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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial activity of pyrazolinones and pyrazoles having benzothiazole moiety

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Abstract A new class of 4-arylhydrazono-1-benzothiazolyl-3-methylpyrazolin-5-ones (**3a–j**) and 4-arylazo-1-benzothiazolyl-3,5-dimethylpyrazoles (**4a–j**) were designed as pharmacophore hybrids between pyrazolinone/pyrazole and benzothiazole moiety. The target molecules were efficiently synthesized by the cyclization of various oxobutyrates/pentane-2,4-dione derivatives with 6-chloro-2-hydrazinobenzothiazole in the presence of glacial acetic acid. The compounds were evaluated for their in vitro antimicrobial activity. Preliminary study of the structure–activity relationship revealed that electron-withdrawing groups in phenyl ring had a promising effect on the antimicrobial activity. Also, correlation study has been used to establish the relationships between the antibacterial activity and physicochemical parameter *c*log*P*.

Keywords Benzothiazole · Pyrazole · Pyrazolinone · Antimicrobial activity

Introduction

The introduction of antibiotics is one of the most imperative medical interventions with regard to reducing human morbidity and mortality (Andersson and Hughes, 2010). However, the incidence of systemic microbial infections has been increased severely due to increase of immunocompromised hosts (Hitchock, 1993). Also, the increasing predominance of microbial resistance to huge antibiotics such as sulfonamide, β-lactam, nitroimidazoles, quinolones, tetracyclins, chloramphenicol, and macrolides antibiotics is becoming a foremost apprehension. Several reports are also available on the developments of resistance to vancomycin, the last line of defense agent against Gram-positive infections, and no alternative drug is available for the resistant verities (Gopalakrishnan *et al.*, 2009). Moreover, recent reports had cautioned that the emergence of new antibiotic resistant mechanism in Indian subcontinent is placing the antibiotic therapy in unprecedented danger (Kumaraswamy *et al.*, 2010). Consequently, the expensive treatment, toxicities, and drug-resistance pose new conundrum insisting constant renewed efforts in the development of new classes of antimicrobials with more specific action (Extance, 2010).

Benzothiazole moiety is of great importance to chemists as well as biologists as it is found in a large variety of naturally occurring compounds and it is also chemically useful molecule having diverse biological properties (Bondock *et al.*, 2009). A large range of benzothiazole derivatives were reported having anticancer (Brantley *et al.*, 2006), anticonvulsant (Rana *et al.*, 2008), anti-inflammatory (Naik *et al.*, 1996), and antimicrobial activities (Amir *et al.*, 2009; Bondock *et al.*, 2010; Franchini *et al.*, 2009; Soni *et al.*, 2010; Ebara *et al.*, 2005) (Fig. 1). Moreover, a recent study showed that chloro substitution at 6th position of benzothiazole moiety led to maximal antimicrobial activity (Patel and Agravat, 2009). Furthermore, pyrazoles and pyrazolinones have also emerged as a group of compounds possessing a broad spectrum of useful medicinal properties such as anti-inflammatory (Amir *et al.*, 2008a), anticancer (Cheng *et al.*, 2010; Demirayak *et al.*, 2010), anti-tubercular (Castagnolo *et al.*, 2009), and antimicrobial activities (Gouda *et al.*, 2010; Ragavan *et al.*, 2010; Ozdemir *et al.*, 2010; Anand and Remers, 2003) (Fig. 1).

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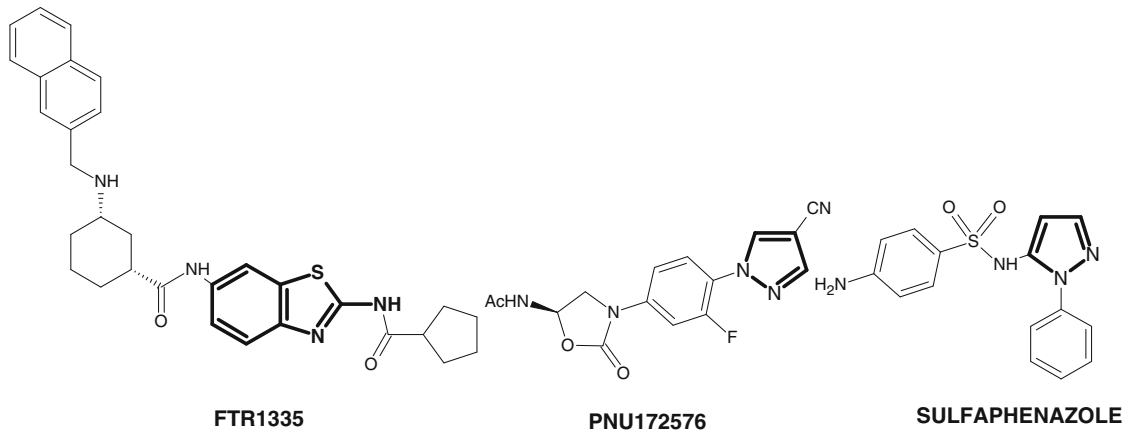


Fig. 1 Representative structures having benzothiazole and pyrazole moieties as antimicrobial agents

Prompted by the above findings and in continuation of our interest in the synthesis of heterocyclic compounds (Amir *et al.*, 2008b, 2010), we thought it worthwhile to synthesize a new series of hybrid compounds having pyrazolinone or pyrazole moieties along with 6-chlorobenzothiazole pharmacophore with the hope that hybridization of two different molecules will have synergistic biological effect giving potent antimicrobial agents.

