Facile Synthesis of New [1,2,4]Triazolo[4,3-*b*]pyridazine

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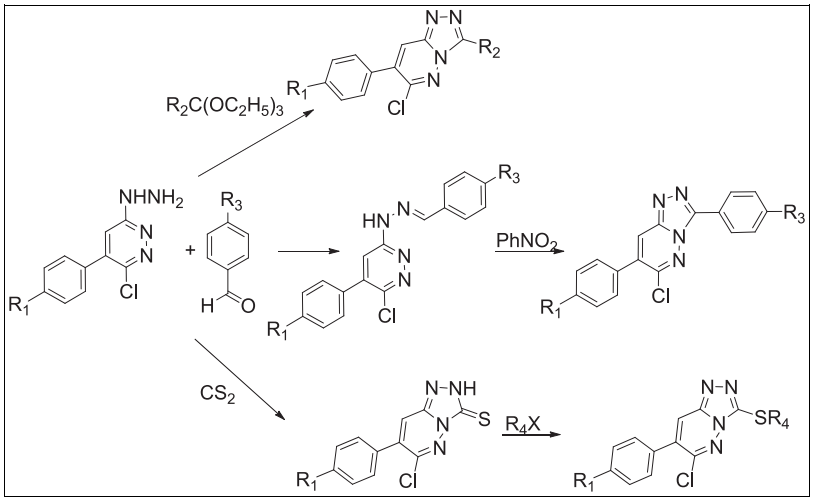

A number of new [1,2,4]triazolo[4,3-*b*]pyridazines were prepared by either cyclocondesation of substituted hydrazinopyridazines with orthoesters or oxidative cyclization of their hydrazone analogs in nitrobenzene as an oxidizing agent. A host of other new [1,2,4]triazolo[4,3-*b*]pyridazine derivatives were synthesized by sequential treatment of the latter compounds with carbon disulfide and alkyl halides.

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INTRODUCTION

In the last decades, the chemistry of triazolo[4,3-*b*] pyridazine derivatives has received considerable attention owing to their varied biological activities, such as antiviral [1], antitumor [2,3], sedative/hypnotic [4], anti-anxiety [5–7], adenine receptor ligand [8,9], hypotensive[10], herbicidal, pesticidal [11], bactericidal [12] and anti-HAV activity [13]. In the light of these information and due to our continuing interest in the synthesis of biologically important heterocycles [14–16] in this paper, we wish to report the facile syntheses of some new derivatives of triazolo[4,3-*b*]pyridazines.

RESULTS AND DISCUSSION

6-Choloro-5-(4-substituted phenyl)-3-pyridazinylhydrazines **5a–c** as key compounds were synthesized in four steps. Initially a set of aryl iodides **1a–c** reacted with fumaric acid in a Heck-type reaction to yield the 2-(4-substituted phenyl)-2-butenedioic acids **2a–c** [17]. Treatment of these compounds with hydrazine hydrochloride gave the 4-(4-substituted phenyl)1,2,3,6-tetrahydro-3,6-pyridazinediones **3a–c**. Chlorination of the latter compounds with phosphoryl chloride in the presence of *N*,*N*-diethyl aniline afforded the 3,6-dicholoro-4-(4-substitutedphenyl)pyridazines **4a–c** in high yields. Compounds **4a–c** were subsequently converted to their hydrazine derivatives **5a–c** by selective displacement of six-chlorine atom [18] with hydrazine hydrate in ethanol at reflux condition (Scheme 1).

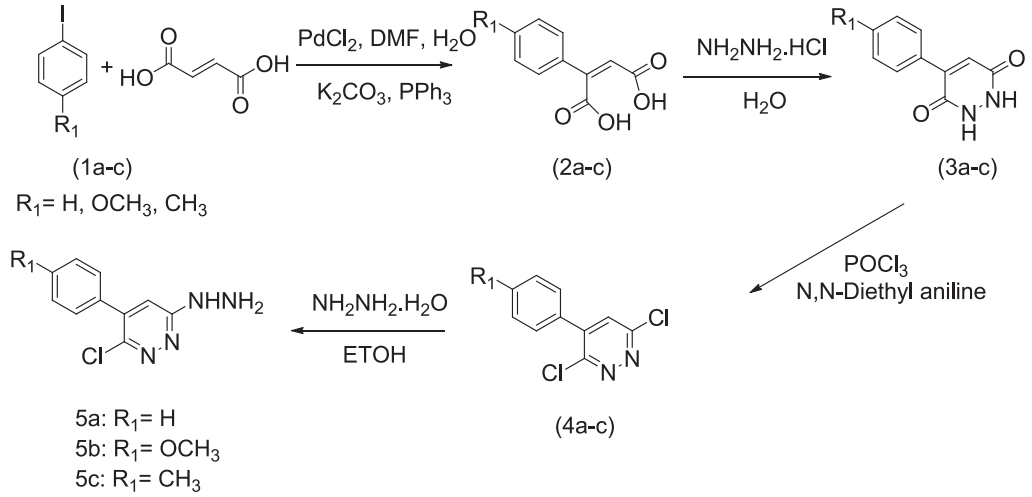
The ^{1}H nmr spectra of these products showed a chemical shift displacement of pyridazine hydrogen, from δ 7.80 ppm, of compounds **4a–c** to δ 7.20 ppm for compounds **5a–c** due to resonance electron donation of hydrazine group to the neighboring atom.

Treatment of these precursors **5a–c** with orthoesrters [$RC(OEt)_3$, R = -H, -CH_3, -C_2H_5] in refluxing acetic acid gave the new derivatives **6a–i**, respectively (Scheme 2).

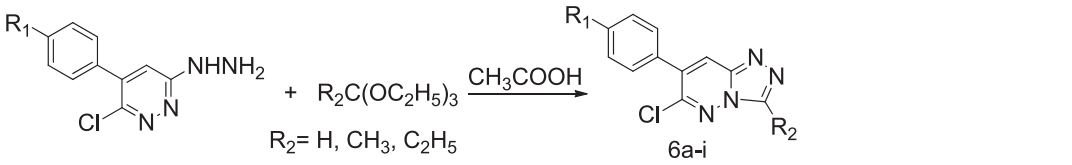
The structural assignments of these compounds were based upon spectral and microanalytical data. For example, the IR spectrum of **6a** was devoid of the absorption bands at 3300–3200/cm (NH–NH_2). The ^{1}H nmr spectrum also showed the disappearance of two broad signals belonging to NH_2 and NH moieties of compound **5a** but the appearance of a sharp signal (1H) at δ 9.5 ppm for triazole ring of **6a** indicates the construction of this heterocyclic ring.

The synthesis of 1,2,4-triazolo derivatives from hydrazones has remarkably wide scope of applications. Hydrazones of aromatic aldehydes with both electron-withdrawing and electron-donating substituents **7a–o** were

Scheme 1. General procedure for the synthesis of precursor's **5a–c**.



Scheme 2. General procedure for the synthesis of **6a–i**.



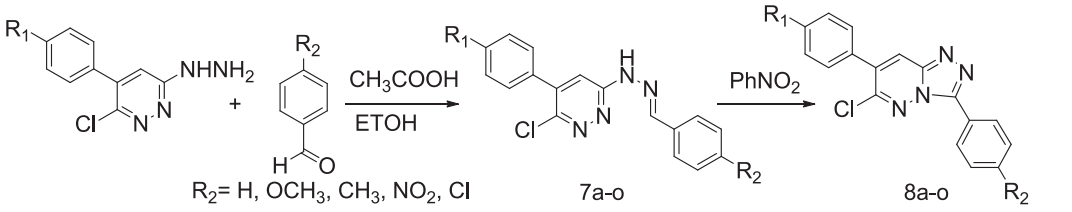
oxidized to give the corresponding [1,2,4]triazolo[4,3-*b*] pyridazines **8a–o** (Scheme 3).

