol) in 25 cm^3 ethanol was refluxed for 8 h (TLC). The reaction mixture was cooled, the precipitate was filtered off, and recrystallized from ethanol to give **6a–6c** in 73–75% yields, and **7a–7c** in 80–89% yields.

3-(Biphenyl-4-yl)-5-phenyl-4,5-dihydro-1H-pyrazole (**6a**, $C_{21}H_{18}N_2$)
Pale yellow powder (75%); $R_f = 0.30$ (petroleum ether: CH_2Cl_2, 2:1); mp 125–127°C; IR (KBr): $\bar{\nu} = 3375$ (NH), 1690 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, 250 MHz): $\delta =$ 3.00, 3.51 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 4.98 (t, $J = 3.6$ Hz, pyrazoline-H-5), 7.08 (br s, NH), 7.12–7.23 (m, Ar–H), 7.33–7.50 (m, Ar–H), 7.70–7.84 (m, Ar–H), 7.90–7.99 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 321 [$(M + Na)^+$, 66].

3-(Biphenyl-4-yl)-5-(4-bromophenyl)-4,5-dihydro-1H-pyrazole (**6b**, $C_{21}H_{17}BrN_2$)
Pale yellow powder (75%); $R_f = 0.34$ (petroleum ether: CH_2Cl_2, 2:1); mp 144–145°C; IR (KBr): $\bar{\nu} = 3380$ (NH), 1695 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, 250 MHz): $\delta =$ 3.03, 3.57 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 4.90 (t, $J = 3.6$ Hz, pyrazoline-H-5), 7.00 (br s, NH), 7.10–7.20 (m, Ar–H), 7.30–7.40 (m, Ar–H), 7.60–7.70 (m, Ar–H), 7.80–7.90 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 399 [$(M + Na)^+$, 45].

3-(Biphenyl-4-yl)-5-(3-nitrophenyl)-4,5-dihydro-1H-pyrazole (**6c**, $C_{21}H_{17}N_3O_2$)
Pale yellow powder (73%); $R_f = 0.32$ (petroleum ether: CH_2Cl_2, 2:1); mp 173–175°C; IR (KBr): $\bar{\nu} = 3370$ (NH), 1694 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, 250 MHz): $\delta = 3.00$, 3.50 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 4.95 (t, $J = 3.6$ Hz, pyrazoline-H-5), 7.02 (br s, NH), 7.15–7.25 (m, Ar–H), 7.37–7.50 (m, Ar–H), 7.70–7.80 (m, Ar–H), 7.90–7.95 (m, Ar–H), 8.05–8.17 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 366 [$(M + Na)^+$, 66].

3-(Biphenyl-4-yl)-1,5-diphenyl-4,5-dihydro-1H-pyrazole (**7a**, $C_{27}H_{22}N_2$)
Yellow powder (85%); $R_f = 0.52$ (petroleum ether:CH_2Cl_2, 2:1); mp 205–207°C; ^1H NMR (*DMSO*-d_6, 250 MHz): $\delta =$ 3.15, 3.95 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 5.50 (t, $J = 3.6$ Hz, pyrazoline-H-5), 6.71–6.90 (m, Ar–H), 7.07–7.20 (m, Ar–H), 7.29–7.35 (m, Ar–H), 7.40–7.55 (m, Ar–H), 7.70–7.85 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 397 [$(M + Na)^+$, 70].

3-(Biphenyl-4-yl)-5-(4-bromophenyl)-1-phenyl-4, 5-dihydro-1H-pyrazole (**7b**, $C_{27}H_{21}BrN_2$)
Yellow powder (89%); $R_f = 0.66$ (petroleum ether:CH_2Cl_2, 2:1); mp 190–192°C; ^1H NMR (*DMSO*-d_6, 250 MHz): $\delta =$ 3.15, 3.87 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 5.46 (t, $J = 3.6$ Hz, pyrazoline-H-5), 6.84–6.95 (m, Ar–H), 7.21–7.33 (m, Ar–H), 7.39–7.45 (m, Ar–H), 7.49–7.73 (m, Ar–H), 7.79–7.87 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 475 [$(M + Na)^+$, 51].

3-(Biphenyl-4-yl)-5-(3-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**7c**, $C_{27}H_{21}N_3O_2$)
Yellow powder (80%); $R_f = 0.54$ (petroleum ether:CH_2Cl_2, 2:1); mp 164–166°C; ^1H NMR (*DMSO*-d_6, 250 MHz): $\delta =$ 3.18, 3.96 (2dd, $J = 8.0$, 3.6 Hz, pyrazoline-H-4), 5.42 (t, $J = 3.6$ Hz, pyrazoline-H-5), 6.85–6.99 (m, Ar–H), 7.19–7.29 (m, Ar–H), 7.39–7.50 (m, Ar–H), 7.59–7.66 (m, Ar–H), 7.79–7.85 (m, Ar–H), 8.13–8.25 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 442 [$(M + Na)^+$, 45].

*General Procedure for the Preparation of Isoxazolines **8a–8c***
A mixture of **1a–1c** (5 mmol), 0.16 g $HONH_2 \cdot HCl$ (5 mmol), and 0.5 g NaOH (12 mmol) in 60 cm^3 ethanol was refluxed for 8 h (TLC). The reaction mixture was cooled and poured onto crushed ice. The precipitate was filtered off, washed with H_2O, and purified by silica gel column chromatography using CH_2Cl_2 in petroleum ether (3:7 *v*/*v*) to give **8a–8c** in 80–86% yields.