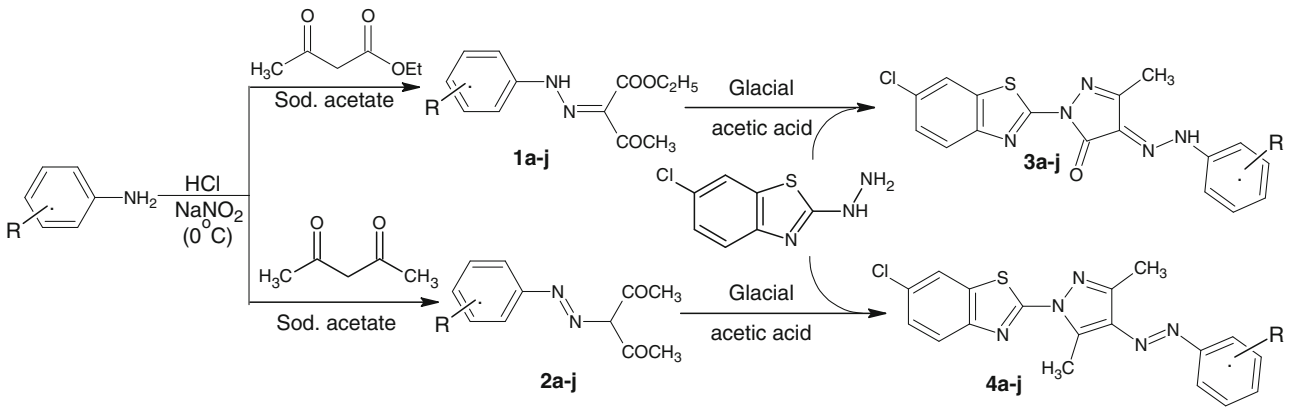
Results and discussion

Chemistry

Benzothiazole derivatives were prepared by a series of reactions as illustrated in Scheme 1. The intermediate 6-chloro-2-hydrazinobenzothiazole (CHB) was synthesized by the reaction of 2-amino-6-chlorobenzothiazole with hydrazine hydrate in the presence of ethylene glycol following the method reported in literature, m.p. 197–199°C (Patel *et al*. 2010). The reaction of aryl diazonium chlorides with ethylacetoacetate and acetyl acetone in the presence of sodium acetate afforded the corresponding ethyl-2-(aryl hydrazono)-3-oxobutyrates (**1a–j**) and 3-aryldiazenylpentane-2,4-dione (**2a–j**), respectively. Finally, the target compounds 1-(6′-Chlorobenzothiazol-2-yl)-3-methyl-4-(arylhydrazono)-2-pyrazolin-5-one (**3a–j**) and 1-(6′-Chlorobenzothiazol-2-yl)-3,5-dimethyl-4-(arylazo)pyrazole (**4a–j**) were synthesized by treating CHB with compounds **1a–j** and **2a–j**, respectively in the presence of glacial acetic acid.

The structure of newly synthesized compounds was confirmed by IR, ^{1}H NMR, and Mass spectra. IR spectrum of compound **3f** showed C=O stretching vibrations at 1666 cm^{-1}. The ^{1}H NMR spectral data of compound **3f** showed a singlet at δ 2.46 for CH_3 protons present at 3rd position of pyrazolinone ring. The 3″, 5″ ArH which are ortho to fluoro group were observed as a triplet at δ 7.15–7.19 showing the ^{1}H–^{19}F interaction in the phenyl ring. 5′ and 7′ ArH of the benzothiazole ring were observed as a doublet at δ 7.94–7.91 and 7.823–7.828, respectively. Thus, appearance of aromatic protons and disappearance of signal of hydrazino protons (NH–NH_2) of benzothiazole moiety confirms the formation of pyrazolinone ring. ^{13}C-NMR spectral data of the compound showed a methyl group carbon at δ 11.99 and a carbonyl carbon downfield at δ 162.46. The other peaks of carbon were observed at δ 160.0, 157.11, 154.60, 154.24, 148.44, 136.87, 133.30, 130.09, 127.25, 126.45, 123.33, 120.88, 117.87, 117.05, and 116.82 confirming the presence of seventeen carbons in the compound. The structure of compound (**3f**) was further confirmed by mass spectral data which showed molecular ion peak M^+ at *m/z* 387 corresponding to molecular formula $C_{17}H_{11}ClFN_5OS$.

The IR spectra of compound **4d** showed N=N stretching vibration at 1572 cm^{-1}. ^{1}H NMR spectra of compound **4d** showed three singlet at δ 3.91, 3.16, and 2.59 ppm indicating the presence of one OCH_3 and two CH_3 groups at 3rd and 5th position of pyrazoline ring. A multiplet was observed in the aromatic region at δ 7.82–7.87 indicating the presence of 4′,7′ protons of benzothiazole ring and 2″,6″ protons of phenyl ring. A double doublet was also obtained at δ 7.39–7.43 indicating the presence of 5th proton of the benzothiazole ring. The 3″,5″ protons were observed at δ 7.00–7.03. Thus, appearance of aromatic protons and disappearance of signal of hydrazino protons (NH–NH_2) of benzothiazole moiety also confirms the formation of pyrazoline ring. ^{13}C-NMR spectral data of the compound showed two methyl and a methoxy group carbon at δ 12.11, 14.80, and 55.59, respectively. The other peaks of carbon were observed at δ 161.57, 150.21, 147.70, 146.21, 141.75, 134.07, 130.44, 127.09, 123.89, 123.35, 120.99, and 114.17 confirming the presence of nineteen carbons in the compound. The structure of compound (**4d**) was further confirmed by the mass spectral data which



R= **a**: *p*-COOH; **b**: *o*-COOH; **c**: *o*-OH; **d**: *p*-OCH_3; **e**: *p*-Br; **f**: *p*-F; **g**: *p*-Cl; **h**: *o*-Cl; **i**: *p*-CH_3; **j**: *o*-CH_3.

Scheme 1 Synthesis of hybrid pyrazoline-5-ones and pyrazoles having benzothiazole moiety

showed molecular ion peak M^+ at *m/z* 397 corresponding to molecular formula $C_{19}H_{16}ClN_5OS$.

Antimicrobial activity

The newly synthesized compounds **3a–j**, **4a–j**, and CHB were evaluated for their antibacterial activity against *Staphylococcus aureus* (ATCC-25923) and *Escherichia coli* (ATCC-25922) (Barry, 1980; Mac Lowry *et al.*, 1970) and antifungal activity against *Aspergillus niger* (ATCC-9029) and *Candida albicans* (ATCC-90028) in DMF by serial plate dilution method (Arthington-Skaggs *et al.*, 2000; Verma *et al.*, 1998). All the results are presented as micro-molar concentration (μM) and as log1/*C*, where *C* represents the molar concentration; the lowest concentration of antimicrobial agent that results in the complete inhibition of visible growth of microorganisms (Table 1).