The required hydrazones **7a–o** were obtained by treating the corresponding hydrazine **5a–c** with aldehydes in ethanol at reflux condition [19]. Heterocyclization was carried out in nitrobenzene as both oxidant and solvent at reflux condition [20].

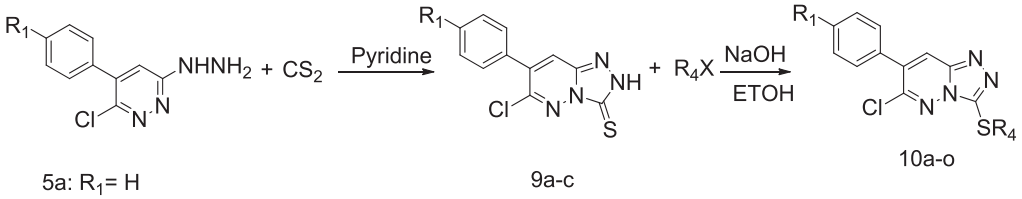
The IR spectra of compounds **7a–o** showed absorption bands at 3200 (NH) and 1600–1610/cm (N=CH). The ^{1}H nmr spectra exhibited a sharp signal (1H, N=CH) in aromatic region and a broad singlet (1H, NH) at δ 11.5 ppm, which was removed on adding D_2O.

The IR spectra of compounds **8a–o** showed absorption bands at 1600–1625/cm (N=C), where ^{1}H nmr spectra showed no signal for NH and N=CH after ring closure. It is notable that the displacement of chemical shift for 2H (H-2,6) of the phenylhydrazone moiety to downfield can be attributed to anisotropic effect of the triazolo ring.

Scheme 3. General procedure for the synthesis of **8a–o**.



Scheme 4. General procedure for the synthesis of **10a–o**.



5a: R_1= H
5b: R_1= OCH_3
5c: R_1= CH_3

R_4X= $(CH_3)_2SO_2$, C_2H_5Br, C_3H_7Br, C_4H_9Br, $PhCH_2Cl$

10a:R_1,R_2= H, CH_3 10f:R_1,R_2= OCH_3, CH_3 10k:R_1,R_2= CH_3, CH_3
10b:R_1,R_2= H, C_2H_5 10g:R_1,R_2= OCH_3, C_2H_5 10l:R_1,R_2= CH_3, C_2H_5
10c:R_1,R_2= H, C_3H_7 10h:R_1,R_2= OCH_3, C_3H_7 10m:R_1,R_2= CH_3, C_3H_7
10d:R_1,R_2= H, C_4H_9 10i:R_1,R_2= OCH_3, C_4H_9 10n:R_1,R_2= CH_3, C_4H_9
10e:R_1,R_2= H, CH_2Ph 10j:R_1,R_2= OCH_3, CH_2Ph 10o:R_1,R_2= CH_3, CH_2Ph

The reaction of **5a–c** with carbon disulfide in dry pyridine [13] yielded the corresponding thiones **9a–c** (Scheme 4). The IR spectra showed absorption bands assignable to the (NH) and (C=S) groups along with their ^{1}H nmr spectra, which revealed a signal at aromatic region for the NH proton (D_2O exchangeable).

Finally, The S-alkylated compounds **10a–o** were prepared by reacting thiones **9a–c** with appropriate alkyl halides in the presence of sodium hydroxide [13] (Scheme 4).

The structure of aforementioned compounds was assigned on the basis of elemental analysis and compatible spectroscopic data. The ^{1}H nmr spectra showed corresponding alkyl signals, whereas the ir spectra did not exhibit absorption band at 3200/cm (NH).

CONCLUSION

In summary, we have synthesized a wide variety of [1,2,4]triazolo[4,3-*b*]pyridazines by two facile routes, cyclocondensation of substituted hydrazino pyridazines with orthoesters and oxidative cyclization of their hydrazone analogs in nitrobenzene as an oxidizing agent.

EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on an AVATAR 370 FT-IR Thermo Nicolet spectrometer. ^{1}H nmr spectra were measured at 100 and 400 MHz on Bruker spectrometers with tetramethylsilane (Me_4Si) as an internal reference and deuteriochloroform or DMSO-d_6 as solvent. The Mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

General procedure for preparation of (Z)-2-(4-substituted phenyl)-2-butenedioic acids (2a–c). A mixture of fumaric acid (1.45 g, 12.5 mmol), 4-substituted aryliodides (**1a–c**), (12.5 mmol), K_2CO_3 (3.45 g, 25 mmol), Ph_3P (0.055 g, 0.20 mmol, 1.6 mol%), DMF (12 mL), H_2O (12 mL) and $PdCl_2$ [0.5 mL of 0.1*M* aqueous solution, 0.05 mmol, 0.4 mol%] was stirred under argon at 100–105°C for indicated time. The solvent was evaporated in vacuo, the residue washed with EtOAc (26 mL), dried, suspended in water (15 mL) and treated with concentrated HCl (5 mL). Precipitation might take 3 h at RT to give the crude arylmaleic acid. The product was dried in air before it crystallizes from ethanol.

(Z)-2-phenyl-2-butenedioic acid (2a). This compound was obtained as a yellow powder after 22 h in 45% yield, mp 220–222°C; IR (potassium bromide): (–CO_2H) 3434, (=C–H) 3155, (C=O) 1673, 1612 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.22 (br s, 2H, 2(CO_2H), D_2O exchangeable), 6.21 (s, 1H, CH-pyridazine), 7.2–7.5 (m, 5H, Ar–H); *Anal*. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.39; H, 4.05.

(Z)-2-(4-methoxyphenyl)-2-butenedioicacid (2b). This compound was obtained as a yellow powder after 8:30 AM in 90% yield, mp 240°C (dec); IR (potassium bromide): (–CO_2H) 3407, (=C–H) 3077–3002, (–C–H) 2958–2835, (C=O) 1669, 1600 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.91 (s, 3H, OCH_3) 4.10 (br s, 2H, 2(CO_2H), D_2O exchangeable), 6.11 (s, 1H, CH-pyridazine), 6.82 (d, 2H, Ar–H), 7.30 (d, 2H, Ar–H); *Anal*. Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.29; H, 4.15.

(Z)-2-(4-methyphenyl)-2-butenedioic acid (2c). This compound was obtained as a pale yellow powder after 12 h in 50% yield, mp 213–214°C; IR (potassium bromide): (–CO_2H) 3423, (=C–H) 3076, (–C–H) 2913–2847, (C=O) 1672, 1604 cm^{-1}; ^{1}H nmr (deuteriochloroform, DMSO-d_6): δ 2.06 (s, 3H, CH_3), 3.04 (br s, 2H, 2(CO_2H), D_2O exchangeable), 5.90 (s, 1H, CH-pyridazine), 6.01 (d, 2H, Ar–H), 7.01 (d, 2H, Ar–H); ms: m/z 187 (M–H_2O); *Anal*. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.00; H, 4.65.

General procedure for preparation of 4-(4-substituted phenyl)-1,2,3,6-tetrahydro-3,6-pyridazinedione (3a–c). A mixture of **2a–c** (10 mmol) and hydrazine hydrochloride (0.856 gr, 1.2 eq mmol) in 50 mL H_2O was refluxed vigorously for 4 h. After completion, the reaction was allowed to cool to RT, then the yellow precipitate was filtered, dried and crystallized from ethanol.