3-(Biphenyl-4-yl)-5-phenyl-4,5-dihydroisoxazole (**8a**, $C_{21}H_{17}NO$)
White powder (85%); $R_f = 0.34$ (petroleum ether:CH_2Cl_2, 2:1); mp 130–132°C; ^1H NMR (*DMSO*-d_6, 250 MHz): $\delta =$ 3.58, 3.86 (2dd, $J = 8.0$, 3.5 Hz, isoxazoline-H-4), 5.92 (t, $J = 3.5$ Hz, isoxazoline-H-5), 7.19–7.25 (m, Ar–H), 7.37–7.50 (m, Ar–H), 7.69–7.83 (m, Ar–H), 7.89–7.98 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 322 [$(M + Na)^+$, 45].

3-(Biphenyl-4-yl)-5-(4-bromophenyl)-4,5-dihydroisoxazole (**8b**, $C_{21}H_{16}BrNO$)
White powder (86%); $R_f = 0.37$ (petroleum ether:CH_2Cl_2, 2:1); mp 144–146°C; ^1H NMR (*DMSO*-d_6, 250 MHz): $\delta =$ 3.60, 3.90 (2dd, $J = 8.0$, 3.5 Hz, isoxazoline-H-4), 5.97 (t, $J = 3.5$ Hz, isoxazoline-H-5), 7.00–7.11 (m, Ar–H), 7.22–7.33 (m, Ar–H), 7.40–7.59 (m, Ar–H), 7.89–7.92 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 400 [$(M + Na)^+$, 33].

3-(Biphenyl-4-yl)-5-(3-nitrophenyl)-4,5-dihydroisoxazole (**8c**, $C_{21}H_{16}N_2O_3$)
Pale yellow powder (80%); $R_f = 0.39$ (petroleum ether:CH_2Cl_2, 2:1); mp 166–167°C; ^1H NMR (*DMSO*-d_6, 250 MHz): $\delta =$

3.62, 3.87 (2dd, $J = 8.0$, 3.5 Hz, isoxazoline-H-4), 5.91 (t, $J = 3.5$ Hz, isoxazoline-H-5), 7.50–7.69 (m, Ar–H), 7.80–7.95 (m, Ar–H), 8.18–8.28 (m, Ar–H) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 367 [$(M + Na)^+$, 40].

General Procedure for the Preparation of 5,6-Dihydropyrimidine-2(1H)-thiones ***9a–9c***

A mixture of **1a–1c** (10 mmol), 0.1 g thiourea (14 mmol), and 1.0 g NaOH (25 mmol) in 30 cm^3 ethanol was refluxed for 6 h. The reaction mixture was concentrated, cooled, and filtered. The precipitate was recrystallized from ethanol to give **9a–9c** in 75–80% yields.

4-(Biphenyl-4-yl)-6-phenyl-5,6-dihydropyrimidine-2(1H)-thione (**9a**, $C_{22}H_{18}N_2S$)

Pale yellow crystals (80%); $R_f = 0.52$ (petroleum ether: CH_2Cl_2, 2:1); mp 198–199°C; IR (KBr): $\bar{\nu} = 3320$ (NH), 2450 (SH), 1690 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, 250 MHz): $\delta = 5.06$, 5.23 (2dd, $J = 7.0$, 3.0 Hz, dihydro-2-thioxopyrimidine-H-5), 5.45 (t, $J = 3.0$ Hz, dihydro-2-thioxopyrimidine-H-6), 7.20–7.38 (m, Ar–H), 7.49–7.65 (m, Ar–H), 12.76 (br s, SH) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 365 [$(M + Na)^+$, 40].

4-(Biphenyl-4-yl)-6-(4-bromophenyl)-5,6-dihydropyrimidine-2(1H)-thione (**9b**, $C_{22}H_{17}BrN_2S$)

Pale yellow crystals (80%); $R_f = 0.55$ (petroleum ether: CH_2Cl_2, 2:1); mp 207–209°C; IR (KBr): $\bar{\nu} = 3330$ (NH), 2455 (SH), 1690 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, 250 MHz): $\delta = 5.11$, 5.25 (2dd, $J = 7.0$, 3.0 Hz, dihydro-2-thioxopyrimidine-H-5), 5.53 (t, $J = 3.0$ Hz, dihydro-2-thioxopyrimidine-H-6), 7.20–7.40 (m, Ar–H), 7.50–7.63 (m, Ar–H), 12.74 (br s, SH) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 443 [$(M + Na)^+$, 22].

4-(Biphenyl-4-yl)-6-(3-nitrophenyl)-5,6-dihydropyrimidine-2(1H)-thione (**9c**, $C_{22}H_{17}N_3O_2S$)

Yellow crystals (75%); $R_f = 0.55$ (petroleum ether:CH_2Cl_2, 2:1); mp 222–224°C; IR (KBr): $\bar{\nu} = 3335$ (NH), 2460 (SH), 1690 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6, 250 MHz): $\delta = 5.09$, 5.23 (2dd, $J = 7.0$, 3.0 Hz, dihydro-2-thioxopyrimidine-H-5), 5.59 (t, $J = 3.0$ Hz, dihydro-2-thioxopyrimidine-H-6), 7.20–7.40 (m, Ar–H), 7.50–7.69 (m, Ar–H), 8.10–8.19 (m, Ar–H), 12.80 (br s, SH) ppm; MS (MALDI, positive mode, Matrix: DHB): m/z (%) = 410 [$(M + Na)^+$, 22].

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