The pharmacophore 2-amino-6-chlorobenzothiazole, which was earlier reported to have promising antimicrobial activity (Patel and Agravat, 2009), was assumed as the lead compound in the designing of hybrid molecule with pyrazolinone/pyrazole moieties. In this study, substituents of different sizes and electronic properties are tried on the hydrzono/azophenyl ring to see if stereo-electronic factors have any effect on antimicrobial activity. The substituents on phenyl ring were also considered on the basis of lipophilic (π) and electronic (σ) attributes as defined by Craig's plot, like lipophilic electron-withdrawing groups ($+\sigma/+\pi$) Cl, F, and Br; hydrophilic electron-donating groups ($-\sigma/-\pi$) OH, OCH_3; hydrophilic electron-withdrawing groups ($+\sigma/-\pi$) COOH; and lipophilic electron-releasing groups ($-\sigma/+\pi$) CH_3 (van der Waterbeemed, 1996).

The results of this study with regard to antimicrobial activity have been found to be interesting against *S. aureus.* Among the pyrazoline-5-one derivatives (**3a–j**), compound **3e** (MIC 13.95 μM) having a *p*-bromo group on the phenyl ring was found to be most potent antibacterial agent against Gram-positive *S. aureus* compared to the standard drug ciprofloxacin (MIC 18.86 μM). Compounds **3f** (MIC 32.29 μM) and **3g** (MIC 31.01 μM) having *p*-fluoro and *p*-chloro substituent on phenyl ring, respectively also showed good antibacterial activity against *S. aureus*. However, the presence of an electron-releasing methyl group in the same position resulted in decrease of activity (**3i**; MIC 65.27 μM). Thus, among the different isoelectronic halogens, the highest activity measured for **3e** indicated the lipophilic bromine substituent as the most suitable one at the para position of phenyl ring. Moreover, it is interesting to note that the introduction of hydrophilic groups irrespective of electronic property, such as carboxy (**3a**) and methoxy (**3d**), at the para position of phenyl ring had caused a significant reduction in antibacterial activity against *S. aureus* (MIC 121.06 and 125.31 μM, respectively). However, ortho substituted phenyl derivatives showed interesting pattern of 2-fold reduction of antibacterial activity in comparison with para substituted phenyl derivatives, suggesting the unfavorable steric interactions. Among the pyrazole derivatives, compound **4g** (MIC 15.58 μM against *S. aureus*) and **4f** (MIC 32.46 μM against *E. coli*) having *p*-chloro and *p*-fluoro group in the phenyl ring, respectively, showed significant antibacterial activity. Rest of the compounds showed good to moderate antibacterial activity against both *S. aureus* and *E. Coli.*

All the synthesized compounds were also evaluated for their antifungal activity. Compound **4g** having a *p*-chloro group at the phenyl ring showed significant antifungal activity (MIC 31.16 μM) against *A. niger* in comparison to the standard drug ketoconazole (MIC 11.76 μM). Rests of the compounds tested were found to have good to moderate antifungal activity. The results of antibacterial and antifungal activities showed that compounds having lipophilic electron-withdrawing group at the para position of phenyl

Table 1 Antimicrobial screening of synthesized compounds **3a–j** and **4a–j**

Compound	R	*c*Log*P*[a]	MIC in μM[b]			
			S. aureus ATCC 25923	*E. coli* ATCC 25922	*A. niger* ATCC 9029	*C. albicans* ATCC 90028
3a	4-COOH	3.35	121.06 (3.91)	242.13 (3.61)	484.26 (3.31)	242.13 (3.61)
3b	2-COOH	4.04	242.13 (3.61)	484.26 (3.31)	484.26 (3.31)	121.06 (3.91)
3c	2-OH	2.88	129.87 (3.88)	259.74 (3.58)	519.48 (3.28)	259.74 (3.28)
3d	4-OCH_3	3.19	125.31 (3.90)	250.62 (3.6)	501.24 (3.30)	250.62 (3.6)
3e	4-Br	4.41	13.95 (4.85)	111.60 (3.95)	223.20 (3.65)	111.60 (3.95)
3f	4-F	3.69	32.29 (4.49)	129.19 (3.88)	129.19 (4.19)	64.59 (4.19)
3g	4-Cl	4.23	31.01 (4.50)	62.02 (4.20)	124.04 (3.90)	124.04 (3.90)
3h	2-Cl	3.75	62.03 (4.20)	124.06 (3.9)	248.12 (3.60)	248.12 (3.60)
3i	4-CH_3	3.70	65.27 (4.18)	130.54 (3.88)	261.08 (3.58)	522.16 (3.28)
3j	2-CH_3	3.70	130.54 (3.88)	261.08 (3.58)	261.08 (3.58)	522.16 (3.28)
4a	4-COOH	6.60	121.65 (3.91)	243.30 (3.61)	243.30 (3.61)	243.30 (3.91)
4b	2-COOH	7.04	121.65 (3.91)	486.60 (3.31)	121.65 (3.91)	243.30 (3.61)
4c	2-OH	5.74	522.19 (3.28)	522.19 (3.28)	522.19 (3.28)	261.09 (3.58)
4d	4-OCH_3	6.37	251.88 (3.59)	251.88 (3.59)	503.76 (3.29)	62.97 (4.59)
4e	4-Br	7.57	112.10 (3.95)	112.10 (3.95)	56.05 (4.25)	112.10 (3.95)
4f	4-F	6.85	64.93 (4.18)	32.46 (4.48)	129.86 (3.88)	259.74 (4.18)
4g	4-Cl	7.39	15.58 (4.80)	124.68 (3.9)	31.16 (4.5)	249.37 (4.2)
4h	2-Cl	7.10	498.75 (3.30)	249.37 (3.60)	124.68 (3.90)	124.68 (3.9)
4i	4-CH_3	7.02	131.23 (3.88)	65.61 (4.18)	262.46 (3.58)	131.23 (3.88)
4j	2-CH_3	7.02	262.46 (3.58)	262.46 (3.58)	524.92 (3.27)	262.46 (3.58)
CHB	–	2.31	250.42 (3.60)	500.84 (3.30)	1001.70 (2.99)	500.84 (3.30)
Ciprofloxacin[c]	–	–	18.86 (4.72)	18.86 (4.72)	–	–
Ketoconazole[d]	–	–	–	–	11.76 (4.92)	5.88 (5.23)

CHB: 6-chloro-2-hydrazinobenzothiazole

[a] Partition coefficients of the compounds were calculated using the software ACD/Log P 1.0

[b] Value in the parenthesis indicates the log1/*C*

[c] Calculated as Ciprofloxacin ($C_{17}H_{18}FN_3O_3$, Mol.Wt. 331.346)

[d] Calculated as Ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$, Mol.Wt. 531.43)

ring were more active than compounds having electron-donating groups. In order to study the synergistic effect of 6-chlorobenzothiazole pharmacophore on hybrid derivatives **3a–j** and **4a–j**, these compounds were compared with the antimicrobial activity of CHB. CHB showed MIC of 250.42 μM against *S. aureus* and 500.84 μM against *E. coli*, whereas it showed MIC of 1001.70 μM against *A. niger* and 500.84 μM against *C. albican* indicating that cyclization of CHB into its pyrazolinone and pyrazole derivatives resulted in enhanced antibacterial and antifungal activities.