4-Phenyl-1,2,3,6-tetrahydro-3,6-pyridazinedione (3a). This compound was obtained as a yellow powder in 72% yield, mp 276–278°C; IR (potassium bromide): (NH) 3476, 3411, (C=O) 1654, 1564 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 7.22 (s, 1H, CH-pyridazine), 7.41 (m, 3H, Ar–H), 7.80 (m, 2H, Ar–H), 11.10 (br s, 1H, NH, D_2O exchangeable), 12.13 (br s, 1H, NH, D_2O exchangeable); *Anal*. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.58; H, 4.05; N, 14.31. The ^{1}H nmr spectra data were compared with the authentic sample of ref. [21].

4-(4-Methoxyphenyl)-1,2,3,6-tetrahydro-3,6-pyridazinedione (3b). This compound was obtained as a yellow powder in 86% yield, mp 260–262°C; IR (potassium bromide): (NH) 3110, 3105, (C=O) 1654, 1609 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.86 (s, 3H, OCH_3), 6.81 (s, 1H, CH-pyridazine), 7.01 (d, 2H, Ar–H), 8.02 (d, 2H, Ar–H), 11.11 (br s, 1H, NH, D_2O exchangeable), 11.90 (br s, 1H, NH, D_2O exchangeable); *Anal.* Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.15; H, 4.10; N, 12.40.

4-(4-Methylphenyl)-1,2,3,6-tetrahydro-3,6-pyridazinedione (3c). This compound was obtained as a yellow powder in 90% yield, mp 269–270°C; IR (potassium bromide): (NH) 3170, (C=O) 1739, 1652 cm^{-1}; ^1H nmr (deuteriochloroform, DMSO-d_6): δ 2.20 (s, 3H, CH_3), 6.87 (s, 1H, CH-pyridazine), 7.05 (d, 2H, Ar–H), 7.48 (d, 2H, Ar–H), 11.05 (br s, 2H, NH, D_2O exchangeable); *Anal.* Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85; Found: C, 65.00; H, 4.69; N, 13.70.

General procedure for preparation of 3,6-dichloro-4-(4-substitutedphenyl)-pyridazine (4a–c). A mixture of **3a–c** (10 m*M*) and phosphoryl chloride ($POCl_3$, 9 mL) in 2 mL *N*, *N*-diethyl aniline was heated under reflux for 2 h. The reaction mixture was cooled, and then cautiously was poured onto crushed ice. The crude 3,6 dichloro pyridazine was collected by filtration, dissolved in 100 mL dry chloroform or petroleum ether and dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was crystallized from ethanol.

3,6-Dichloro-4-phenylpyridazine (4a). This compound was obtained as a white crystal in 93% yield, mp 90–91°C; IR (potassium bromide): (=C–H) 3056–3031 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.41 (s, 1H, CH-pyridazine), 7.52–7.81 (m, 5H, Ar–H); ms: m/z 225, 227 (M^+); *Anal.* Calcd for $C_{10}H_6Cl_2N_2$: C, 53.36; H, 2.69; N, 12.45. Found: C, 53.48; H, 2.41; N, 12.22. The ^1H nmr spectra data were compared with the authentic sample of ref. [21].

3,6-Dichloro-4-(4-methoxyphenyl)pyridazine (4b). This compound was obtained as a yellow crystal in 90% yield, mp 112–124°C; IR (potassium bromide): (=C–H) 3080–3022, (–C–H) 2962–2843 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.94 (s, 3H, OCH_3), 7.01 (d, 2H, Ar–H), 7.52 (s, 1H, CH-pyridazine), 7.55 (d, 2H, Ar–H); *Anal.* Calcd for $C_{11}H_8Cl_2N_2O$: C, 51.79; H, 3.16; N, 10.98. Found: C, 52.58; H, 3.16; N, 9.99.

3,6-Dichloro-4-(4-methylphenyl)pyridazine (4c). This compound was obtained as a yellow crystal in 92% yield, mp 95–97°C; IR (potassium bromide): (=C–H) 3027, (–C–H) 2921 cm^{-1};^1H nmr (deuteriochloroform): δ 2.43 (s, 3H, CH_3), 7.8 (s, 1H, CH-pyridazine), 7.50 (m, 4H, Ar–H); *Anal.* Calcd for $C_{11}H_8Cl_2N_2$: C, 55.26; H, 3.37; N, 11.72. Found: C, 54.98; H, 3.00; N, 11.65.

General procedure for preparation of 6-chloro-5-(4-substitutedphenyl)-3-pyridazinyl hydrazine (5a–c). A mixture of **4a–c** (10 mmol) in ethanol (15 mL), hydrazine hydrate (4 mL, 99%, and 10 eq mmol) was added. The reaction was refluxed for 4 h after cooling to RT. The precipitate was filtered off, dried and crystallized from ethanol.

6-Chloro-5-phenyl-3-pyridazinylhydrazine (5a). This compound was obtained as a white powder in 95% yield, mp 195–196°C; IR (potassium bromide): ($NHNH_2$) 3246–3142 cm $^{-1}$;^1H nmr (DMSO-d_6): δ 3.55 (br s, 2H, NH_2), 6.42–8.50 (m, 7H, CH-pyridazine, Ar–H, NH), after D_2O exchangeable: 7.10 (s, 1H, CH-pyridazine), 7.52 (m, 5H, Ar–H); *Anal.* Calcd for $C_{10}H_9ClN_4$: C, 54.43; H, 4.11; N, 25.39. Found: C, 54.21; H, 4.00; N, 25.21. The ^1H nmr spectra data were compared with the authentic sample of ref. [21].

6-Chloro-5-(4-methoxyphenyl)-3-pyridazinylhydrazine (5b). This compound was obtained as a white powder in 90% yield, mp 201–203°C; IR (potassium bromide): ($NHNH_2$) 3305–3252 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.90 (s, 3H, OCH_3), 4.20 (br s, 2H, NH_2, D_2O exchangeable), 7.02 (s, 1H, CH-pyridazine), 7.10 (d, 2H, Ar–H), 7.53 (d, 2H, Ar–H), 8.37 (br s, 1H, NH, D_2O exchangeable); *Anal.* Calcd for $C_{11}H_{11}ClN_4O$: C, 52.70; H, 4.42; N, 22.35. Found: C, 52.65; H, 4.12; N, 22.05.

6-Chloro-5-(4-methylphenyl)-3-pyridazinylhydrazine (5c). This compound was obtained as a white powder in 92% yield, mp 182–183°C; IR (potassium bromide): ($NHNH_2$) 3313, 3249 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 3.42 (br s, 2H, NH_2, D_2O exchangeable), 7.28 (d, 2H, Ar–H), 7.71 (s, 1H, CH-pyridazine), 7.85 (d, 2H, Ar–H,), 13.17 (br s, 1H, NH, D_2O exchangeable); ms: m/z 233 (M^+); *Anal.* Calcd for $C_{11}H_{11}ClN_4$: C, 56.30; H, 4.72; N, 23.87. Found: C, 55.99; H, 4.30; N, 23.66.

General procedure for preparation of (6a–i). To a mixture of **5a–c** (2 mmol) in acetic acid (4 mL), appropriate orthoester (20 mmol) was added. The reaction was refluxed for 5 h.the solvent was removed under reduced pressure and the residue crystallized from methanol.

6-Chloro-7-phenyl-[1,2,4]triazolo[4,3-b]pyridazine (6a). This compound was obtained as a white crystal in 40% yield, mp 160–162°C; IR (potassium bromide): (N=CH) 3134 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.41–7.70 (m, 5H, Ar–H), 8.5 (s, 1H, CH-pyridazine), 9.7 (s, 1H, CH-triazole); ms: m/z 230, 232 (M^+); *Anal.* Calcd for $C_{11}H_7ClN_4$: C, 57.28; H, 3.06; N, 24.29. Found: C, 57.42; H, 3.30; N, 24.20. The ^1H nmr spectra data were compared with the authentic sample of ref. [22].