Furthermore, hydrophobic properties have been quantized for correlation of structure with biological activity. Calculated log*P* (*c*log*P*) values were taken from the software ACD/Log P 1.0, and the results are shown in Table 1. The linear relationship between the antimicrobial activities (log1/*C*) and the calculated log*P* has been fitted. The following general regression equation was therefore applied.

$Y = Ax + B$; where, $Y = \log\ 1/C$; $A =$ Calculated log*P*; and x and B are constants.

The correlation between *c*log*P* and log1/*C* showed positive but weak correlations against both the series **3a–j** and **4a–j** ($r^2 = 0.1904$–0.412) (Fig. 2). These non-significant correlation results may be explained by the literature results which revealed that lipophilicity of the molecule and hence penetration into bacterial cell is not the only factor which can affect its activity, indeed, optimal drug-receptor interaction can affect their potency (El-Din *et al.*, 2009). Therefore, further studies regarding quantitative structure–activity relationships (QSARs) incorporating other descriptors are in progress in our laboratory.

In conclusion, we herein report the synthesis and antimicrobial activities of a new series of hybrid molecules having pyrazolinone/pyrazole and benzothiazole moieties. The screening results have showed that the incorporation of 6-chlorobenzothiazole pharmacophore in the pyrazolinone/

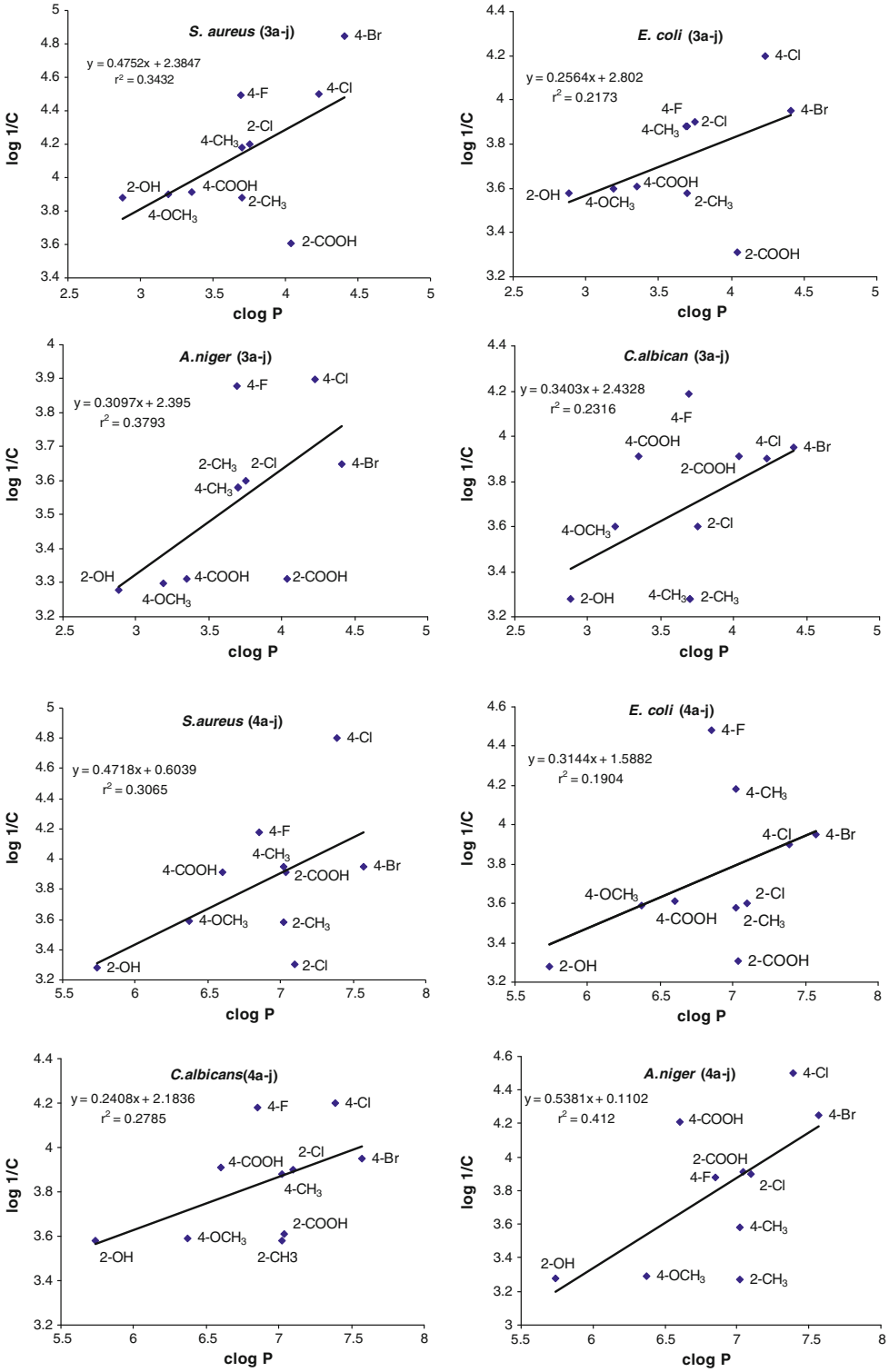


Fig. 2 Correlation between *c*log*P* and log1/*C*

pyrazole derivatives enhanced the antimicrobial activity. Furthermore, it was also observed that compounds having electron-withdrawing groups were more active than compounds having electron-releasing groups at the phenyl ring attached by hydrazono/azo linkage at the 4th position of pyrazolinone/pyrazole moieties. Thus, the series provided a new opportunity for possible modification of pharmacophoric requirements and future exploitations.

Experimental procedure

All the chemicals used in this study were purchased from E. Merck. The melting points were determined in open capillary tubes in a Hicon melting point apparatus and are uncorrected. The elemental analyses (C, H, and N) of all compounds were performed on the CHNS Elimentar (Analysen systime, GmbH) Germany Vario EL III. All the Fourier transform infra red (FT-IR) spectra were recorded in KBr pellets on a Jasco FT/IR 410 spectrometer. The ^{1}H NMR spectra were taken on a Bruker 300 MHz NMR spectrometer. ^{13}C NMR spectra were measured on Bruker 400 MHz NMR instrument (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS). Mass spectra were recorded on Jeol SX-102 (FAB) spectrometer. The purity of the compounds was checked by TLC using silica gelG-coated Al-plates (0.5-mm thickness, Merck), and spots were visualized under UV radiation.

General procedure for the preparation of ethyl-2-(arylhydrazono)-3-oxobutyrates (Amir and Agarwal, 1997) (**1a**–**j**)

To a stirred solution of substituted anilines (0.01 mol) and concentrated HCl (15 ml) in water (15 ml) at 0°C, the saturated solution of sodium nitrite (0.15 mol) was added. The diazonium salt thus formed was added slowly into a cooled solution of ethylacetoacetate (0.1 mol) in ethanol (50 ml) and sodium acetate (2.0 mol) in water (75 ml). The solid mass thus obtained was filtered, washed with water, and recrystallized from methanol. **1d**: IR (KBr, cm^{-1}): 3420 (N–H), 1672 (C=O), 1612 (C=N). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 11.88 (s, 1H, NH), 6.92–7.27 (m, 4H, ArH), 4.38–4.41 (q, 2H, CH_2CH_3), 3.95 (s, 3H, OCH_3), 2.60 (s, 3H, $COCH_3$), 1.41–1.43 (t, 3H, CH_2CH_3). **1e**: IR (KBr, cm^{-1}): 3378 (N–H), 1684 (C=O), 1626 (C=N). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 10.12 (s, 1H, NH), 7.18–7.88 (m, 4H, ArH), 4.26–4.30 (q, 2H, CH_2CH_3), 2.62 (s, 3H, $COCH_3$) 1.28–1.31 (t, 3H, CH_2CH_3).

General procedure for the preparation of aryl-3-diazenyl pentane-2,4-dione (Jain and Pandey, 1987) (**2a**–**j**)

To a stirred solution of substituted anilines (0.01 mol) and concentrated HCl (15 ml) in water (15 ml) at 0–5°C, the saturated solution of sodium nitrite (0.15 mol) was added. The diazonium salt thus formed was added into a cooled acetylacetone (0.10 mol) in ethanol (50 ml) and sodium acetate (2.0 mol) in water (75 ml). The solid mass thus obtained was filtered, washed with water, and recrystallized from methanol. **2g**: IR (KBr, cm^{-1}): 1658 (C=O), 1582 (N=N). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.06–7.48 (m, 4H, ArH), 3.14 (s, 1H, CH), 2.27 (s, 6H, $COCH_3$). **2i**: IR (KBr, cm^{-1}): 1662 (C=O), 1578 (N=N). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.20–7.72 (m, 4H, ArH), 3.16 (s, 1H, CH), 2.18 (s, 6H, $COCH_3$), 2.10 (s, 3H, CH_3–ArH).

General procedure for the preparation of 1-(6′-chlorobenzothiazol-2-yl)-3-methyl-4-(arylhydrazono)-2-pyrazolin-5-one (**3a**–**j**)

To ethyl-2-(arylhydrazono)-3-oxobutyrate (1) (0.005 mol) dissolved in glacial acetic acid (20 ml), a solution of CHB (0.005 mol) in glacial acetic acid (25 ml) was added, and the mixture was refluxed for 3–5 h. It was then cooled and allowed to stand overnight. The solids thus separated were filtered, washed with water, dried, and recrystallized from ethanol.

1-(6′-Chlorobenzothiazol-2-yl)-3-methyl-4-(4″-carboxyphenylhydrazono)-2-pyrazolin-5-one (**3a**)

Yield 82%; m.p. 222–224°C; IR (KBr, cm^{-1}): 3410 (N–H), 1642 (C=O), 1610 (C=N). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 12.40 (1H, *s*, COOH), 11.52 (1H, *s*, NH), 7.80–7.82 (1H, *d*, $J = 7.4$ Hz, 5′ArH), 7.78 (1H, *s*, 7′ArH), 7.30–7.38 (3H, *m*, 4′,2″,6″ArH), 6.98–7.0 (2H, *d*, $J = 7.6$ Hz, 3″,5″ArH), 2.14 (3H, *s*, CH_3); MS: *m/z* 413 (M^+). Elemental analysis: Calc. for $C_{18}H_{12}ClN_5O_3S$: C, 52.24; H, 2.92; N, 16.92; found: C, 52.18; H, 2.94; N, 16.95%.

1-(6′-Chlorobenzothiazol-2-yl)-3-methyl-4-(2″-carboxyphenyl hydrazono)-2-pyrazolin-5-one (**3b**)

Yield 74%; m.p. 186–184°C; IR (KBr, cm^{-1}): 3420 (N–H), 1654 (C=O), 1612 (C=N). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 12.22 (1H, *s*, COOH), 11.20 (1H, *s*, NH), 8.32-8.34 (1H, *d*, $J = 7.5$ Hz, 5′ArH), 8.12 (1H, *s*, 7′ArH), 7.84–7.86 (1H, *d*, $J = 7.6$ Hz, 4′ArH), 7.12–7.19 (4H, *m*, 3″,4″,5″, 6″ArH), 2.24 (3H, *s*, CH_3); MS: *m/z* 413 (M^+). Elemental analysis: Calc. for $C_{18}H_{12}ClN_5O_3S$: C, 52.24; H, 2.92; N, 16.92; found: C, 52.28; H, 2.86; N, 16.84%.