3-Methyl-7-phenyl-[1,2,4]triazolo[4,3-b]pyridazine-6-ylchloride (6b). This compound was obtained as a white crystal in 25% yield, mp 229–230°C; IR (potassium bromide): (=C–H) 2970 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.70 (s, 3H, CH_3), 7.40–7.66 (m, 5H, Ar–H), 8.41 (s, 1H, CH-pyridazine); ms: m/z 244, 246 (M^+); *Anal.* Calcd for $C_{12}H_9ClN_4$: C, 58.90; H, 3.71; N, 22.90. Found: C, 58.50; H, 3.60; N, 22.82. The ^1H nmr spectra data were compared with the authentic sample of ref. [22].

3-Ethyl-7-phenyl-[1,2,4]triazolo[4,3-b]pyridazine-6-ylchloride (6c). This compound was obtained as a white powder in 50% yield, mp 176–177°C; IR (potassium bromide): (=C–H) 2989–2848 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.53 (t, 3H, CH_3), 3.22 (q, 2H, CH_2), 7.31–7.75 (m, 5H, Ar–H), 8 (s, 1H, CH-pyridazine); ms: m/z 258, 260 (M^+); *Anal.* Calcd for $C_{13}H_{11}ClN_4$: C, 60.35; H, 4.29; N, 21.66. Found: C, 60.02; H, 4.00; N, 21.45.

6-Chloro-7-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-b]pyridazine (6d). This compound was obtained as a white crystal in 38% yield, mp 206–208°C; IR (potassium bromide): (N=CH) 3096 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.90 (s, 3H, OCH_3), 7.11 (d, 2H, Ar–H), 7.54 (d, 2H, Ar–H), 8.20 (s, 1H, CH-pyridazine), 9.4 (s, 1H, CH-triazole); ms: m/z 260, 262 (M^+); *Anal.* Calcd for $C_{12}H_9ClN_4O$: C, 55.29; H, 3.48; N, 21.49. Found: C, 55.19; H, 3.46; N, 21.30.

3-Methyl-7-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-b]pyridazine-6-ylchloride (6e). This compound was obtained as a white crystal in 35% yield, mp 225–226°C; IR (potassium bromide): (–C–H) 2998–2831 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.75 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.11 (d, 2H, Ar–H), 7.64 (d, 2H, Ar–H), 8.41 (s, 1H, CH-pyridazine); ms: m/z 274, 276 (M^+); *Anal.* Calcd For

$C_{13}H_{11}ClN_4O$: C, 56.84; H, 4.04; N, 20.40. Found: C, 56.37; H, 4.11; N, 20.65.

3-Ethyl-7-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-b]pyridazine-6-ylchloride (6f). This compound was obtained as a white crystal in 20% yield, mp 103–104°C; IR (potassium bromide): (–C–H) 2995–2835 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.56 (t, 3H, CH_3), 3.27 (q, 2H, CH_2), 3.91 (s, 3H, OCH_3), 7.05 (d, 2H, Ar–H), 7.44 (d, 2H, Ar–H), 8.02 (s, 1H, CH-pyridazine); ^{13}C NMR (400 MHz, deuteriochloroform): δ 160.72, 150.97, 149.68, 143.64, 134.51, 130.73, 126.83, 124.17, 114.21, 55.47, 17.86, 10.94; ms: m/z 288, 290 (M^+); *Anal*. Calcd for $C_{14}H_{13}ClN_4O$: C, 58.24; H, 4.54; N, 19.40. Found: C, 57.57; H, 4.35; N, 19.18.

6-Chloro-7-(4-methylphenyl)-[1,2,4]triazolo[4,3-b]pyridazine (6g). This compound was obtained as a white powder in 37% yield, mp 218–219°C; IR (potassium bromide): (N=CH) 3105 cm^{-1}; ^1H NMR (deuteriochloroform): δ 2.45 (s, 3H, CH_3), 7.45 (m, 4H, Ar–H), 8.10 (s, 1H, CH-pyridazine), 9.12 (s, 1H, CH-triazole); ms: m/z 244, 246 (M^+); *Anal*. Calcd for $C_{12}H_9ClN_4$: C, 58.90; H, 3.71; N, 22.90. Found: C, 58.38; H, 3.64; N, 22.61.

3-Methyl-7-(4-methylphenyl)-[1,2,4]triazolo[4,3-b]pyridazine-6-ylchloride (6h). This compound was obtained as a white crystal in 30% yield, mp 193–194°C; IR (potassium bromide): (–C–H) 2999–2856 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.40 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 7.45 (m, 4H, Ar–H), 8.01 (s, 1H, CH-pyridazine); ms: m/z 258, 260 (M^+); *Anal*. Calcd for $C_{13}H_{11}ClN_4$: C, 60.35; H, 4.29; N, 21.66. Found: C, 59.81; H, 4.17; N, 22.29.

3-Ethyl-7-(4-methylphenyl)-[1,2,4]triazolo[4,3-b]pyridazine-6-ylchloride (6i). This compound was obtained as a white powder in 60% yield, mp 171–172°C; IR (potassium bromide): (–C–H) 2989–2913 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.50 (t, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.25 (q, 2H, CH_2), 7.4 (m, 4H, Ar–H), 8.04 (s, 1H, CH-pyridazine); ms: m/z 272, 274 (M^+); *Anal*. Calcd for $C_{14}H_{13}ClN_4$: C, 61.65; H, 4.80; N, 20.54. Found: C, 61.45; H, 4.47; N, 20.39.

General procedure for preparation of (7a–o). A mixture of **5a–c** (3 mmol) and appropriate aromatic aldehyde (3 mmol) in ethanol (15 mL) and 5 drops of acetic acid was heated under reflux for 3 h and cooled. The product was separated, filtered and washed with saturated sodium carbonate solution before washing with water, then dried and recrystallized from ethanol.

6-(2-Benzylidenehydrazinyl)-3-chloro-4-phenylpyridazine (7a). This compound was obtained as a light yellow powder in 55% yield, mp 350°C (dec); IR (potassium bromide): (NH) 3215, (N=CH) 1610 cm^{-1}; ^1H nmr (DMOS-d_6): δ 7.31–7.81 (m, 11H, N=CH, Ar–H), 8.20 (s, 1H, CH-pyridazine), 11.85 (br s, 1H, NH, D_2O exchangeable); *Anal*. Calcd for $C_{17}H_{13}ClN_4$: C, 66.13; H, 4.24; N, 18.15. Found: C, 65.88; H, 4.01; N, 17.89. The ^1H nmr spectra data were compared with the authentic sample of ref. [21].

3-Chloro-6-(2-(4-methoxybenzylidene)hydrazinyl)-4-phenylpyridazine (7b). This compound was obtained as a yellow powder in 35% yield, mp 170–171°C; IR (potassium bromide): (NH) 3203, (–C–H) 2966–2839, (N=CH) 1604 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.90 (s, 3H, OCH_3), 7.02 (d, 2H, Ar–H), 7.51–7.72 (m, 5H, Ar–H), 7.73 (d, 2H, Ar–H), 8.10 (s, 1H, CH-pyridazine), 8.60 (s, 1H, N=CH), 11.6 (br s, 1H, NH, D_2O exchangeable); *Anal*. Calcd for $C_{18}H_{15}ClN_4O$: C, 63.81; H, 4.46; N, 16.54. Found: C, 63.55; H, 4.45; N, 16.19.

3-Chloro-6-(2-(4-methylbenzylidene)hydrazinyl)-4-phenylpyridazine (7c). This compound was obtained as a yellow powder in 40% yield, mp 276–277°C; IR (potassium bromide): (NH) 3182, (–C–H) 2974–2834, (N=CH) 1610 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.30 (s, 3H, CH_3), 7.20 (d, 2H, Ar-H), 7.41- 7.65 (m, 5H, Ar-H), 7.73 (d, 2H, Ar-H), 8.10 (s, 1H, N=CH), 8.60 (s, 1H, CH-pyridazine), 11.75 (br s, 1H, NH, D_2O exchangeable); *Anal*. Calcd for $C_{18}H_{15}ClN_4$: C, 66.98; H, 4.68; N, 17.36 Found: C, 66.55; H, 4.63; N, 17.02.

3-Chloro-6-(2-(4-nitrobenzylidene)hydrazinyl)-4-phenylpyridazine (7d). This compound was obtained as an orange powder in 70% yield, mp 270–271°C; IR (potassium bromide): (NH) 3113, (N=CH) 1617 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.56–7.85 (m, 5H, Ar–H), 7.92 (s, 1H, N=CH), 8.01 (s, 1H, CH-pyridazine), 8.11–8.55 (m, 4H, Ar–H), 12.16 (br s, 1H, NH, D_2O exchangeable); *Anal*. Calcd for $C_{17}H_{12}ClN_5O_2$: C, 57.72; H, 3.42; N, 19.80. Found: C, 57.71; H, 3.41; N, 19.78.

3-Chloro-6-(2-(4-chlorobenzylidene)hydrazinyl)-4-phenylpyridazine (7e). This compound was obtained as a yellow powder in 47% yield, mp 280–281°C; IR (potassium bromide): (NH) 3190, (N=CH) 1609 cm^{-1}; ^1H nmr (deuteriochloroform, DMSO-d_6): δ 7.40–8.01 (m, 9H, Ar–H), 8.10 (s, 1H, N=CH), 8.62 (s, 1H, CH-pyridazine), 11.66 (br s, 1H, NH, D_2O exchangeable); *Anal*. Calcd for $C_{17}H_{12}Cl_2N_4$: C, 59.49; H, 3.52; N, 16.32 Found: C, 59.51; H, 3.53; N, 16.40.

6-(2-Benzylidenehydrazinyl)-3-chloro-4-(4-methoxyphenyl) pyridazine (7f). This compound was obtained as a light yellow powder in 30% yield, mp 300°C (dec); IR (potassium bromide): (NH) 3297, (N=CH) 1608 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.9 (s, 3H, OCH_3), 7.14 (d, 2H, Ar–H), 7.32–7.85 (m, 8H, Ar–H, N=CH), 8.20 (s, 1H, CH-pyridazine), 11.86 (br s, 1H, NH, D_2O exchangeable); *Anal*. Calcd for $C_{18}H_{15}ClN_4O$: C, 63.81; H, 4.46; N, 16.54. Found: C, 63.45; H, 4.09; N, 16.50.

3-Chloro-6-(2-(4-methoxybenzylidene)hydrazinyl)-4-(4-methoxyphenyl)pyridazine (7g). This compound was obtained as a yellow powder in 50% yield, mp 173–174°C; IR (potassium bromide): (NH) 3191, (–C–H) 2974–2835, (N=CH) 1603 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.92 (s, 6H, 2(OCH_3)), 6.93–7.26 (m, 4H, Ar–H), 7.62–7.97 (m, 4H, Ar–H), 8.10 (s, 1H, CH-pyridazine), 8.60 (s, 1H, N=CH), 10.49 (br s, 1H, NH, D_2O exchangeable); *Anal*. Calcd for $C_{19}H_{17}ClN_4O_2$: C, 61.87; H, 4.65; N, 15.19. Found: C, 61.65; H, 4.43; N, 14.89.

3-Chloro-4-(4-methoxyphenyl)-6-(2-(4-methylbenzylidene) hydrazinyl)pyridazine (7h). This compound was obtained as a yellow powder in 40% yield, mp 183–184°C; IR (potassium bromide): (NH) 3187, (–C–H) 2997–2831, (N=CH) 1608 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.50 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 7.15 (d, 2H, Ar–H), 7.12–7.76 (m, 4H, Ar–H), 7.70 (d, 2H, Ar–H), 8.22 (s, 1H, CH-pyridazine), 8.70 (s, 1H, N=CH), 11.05 (br s, 1H, NH, D_2O exchangeable); *Anal.* Calcd for $C_{19}H_{17}ClN_4O$: C, 64.68; H, 4.86; N, 15.88. Found: C, 64.78; H, 4.90; N, 15.89.

3-Chloro-4-(4-methoxyphenyl)-6-(2-(4-nitrobenzylidene) hydrazinyl)pyridazine (7i). This compound was obtained as an orange powder in 20% yield, mp 286- 287°C; ir (Potassium bromide): (NH) 3203, (N=CH) 1594 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.90 (s, 3H, OCH_3) 7.14 (d, 2H, Ar–H), 7.53 (d, 2H, Ar–H), 7.91 (s, 1H, N=CH), 8.10 (s, 1H, CH-pyridazine), 8.15–8.52 (m, 4H, Ar–H), 12.17 (br s, 1H, NH, D_2O exchangeable); ms: m/z 383(M^+); *Anal.* Calcd for $C_{18}H_{14}ClN_5O_3$: C, 56.33; H, 3.68; N, 18.25. Found: C, 56.00; H, 3.66; N, 18.02.

3-Chloro-6-(2-(4-chlorobenzylidene)hydrazinyl)-4-(4-methoxyphenyl)pyridazine (7j). This compound was obtained as a yellow powder in 38% yield, mp 208–209°C; IR (potassium bromide): (NH) 3191, (N=CH) 1609 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.90 (s, 3H, OCH_3), 7.13 (d, 2H, Ar–H), 7.44–7.76 (m, 4H, Ar–H), 7.96 (d, 2H, Ar–H), 8.10 (s, 1H, CH-pyridazine), 8.72 (s, 1H, N=CH), 11.95 (br s, 1H, NH, D_2O exchangeable); *Anal*. Calcd for $C_{18}H_{14}Cl_2N_4O$: C, 57.92; H, 3.78; N, 15.01. Found: C, 57.70; H, 3.55; N, 14.78.

6-(2-Benzylidenehydrazinyl)-3-chloro-4-(p-tolyl)pyridazine (7k). This compound was obtained as a light yellow powder in 60% yield, mp 295–297°C; IR (potassium bromide): (NH) 3199, (N=CH) 1608 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.35 (s, 3H, CH_3), 7.34–7.86 (m, 10H, Ar–H, N=CH), 8.20 (s, 1H, CH-pyridazine), 11.88 (br s, 1H, NH, D_2O exchangeable); *Anal*. Calcd for $C_{18}H_{15}ClN_4$: C, 66.98; H, 4.68; N, 17.36. Found: C, 66.90; H, 4.60; N, 17.23.

3-Chloro-6-(2-(4-methoxybenzylidene)hydrazinyl)-4-(p-tolyl) pyridazine (7l). This compound was obtained as a yellow powder in 35% yield, mp 206–208°C; IR (potassium bromide): (NH) 3182, (–C–H) 2970–2835, (N=CH) 1603 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.45 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 6.93 (d, 2H, Ar–H), 7.30–7.76 (m, 4H, Ar–H), 7.85 (d, 2H, Ar–H), 8.23 (s, 1H, CH-pyridazine), 8.70 (s, 1H, N=CH), 11.17 (br s, 1H, NH, D_2O exchangeable); *Anal*. Calcd for $C_{19}H_{17}ClN_4O$: C, 64.68; H, 4.86; N, 15.88. Found: C, 64.50; H, 4.60; N, 15.87.