1-(6′-Chlorobenzothiazol-2-yl)-3-methyl-4-(2″-hydroxyphenylhydrazono)-2-pyrazolin-5-one (**3c**)

Yield 70%; m.p. 212–214°C; IR (KBr, cm^{-1}): 3582 (OH), 3400 (N–H), 1646 (C=O), 1614 (C=N). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 11.31 (1H, *bs*, OH) 10.63 (1H, *s*, NH), 7.85–7.87 (1H, *d*, $J = 7.8$ Hz, 5′ArH), 7.72 (1H, *s*, 7′ArH), 7.61–7.63 (1H, *d*, $J = 7.8$ Hz, 4′ArH), 6.95–7.04 (4H, *m*, 3″,4″,5″, 6″ArH), 2.36 (3H, *s*, CH_3); MS: *m/z* 385 (M^+). Elemental analysis: Calc. for $C_{17}H_{12}ClN_5O_2S$: C, 52.92; H, 3.13; N, 18.15; found: C, 52.84; H, 3.10; N, 18.10%.

1-(6′-Chlorobenzothiazol-2-yl)-3-methyl-4-(4″-methoxyphenylhydrazono)-2-pyrazolin-5-one (**3d**)

Yield 62%; m.p. 248–250°C; IR (KBr, cm^{-1}): 3412 (N–H), 1671 (C=O), 1628 (C=N). ^1H NMR ($CDCl_3$, 300 MHz) δ: 13.38 (1H, *s*, NH), 7.89–7.92 (1H, *d*, $J = 8.4$ Hz, 5′ArH), 7.79 (1H, *s*, 7′ArH), 7.40–7.42 (3H, *m*, 4′,2″,6″ArH), 6.96–6.99 (2H, *d*, $J = 8.7$ Hz, 3″,5″ArH), 3.84 (3H, *s*, OCH_3), 2.44 (3H, *s*, CH_3); MS: *m/z* 399 (M^+). Elemental analysis: Calc. for $C_{18}H_{14}ClN_5O_2S$: C, 54.07; H, 3.53; N, 17.51; found: C, 54.01; H, 3.49; N, 17.46%.

1-(6′-Chlorobenzothiazol-2-yl)-3-methyl-4-(4″-bromophenylhydrazono)-2-pyrazolin-5-one (**3e**)

Yield 65%; m.p. 254–256°C; IR (KBr, cm^{-1}): 3418 (N–H), 1657 (C=O), 1622 (C=N). ^1H NMR ($CDCl_3$, 300 MHz) δ: 10.74 (1H, *s*, NH), 7.85–7.87 (1H, *d*, $J = 8.2$ Hz, 5′ArH), 7.74 (1H, *s*, 7′ArH), 7.36–7.44 (3H, *m*, 4′,2″,6″ArH), 7.22–7.24 (2H, *d*, $J = 8.6$ Hz, 3″,5″ArH), 2.38 (3H, *s*, CH_3); MS: *m/z* 448 (M^+). Elemental analysis: Calc. for $C_{17}H_{11}BrClN_5O$: C, 45.50; H, 2.47; N, 15.61; found: C, 45.48; H, 2.42; N, 15.54%.

1-(6′-Chlorobenzothiazol-2-yl)-3-methyl-4-(4″-fluorophenylhydrazono)-2-pyrazolin-5-one (**3f**)

Yield 55%; m.p. 210–212°C; IR (KBr, cm^{-1}): 3424 (N–H), 1666 (C=O), 1618 (C=N). ^1H NMR ($CDCl_3$, 400 MHz) δ: 13.28 (1H, *s*, NH), 7.94–7.91 (1H, *d*, $J = 8.8$ Hz, 5′ArH), 7.823–7.828 (1H, *d*, $J = 2$ Hz, 7′ArH), 7.41–7.47 (3H, *m*, 4′,2″,6″ArH), 7.15–7.19 (2H, *t*, $J = 8.8$, 8 Hz, 3″,5″ArH), 2.46 (3H, *s*, CH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 162.46 (C=O), 160.0, 157.11, 154.60, 154.24, 148.44, 136.87, 133.30, 130.09, 127.25, 126.45, 123.33, 120.88, 117.87, 117.05, 116.82, 11.99 (CH_3); MS: *m/z* 387 (M^+). Elemental analysis: Calc. for $C_{17}H_{11}ClFN_5OS$: C, 52.65; H, 2.86; N, 18.06; found: C, 52.58; H, 2.80; N, 17.97%.

1-(6′-Chlorobenzothiazol-2-yl)-3-methyl-4-(4″-chlorophenylhydrazono)-2-pyrazolin-5-one (**3g**)

Yield 62%; m.p. 158–160°C; IR (KBr, cm^{-1}): 3412 (N–H), 1660 (C=O), 1624 (C=N). ^1H NMR ($CDCl_3$, 300 MHz) δ: 10.86 (1H, *s*, NH), 8.03-8.05 (1H, *d*, $J = 8.6$ Hz, 5′ArH), 7.86 (1H, *s*, 7′ArH), 7.46–7.52 (3H, *m*, 4′,2″,6″ArH), 7.33–7.35 (2H, *d*, $J = 8.5$ Hz, 3″,5″ArH), 2.36 (3H, *s*, CH_3); MS: *m/z* 403 (M^+). Elemental analysis: Calc. for $C_{17}H_{11}Cl_2N_5OS$: C, 50.51; H, 2.74; N, 17.32; found: C, 50.44; H, 2.69; N, 16.28%.

1-(6′-Chlorobenzothiazol-2-yl)-3-methyl-4-(2″-chlorophenylhydrazono)-2-pyrazolin-5-one (**3h**)

Yield 75%; m.p. 184–186°C; IR (KBr, cm^{-1}): 3422 (N–H), 1648 (C=O), 1615 (C=N). ^1H NMR ($CDCl_3$, 300 MHz) δ: 11.22 (1H, *s*, NH), 8.05-8.07 (1H, *d*, $J = 7.8$ Hz, 5′ArH), 7.94 (1H, *s*, 7′ArH), 7.80–7.82 (1H, *d*, $J = 7.6$ Hz, 4′ArH), 6.96–7.08 (4H, *m*, 3″,4″,5″, 6″ArH), 2.10 (3H, *s*, CH_3), MS: *m/z* 403 (M^+). Elemental analysis: Calc. for $C_{17}H_{11}Cl_2N_5OS$: C, 50.51; H, 2.74; N, 17.32; found: C, 50.46; H, 2.66; N, 16.26%.