3-Chloro-6-(2-(4-methylbenzylidene)hydrazinyl-4-(p-tolyl) pyridazine (7m). This compound was obtained as a yellow powder in 30% yield, mp 232–234°C; IR (potassium bromide): (NH) 3178, (–C–H) 2945–2847, (N=CH) 1609 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.30 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.15–7.75 (m, 6H, Ar–H), 7.86 (d, 2H, Ar–H), 8.20 (s, 1H, CH-pyridazine), 8.74 (s, 1H, N=CH), 11.77 (br s, 1H, NH, D_2O exchangeable); *Anal*. Calcd for $C_{19}H_{17}ClN_4$: C, 67.75; H, 5.09; N, 16.63. Found: C, 67.80; H, 4.76; N, 16.54.

3-Chloro-6-(2-(4-nitrobenzylidene)hydrazinyl-4-(p-tolyl) pyridazine (7n). This compound was obtained as an orange powder in 80% yield, mp 300–302°C; IR (potassium bromide): (NH) 3207, (N=CH) 1609 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.35 (s, 3H, CH_3) 7.38–7.56 (m, 6H, Ar–H), 7.92 (s, 1H, N=CH), 8.01 (s, 1H, CH-pyridazine), 8.30 (d, 2H, Ar–H), 12.27 (br s, 1H, NH, D_2O exchangeable); *Anal*. Calcd for $C_{18}H_{14}ClN_5O_2$: C, 58.78; H, 3.84; N, 19.04. Found: C, 58.66; H, 3.80; N, 19.14.

3-Chloro-6-(2-(4-chlorobenzylidene)hydrazinyl)-4-(p-tolyl) pyridazine (7o). This compound was obtained as a yellow powder in 40% yield, mp 201–202°C; IR (potassium bromide): (NH) 3190, (N=CH) 1608 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.44 (s, 3H, CH_3), 7.32 (d, 2H, Ar–H), 7.34 (d, 2H, Ar–H), 7.39 (s, 1H, N=CH), 7.49 (d, 2H, Ar–H), 7.78 (d, 2H, Ar–H), 8.13 (s, 1H, CH-pyridazine), 11.87 (br s, 1H, NH, D_2O exchangeable); ms: m/z 219 (M–N=CHC_6H_4Cl); *Anal*. Calcd for $C_{18}H_{14}Cl_2N_4$: C, 60.52; H, 3.95; N, 15.68. Found: C, 60.22; H, 3.86; N, 15.70.

General procedure for preparation of 8a–o. A mixture of appropriate hydrazones **7a–o** (1.2 mmol) and nitrobenzene (7 mL) was refluxed in an oil bath at 216°C for 20 h. Nitrobenzene was removed under reduced pressure and the residue recrystallized in ethanol and methanol-ethyl acetate, respectively.

3,7-Diphenyl-[1,2,4]triazolo[4,3-b]pyridazine-6-ylchloro (8a). This compound was obtained as a pale yellow powder in 90% yield, mp 155–156°C; IR (potassium bromide): (=C–H) 3052–3020 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.52–7.84 (m, 8H, Ar–H), 8.30–8.56 (m, 2H, Ar–H), 8.61 (s, 1H, CH-pyridazine); ms: m/z 306, 308 (M^+); *Anal*. Cald for $C_{17}H_{11}ClN_4$: C, 66.56; H, 3.61; N, 18.26. Found: C, 66.65; H, 3.42; N, 17.71. The ^1H nmr spectra data were compared with the authentic sample of ref. [21,22].

6-Chloro-3-(4-methoxyphenyl)-7-phenyl-[1,2,4]triazolo[4,3-b]pyridazine (8b). This compound was obtained as a yellow powder in 20% yield, mp 140–142°C; IR (potassium bromide): (=C–H) 3060–3039, (–C–H) 2917–2848 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.95 (s, 3H, OCH_3), 7.10 (d, 2H, Ar–H), 7.45–7.67 (m, 5H, Ar–H), 8.10 (s, 1H, CH-pyridazine), 8.55 (d, 2H, Ar–H); ms: m/z 336, 338 (M^+); *Anal*. Cald for $C_{18}H_{13}ClN_4O$: C, 64.19; H, 3.89; N, 16.64. Found: C, 63.87; H, 4.60; N, 16.45.

6-Chloro-7-phenyl-3-(p-tolyl)-[1,2,4]triazolo[4,3-b]pyridazine (8c). This compound was obtained as a pale yellow powder in 45% yield, mp 161–162°C; IR (potassium bromide): (=C–H) 3051–3018, (–C–H) 2912–2855 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.40 (s, 3H, CH_3), 7.45 (d, 2H, Ar–H), 7.54–7.89 (m, 5H, Ar–H), 8.39 (d, 2H, Ar–H), 8.50 (s, 1H, CH-pyridazine); ms: m/z 321, 323 (M^+); *Anal*. Cald for $C_{18}H_{13}ClN_4$: C, 67.40; H, 4.08; N, 17.47. Found: C, 67.20; H, 4.00; N, 17.31.

6-Chloro-3-(4-nithrophenyl)-7-phenyl-[1,2,4]triazolo[4,3-b] pyridazine (8d). This compound was obtained as a light brown powder in 68% yield, mp 220–221°C; IR (potassium bromide): (=C–H) 3068 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.50–7.75 (m, 5H, Ar–H), 8.44–8.77 (m, 5H, CH-pyridazine, Ar–H); ms: m/z 351 (M^+); *Anal.* Cald for $C_{17}H_{10}ClN_5O_2$: C, 58.05; H, 2.84; N, 19.91. Found: C, 58.00; H, 2.63; N, 19.81.

6-Chloro-3-(4-chlorophenyl)-7-phenyl-[1,2,4]triazolo[4,3-b] pyridazine (8e). This compound was obtained as a pale yellow powder in 50% yield, mp 180–181°C; IR (potassium bromide): (=C–H) 3051–3018 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.50–7.91 (m, 7H, Ar–H), 8.39–8.65 (m, 3H, Ar–H, CH-pyridazine); ms: m/z 341, 343 (M^+); *Anal*. Cald for $C_{17}H_{10}Cl_2N_4$: C, 59.84; H, 2.95; N, 16.42. Found: C, 59.77; H, 2.94; N, 16.40.

6-Chloro-7-(4-methoxyphenyl)-3-phenyl-[1,2,4]triazolo[4,3-b] pyridazine (8f). This compound was obtained as a yellow powder in 48% yield, mp 158–159°C; IR (potassium bromide): (=C–H) 3072–3007 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.90 (s, 3H, OCH_3), 7.11 (d, 2H, Ar–H), 7.40–7.84 (m, 5H, Ar–H), 8.11 (s, 1H, CH-pyridazine), 8.54 (d, 2H, Ar–H); ms: m/z 336, 338 (M^+); *Anal.* Cald for $C_{18}H_{13}ClN_4O$: C, 64.19; H, 3.89; N, 16.64. Found: C, 64.18; H, 3.59; N, 16.50.

6-Chloro-3, 7-bis (4-methoxyphenyl)-[1,2,4]triazolo[4,3-b] pyridazine (8g). This compound was obtained as a yellow powder in 35% yield, mp 198–199°C; IR (potassium bromide): (=C–H) 3068, (–C–H) 2957–2839 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.90 (s, 6H, 2(OCH_3)), 6.94–7.27 (m, 4H, Ar–H), 7.53 (d, 2H, Ar–H), 8.13 (s, 1H, CH-pyridazine), 8.50 (d, 2H, Ar–H); ms: m/z 366, 368 (M^+); *Anal*. Cald for $C_{19}H_{15}ClN_4O_2$: C, 62.21; H, 4.12; N, 15.25. Found: C, 61.71; H, 4.19; N, 14.86.

6-Chloro-7-(4-methoxyphenyl)-3-(p-tolyl)-[1,2,4]triazolo[4,3-b]pyridazine (8h). This compound was obtained as a yellow powder in 57% yield, mp 187–188°C; IR (potassium bromide): (=C–H) 3060–3025, (–C–H) 2994–2823 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.50 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.11 (d, 2H, Ar–H), 7.40 (d, 2H, Ar–H), 7.63 (d, 2H, Ar–H), 8.1 (s, 1H, CH-pyridazine), 8.40 (d, 2H, Ar–H); ms: m/z 351, 353 (M^+); *Anal*. Cald for $C_{19}H_{15}ClN_4O$: C, 65.05; H, 4.31; N, 15.97. Found: C, 64.77; H, 4.12; N, 15.81.

6-Chloro-7-(4-methoxyphenyl)-3-(4-nitrophenyl)-[1,2,4]triazolo [4,3-b]pyridazine (8i). This compound was obtained as a yellow powder in 80% yield, mp 225–226°C; IR (potassium bromide): (=C–H) 3045–3040 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.90 (s, 3H, OCH_3), 7.11 (d, 2H, Ar–H), 7.56 (d, 2H, Ar–H), 8.1 (s, 1H, CH-pyridazine), 8.40 (d, 2H, Ar–H), 8.82 (d, 2H, Ar–H); ms: m/z 381, 383 (M^+); *Anal.* Cald for $C_{18}H_{12}ClN_5O_3$: C, 56.63; H, 3.17; N, 18.34. Found: C, 56.59; H, 3.09; N, 18.11.

6-Chloro-3-(4-chlorophenyl)-7-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-b]pyridazine (8j). This compound was obtained as a light yellow powder in 75% yield, mp 203–205°C; IR (potassium bromide): (=C–H) 3064–3032 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.93 (s, 3H, OCH_3), 7.16 (d, 2H, Ar–H), 7.44 (d, 2H, Ar–H), 7.63 (d, 2H, Ar–H), 8.13 (s, 1H, CH-pyridazine), 8.50 (d, 2H, Ar–H); ms: m/z 371, 373 (M^+); *Anal.* Cald for $C_{18}H_{12}Cl_2N_4O$: C, 58.24; H, 3.26; N, 19.10. Found: C, 57.99; H, 3.11; N, 19.12.

6-Chloro-3-phenyl-7-(p-tolyl)-[1,2,4]triazolo[4,3-b]pyridazine (8k). This compound was obtained as a pale brown powder in 45% yield, mp 283–284°C; IR (potassium bromide): (=C–H) 3068–3040 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.53 (s, 3H, CH_3), 7.36–7.75 (m, 7H, Ar–H), 8.22 (s, 1H, CH-pyridazine), 8.5 (m, 2H, Ar–H); ms: m/z 320, 322 (M^+); *Anal*. Cald for $C_{18}H_{13}ClN_4$: C, 67.40; H, 4.08; N, 17.47. Found: C, 67.09; H, 4.07; N, 17.21.

6-Chloro-3-(4-methoxyphenyl)-7-(p-tolyl)-[1,2,4]triazolo[4,3-b] pyridazine (8l). This compound was obtained as a light yellow powder in 15% yield, mp 163–164°C; IR (potassium bromide): (=C–H) 3039–3019, (–C–H) 2966–2843 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.50 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 7.14 (d, 2H, Ar–H), 7.47 (m, 4H, Ar–H), 8.11 (s, 1H, CH-pyridazine), 8.52 (d, 2H, Ar–H); ms: m/z 350, 352 (M^+); *Anal.* Cald for $C_{19}H_{15}ClN_4O$: C, 65.05; H, 4.31; N, 15.97. Found: C, 64.77; H, 4.19; N, 15.69.

6-Chloro-3,7-di-p-tolyl-[1,2,4]triazolo[4,3-b]pyridazine (8m). This compound was obtained as a yellow powder in 60% yield, mp 195–196°C; IR (potassium bromide): (=C–H) 3027, (–C–H) 2917–2847 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.44 (s, 6H, $2CH_3$), 7.31–7.54 (m, 6H, Ar–H), 8.11 (s, 1H, CH-pyridazine), 8.41 (d, 2H, Ar–H); ms: m/z 334, 336 (M^+); *Anal.* Cald for $C_{19}H_{15}ClN_4$: C, 68.16; H, 4.52; N, 16.73. Found: C, 68.00; H, 4.51; N, 16.70.

6-Chloro-3-(4-nitrophenyl)-7-(p-tolyl)-[1,2,4]triazolo[4,3-b] pyridazine (8n). This compound was obtained as a pale yellow powder in 60% yield, mp 270–271°C; IR (potassium bromide): (=C–H) 3031 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.40 (s, 3H, CH_3) 7.30–7.63 (m, 4H, Ar–H), 8.59–8.85 (m, 5H, Ar–H, CH-pyridazine); ms: m/z 363 (M^{-2}); *Anal*. Cald for $C_{18}H_{12}ClN_5O_2$: C, 59.11; H, 3.31; N, 19.15. Found: C, 59.01; H, 3.19; N, 19.19.

6-Chloro-3-(4-chlorophenyl)-7-(p-tolyl)-[1,2,4]triazolo[4,3-b] pyridazine (8o). This compound was obtained as a yellow powder in 45% yield, mp 183–184°C; IR (potassium bromide): (=C–H) 3052–3027 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.40 (s, 3H, CH_3), 7.27 (d, 2H, Ar–H), 7.33 (d, 2H, Ar–H), 7.50 (d, 2H, Ar–H), 8.02 (s, 1H, CH-pyridazine), 8.42 (d, 2H, Ar–H); ms: m/z 355, 357 (M^+); *Anal*. Cald for $C_{18}H_{12}Cl_2N_4$: C, 60.86; H, 3.40; N, 15.77. Found: C, 60.55; H, 3.39; N, 15.45.

General procedure for preparation of 9a–c. A mixture of compound **5a–c** (10 m*M*) and carbon disulfide (10 mL) in dry pyridine (15 mL) was refluxed for 10 h. The solvent was removed under reduced pressure and residue washed with water, dried and recrystallized from ethanol and acetonitrile, respectively.

6-Chloro-7-phenyl-[1,2,4]triazolo[4,3-b]pyridazine-3(2H) thione (9a). This compound was obtained as an orange powder in 90% yield, mp 246–248°C; IR (potassium bromide): 3121 (NH), 1271 (C=S) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 7.40–8.15 (m, 6H, Ar–H, CH-pyridazine), 8.29 (br s, 1H, NH, D_2O exchangeable); ms: m/z 262 (M^{+1}); *Anal*. Cald for $C_{11}H_7ClN_4S$: C, 50.29; H, 2.69; N, 21.33; S, 12.21. Found: C, 50.10; H, 2.49; N, 21.55, S, 12.00.

6-Chloro-7-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-b]pyridazine-3(2H)thione (9b). This compound was obtained as a yellow powder in 85% yield, mp 200–201°C; IR (KBr disk): (NH) 3215, (C=S) 1253 cm^{-1}, ^1H nmr (DMSO-d_6) δ: 3.90 (s, 3H, OCH_3), 7.02 (d, 2H, Ar–H), 7.21–8.65 (m, 4H, Ar–H, CH-pyridazine, NH, D_2O exchangeable); ms: m/z 278 ($M–CH_3$); *Anal*. Cald for $C_{12}H_9ClN_4OS$: C, 49.23; H, 3.10; N, 19.14; S, 10.95. Found: C, 49.01; H, 2.89; N, 19.34, S, 11.35.