1-(6′-Chlorobenzothiazol-2-yl)-3-methyl-4-(4″-methylphenylhydrazono)-2-pyrazolin-5-one (**3i**)

Yield 62%; m.p. 218–220°C; IR (KBr, cm^{-1}): 3412 (N–H), 1642 (C=O), 1621 (C=N). ^1H NMR ($CDCl_3$, 300 MHz) δ: 13.27 (1H, *s*, NH), 7.89–7.92 (1H, *d*, $J = 8.6$ Hz, 5′ArH), 7.80 (1H, *s*, 7′ArH), 7.34–7.42 (3H, *m*, 4’,2″,6″ArH), 7.23–7.25 (2H, *d*, $J = 7.5$ Hz, 3″,5″ArH), 2.45 (3H, *s*, pyrazoline-CH_3), 2.38 (3H, *s*, Ar-CH_3); MS: *m/z* 383 (M^+). Elemental analysis: Calc. for $C_{18}H_{14}ClN_5OS$: C, 56.32; H, 3.68; N, 18.24; found: C, 56.24; H, 3.60; N, 18.18%.

1-(6′-Chlorobenzothiazol-2-yl)-3-methyl-4-(2″-methylphenylhydrazono)-2-pyrazolin-5-one (**3j**)

Yield 58%; m.p. 196–198°C; IR (KBr, cm^{-1}): 3418 (N–H), 1648 (C=O), 1614 (C=N). ^1H NMR ($CDCl_3$, 300 MHz) δ: 9.39 (1H, *s*, NH), 7.82–7.84 (1H, *d*, $J = 7.8$ Hz, 5′ArH), 7.72 (1H, *s*, 7′ArH), 7.60–7.62 (1H, *d*, $J = 8.0$ Hz, 4′ArH), 7.03–7.12 (4H, *m*, 3″,4″,5″, 6″ArH), 2.50 (3H, *s*, pyrazoline-CH_3), 2.32 (3H, *s*, Ar-CH_3); MS: *m/z* 383 (M^+). Elemental analysis: Calc. for $C_{18}H_{14}ClN_5OS$: C, 56.32; H, 3.68; N, 18.24; found: C, 56.26; H, 3.62; N, 18.16%.

General procedure for the preparation of 1-(6′-chlorobenzothiazol-2-yl)-3,5-dimethyl-4-(arylazo)pyrazole (**4a–j**)

To aryl-3-diazenyl pentane-2,4-dione (**2**) (0.005 mol) dissolved in glacial acetic acid (20 ml), a solution of CHB (0.005 mol) in glacial acetic acid (25 ml) was added, and the mixture was refluxed for 4–6 h. It was then cooled and allowed to stand overnight. The solids thus separated were filtered, washed with water, dried, and recrystallized from ethanol.

1-(6′-Chlorobenzothiazol-2-yl)-3,5-dimethyl-4-(4″-carboxyphenylazo)pyrazole (**4a**)

Yield 70%; m.p. 188–190°C; IR (KBr, cm^{-1}): 1622 (C=N), 1575 (–N=N–). ^1H NMR ($CDCl_3$, 300 MHz) δ: 12.42 (1H,

s, COOH), 7.40–7.48 (4H, *m*, 4′,7′,2″,6″ArH), 7.28–7.31 (1H, *dd*, $J = 1.5$, 8.6 Hz, 5′ArH), 7.12–7.14 (2H, *d*, $J = 7.8$ Hz, 3″,5″ArH), 2.61 (3H, *s*, 3-CH_3), 2.41 (3H, *s*, 5-CH_3); MS: *m/z* 411 (M^+). Elemental analysis: Calc. for $C_{19}H_{14}ClN_5O_2S$: C, 55.41; H, 3.43; N, 17.00; found: C, 55.36; H, 3.38; N, 16.95%.

1-(6′-Chlorobenzothiazol-2-yl)-3,5-dimethyl-4-(2″-carboxyphenylazo)pyrazole (**4b**)

Yield 60%; m.p. 174–176°C; IR (KBr, cm^{-1}): 1630 (C=N), 1584 (–N=N–). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 12.14 (1H, *s*, COOH), 7.88 (1H, *d*, $J = 1.8$, 7′ArH), 7.78–7.80 (1H, *dd*, $J = 1.6$, 8.2 Hz, 5′ArH), 7.56–7.58 (1H, *d*, $J = 7.8$ Hz, 4′ArH), 7.26–7.31 (4H, m, 3″,4″,5″,6″ArH), 2.78 (3H, *s*, 3-CH_3), 2.48 (3H, *s*, 5-CH_3); MS: *m/z* 411 (M^+). Elemental analysis: Calc. for $C_{19}H_{14}ClN_5O_2S$: C, 55.41; H, 3.43; N, 17.00; found: C, 55.34; H, 3.36; N, 16.97%.

1-(6′-Chlorobenzothiazol-2-yl)-3,5-dimethyl-4-(2″-hydroxyphenylazo)pyrazole (**4c**)

Yield 70%; m.p. 190–192°C; IR (KBr, cm^{-1}): 3619 (O–H), 1640 (C=N), 1580 (–N=N–). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 11.65 (1H, *s*, OH), 7.41 (1H, *d*, $J = 1.6$, 7′ArH), 7.36–7.38 (1H, *dd*, $J = 1.8$, 7.8 Hz, 5′ArH), 7.13–7.15 (1H, *d*, $J = 7.6$ Hz, 4′ArH), 6.96–7.02 (4H, *m*, 3″,4″,5″,6″ArH), 2.82 (3H, *s*, 3-CH_3), 2.58 (3H, *s*, 5-CH_3); MS: *m/z* 383 (M^+). Elemental analysis: Calc. for $C_{18}H_{14}ClN_5OS$: C, 56.32; H, 3.68; N, 18.24; found: C, 56.26; H, 3.64; N, 18.16%.

1-(6′-Chlorobenzothiazol-2-yl)-3,5-dimethyl-4-(4″-methoxyphenylazo)pyrazole (**4d**)

Yield 62%; m.p. 216–218°C; IR (KBr, cm^{-1}): 1624 (C=N), 1572 (–N=N–). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.82–7.87 (4H, *m*, 4′,7′,2″,6″ArH), 7.39–7.43 (1H, *dd*, $J = 1.5$, 9.3 Hz, 5′ArH), 7.00–7.03 (2H, *d*, $J = 9$ Hz, 3″,5″ArH), 3.91 (3H, *s*, OCH_3), 3.16 (3H, *s*, 3-CH_3), 2.59 (3H, *s*, 5-CH_3); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 161.57, 150.21, 147.70, 146.21, 141.75, 134.07, 130.44, 127.09, 123.89, 123.35, 120.99, 114.17, 55.59 (OCH_3), 14.80 (CH_3), 12.11 (CH_3); MS: *m/z* 397 (M^+). Elemental analysis: Calc. for $C_{19}H_{16}ClN_5OS$: C, 57.35; H, 4.05; N, 17.60; found: C, 57.27; H, 4.01; N, 17.54%.

1-(6′-Chlorobenzothiazol-2-yl)-3,5-dimethyl-4-(4″-bromoyphenylazo)pyrazole (**4e**)

Yield 60%; m.p. 238–240°C; IR (KBr, cm^{-1}): 1610 (C=N), 1578 (–N=N–). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.83–7.87 (4H, *m*, 4′,7′,2″,6″ArH), 7.43–7.45 (1H, *dd*, $J = 1.8$, 8.6 Hz, 5′ArH), 6.95-6.97 (2H, *d*, $J = 8.2$ Hz, 3″,5″ArH), 3.91 (3H, *s*, OCH_3), 2.59 (3H, *s*, 3-CH_3), 2.46 (3H, *s*, 5-CH_3); MS: *m/z* 446 (M^+). Elemental analysis: Calc. for $C_{18}H_{13}BrClN_5S$: C, 48.39; H, 2.93; N, 15.68; found: C, 48.34; H, 2.90; N, 15.62%.

1-(6′-Chlorobenzothiazol-2-yl)-3,5-dimethyl-4-(4″-fluorophenylazo)pyrazole (**4f**)

Yield 55%; m.p. 180–182°C; IR (KBr, cm^{-1}): 1634 (C=N), 1588 (–N=N–). ^{1}H NMR ($CDCl_3$, 300 MHz) δ:7.83–7.88 (4H, *m*, 4′,7′,2″,6″ArH), 7.62–7.65 (1H, *dd*, $J = 1.6$, 8.2 Hz, 5′ArH), 7.10–7.12 (2H, *t*, $J = 8.2$, 8.4 Hz, 3″,5″ArH), 2.62 (3H, *s*, 3-CH_3), 2.24 (3H, *s*, 5-CH_3); MS: *m/z* 385 (M^+). Elemental analysis: Calc. for $C_{18}H_{13}ClFN_5S$: C, 56.03; H, 3.40; N, 18.15; found: C, 55.97; H, 3.33; N, 18.11%.

1-(6′-Chlorobenzothiazol-2-yl)-3,5-dimethyl-4-(4″-chlorophenylazo)pyrazole (**4g**)

Yield 58%; m.p. 218–220°C; IR (KBr, cm^{-1}): 1632 (C=N), 1576 (–N=N–). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.41–7.46 (4H, *m*, 4′,7′,2″,6″ArH), 7.32–7.35 (1H, *dd*, $J = 1.6$, 8.2 Hz, 5′ArH), 6.96-6.98 (2H, *d*, $J = 8.7$ Hz, 3″,5″ArH), 2.48 (3H, *s*, 3-CH_3), 2.20 (3H, *s*, 5-CH_3); MS: *m/z* 401 (M^+). Elemental analysis: Calc. for $C_{18}H_{13}Cl_2N_5S$: C, 53.74; H, 3.26; N, 17.41; found: C, 53.70; H, 3.21; N, 17.37%.

1-(6′-Chlorobenzothiazol-2-yl)-3,5-dimethyl-4-(2″-chlorophenylazo)pyrazole (**4h**)

Yield 60%; m.p. 240–242°C; IR (KBr, cm^{-1}): 1624 (C=N), 1586 (–N=N–). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.86 (1H, *d*, $J = 1.8$, 7′ArH), 7.74–7.77 (1H, *dd*, $J = 1.6$, 7.6 Hz, 5′ArH), 7.56–7.58 (1H, *d*, $J = 8$ Hz, 4′ArH), 7.19–7.24 (4H, *m*, 3″,4″,5″,6″ArH), 2.65 (3H, *s*, 3-CH_3), 2.48 (3H, *s*, 5-CH_3); MS: *m/z* 401 (M^+). Elemental analysis: Calc. for $C_{18}H_{13}Cl_2N_5S$: C, 53.74; H, 3.26; N, 17.41; found: C, 53.68; H, 3.24; N, 17.34%.

1-(6′-Chlorobenzothiazol-2-yl)-3,5-dimethyl-4-(4″-methylphenylazo)pyrazole (**4i**)

Yield 72%; m.p. 216–218°C; IR (KBr, cm^{-1}): 1616 (C=N), 1564 (–N=N–). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.67–7.72 (4H, *m*, 4′,7′,2″,6″ArH), 7.47–7.49 (1H, *dd*, $J = 1.8$, 8.4 Hz, 5′ArH), 6.98–7.0 (2H, d, $J = 8.4$ Hz, 3″,5″ArH), 2.60 (3H, *s*, 3-CH_3), 2.42 (3H, *s*, 5-CH_3) 2.12 (3H, *s*, Ar-CH_3); MS: *m/z* 381 (M^+). Elemental analysis: Calc. for $C_{19}H_{16}ClN_5S$: C, 59.76; H, 4.22; N, 18.34; found: C, 59.72; H, 4.16; N, 18.30%.

1-(6′-Chlorobenzothiazol-2-yl)-3,5-dimethyl-4-(2″-methylphenylazo)pyrazole (**4j**)

Yield 72%; m.p. 216–218°C; IR (KBr, cm^{-1}): 1622 (C=N), 1568 (–N=N–). ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.86 (1H, *d*, $J = 1.6$, 7′ArH), 7.72–7.75 (1H, *dd*, $J = 1.5$, 7.4 Hz, 5′ArH), 7.52–7.54 (1H, *d*, $J = 7.8$ Hz, 4′ArH), 7.27–7.32 (4H, *m*, 3″,4″,5″,6″ArH), 2.54 (3H, *s*, 3-CH_3), 2.44 (3H, *s*, 5-CH_3), 2.32 (3H, *s*, Ar-CH_3); MS: *m/z* 381 (M^+). Elemental analysis: Calc. for $C_{19}H_{16}ClN_5S$: C, 59.76; H, 4.22; N, 18.34; found: C, 59.70; H, 4.17; N, 18.27%.

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