6-Chloro-7-(4-methyphenyl)-[1,2,4]triazolo[4,3-b]pyridazine-3(2H)thione (9c). This compound was obtained as a yellow powder in 87% yield, mp 272–271°C; IR (potassium bromide): (NH) 3125, (C=S) 1271 cm^{-1}, ^1H nmr (DMSO-d_6) δ: 2.35 (s, 3H, CH_3), 7.39–7.95 (m, 6H, Ar–H, CH-pyridazine, NH, D_2O exchangeable); ms: m/z 276 (M^{+1}); *Anal*. Cald for $C_{12}H_9ClN_4S$: C, 52.08; H, 3.28; N, 20.24; S, 11.59. Found: C, 52.00; H, 3.43; N, 19.99, S, 11.23.

General procedure for preparation of 10a–o. A solution of compound **9a–c** (1 m*M*) and sodium hydroxide (0.04 g, 1 mmol) in ethanol (50 mL) was treated with appropriate alkylation reagent (2 mmol), and the reaction mixture was warmed on a steam bath at 70°C for 6–8 h. The solvent was removed under reduced pressure and residue washed with water and recrystallized from ethanol, ethyl acetate and 1,4-dioxan, respectively.

6-Chloro-3-(methylthio)-7-phenyl-[1,2,4]triazolo[4,3-b]pyridazine (10a). This compound was obtained as a light yellow powder in 25% yield, mp 275–277°C; IR (potassium bromide): (–C–H) 2927 cm^{-1}; ^1H nmr (deuteriochloroform) δ: 2.70 (s, 3H, SCH_3), 7.55–7.77 (m, 5H, Ar–H), 7.93 (s, 1H, CH-pyridazine); ms: m/z 274 (M^{-2}); *Anal*. Cald for $C_{12}H_9ClN_4S$: C, 52.08; H, 3.28; N, 20.24; S, 11.59. Found: C, 52.01; H, 3.04; N, 20.21; S, 11.39.

6-Chloro-3-(ethylthio)-7-phenyl-[1,2,4]triazolo[4,3-b]pyridazine (10b). This compound was obtained as a pale yellow powder 33% yield, mp 250–251°C. IR (potassium bromide): (–C–H) 2967–2864 cm^{-1}; ^1H nmr (deuteriochloroform) δ: 1.38 (t, 3H, CH_3), 3.36 (q, 2H, SCH_2), 7.55–7.87 (m, 5H, Ar–H), 7.93 (s, 1H, CH-pyridazine); ms: m/z 289 (M^{-1}); *Anal*. Cald for $C_{13}H_{11}ClN_4S$: C, 53.70; H, 3.81; N, 19.27; S, 11.03. Found: C, 53.66; H, 3.75; N, 19.23; S, 10.01.

6-Chloro-7-phenyl-3-(propylthio)-[1,2,4]triazolo[4,3-b]pyridazine (10c). This compound was obtained as a pale yellow powder 33% yield, mp 213°C (dec); IR (potassium bromide): (–C–H) 2963–2868 cm^{-1}; ^1H nmr (deuteriochloroform) δ: 0.93 (t, 3H, CH_3), 1.76 (m, 2H, CH_2), 3.23 (t, 2H, SCH_2), 7.57–7.88 (m, 5H, Ar–H), 7.95 (s, 1H, CH-pyridazine); ms: m/z 301 (M^{-3}); *Anal*. Cald for $C_{14}H_{13}ClN_4S$: C, 55.17; H, 4.30; N, 18.38; S, 10.52. Found: C, 55.16; H, 4.29; N, 18.30; S, 10.22.

3-(Butylthio)-6-chloro-7-phenyl-[1,2,4]triazolo[4,3-b]pyridazine (10d). This compound was obtained as a light yellow powder 25% yield, mp 210–212°C; IR (potassium bromide): (–C–H) 2969–2955 cm^{-1}; ^1H nmr (deuteriochloroform) δ: 0.92 (t, 3H, CH_3), 1.29–1.77 (m, 4H, CH_2CH_2), 3.24 (t, 2H, SCH_2), 7.49–7.75 (m, 5H, Ar–H), 7.81 (s, 1H, CH-pyridazine); ms: m/z 315 (M^{-3}); *Anal*. Cald for $C_{15}H_{15}ClN_4S$: C, 56.51; H, 4.74; N, 17.57; S, 10.06. Found: C, 56.23; H, 4.35; N, 17.52; S, 10.00.

3-(Benzylthio)-6-chloro-7-phenyl-[1,2,4]triazolo[4,3-b]pyridazine (10e). This compound was obtained as a pale yellow powder 35% yield, mp 242–243°C; IR (potassium bromide): (–C–H) 2980 cm^{-1}; ^1H nmr (deuteriochloroform) δ: 4.50 (s, 2H, SCH_2), 7.16–7.37 (m, 5H, Ar–H), 7.44–7.76 (m, 5H, Ar–H), 7.84 (s, 1H, CH-pyridazine); ms: m/z 352 (M^{+1}); *Anal*. Cald for $C_{18}H_{13}ClN_4S$: C, 61.27; H, 3.71; N, 15.88; S, 9.09. Found: C, 61.05; H, 3.60; N, 15.66; S, 9.02.

6-Chloro-7-(4-methoxyphenyl)-3-(methylthio)-[1,2,4]triazolo [4,3-b]pyridazine (10f). This compound was obtained as a yellow powder 29% yield, mp 267–268°C IR (potassium bromide): (–C–H) 2925–2737 cm^{-1}; ^1H nmr (deuteriochloroform) δ: 2.75 (s, 3H, SCH_3), 3.93 (s, 3H, OCH_3), 7.10 (d, 2H, Ar–H), 7.58 (d, 2H, Ar–H), 7.81 (s, 1H, CH-pyridazine); ms: m/z 306 (M^{+1}); *Anal*. Cald for $C_{13}H_{11}ClN_4OS$: C, 50.90; H, 3.61; N, 18.26; S, 10.45. Found: C, 50.88; H, 3.55; N, 18.21; S, 10.12.

6-Chloro-3-(ethylthio)-7-(4-methoxyphenyl)-[1,2,4]triazolo [4,3-b]pyridazine (10g). This compound was obtained as a yellow powder 60% yield, mp 258°C (dec); IR (potassium bromide): (–C–H) 2962–2839 cm^{-1}; ^1H nmr (deuteriochloroform) δ: 1.20 (t, 3H, CH_3), 3.12 (q, 2H, SCH_2), 3.84 (s, 3H, OCH_3), 7.01 (d, 2H, Ar–H), 7.49 (d, 2H, Ar–H), 7.73 (s, 1H, CH-pyridazine); ms: m/z 316 (M^{-4}); *Anal*. Cald for $C_{14}H_{13}ClN_4OS$: C, 52.42; H, 4.08; N, 17.46; S, 10.00. Found: C, 52.39; H, 3.98; N, 17.11; S, 9.01.

6-Chloro-7-(4-methoxyphenyl)-3-(propylthio)-[1,2,4]triazolo [4,3-b]pyridazine (10h). This compound was obtained as a yellow powder 52% yield, mp 270–272°C; IR (potassium bromide): (–C–H) 2960–2838 cm^{-1}; ^1H nmr (deuteriochloroform) δ: 0.92 (t, 3H, CH_3), 1.64 (q, 2H, CH_2), 3.21 (t, 2H, SCH_2), 3.90 (s, 3H, OCH_3), 7.12 (d, 2H, Ar–H), 7.63 (d, 2H, Ar–H), 7.81 (s, 1H, CH-pyridazine); ms: m/z 331 (M^{-3}); *Anal*. Cald for $C_{15}H_{15}ClN_4OS$: C, 53.81; H, 4.52; N, 16.73; S, 9.58. Found: C, 53.72; H, 4.52; N, 16.70; S, 9.31.

3-(Butylthio)-6-chloro-7-(4-methoxyphenyl)-[1,2,4]triazolo [4,3-b]pyridazine (10i). This compound was obtained as a pale yellow powder 15% yield, mp 145–146°C; IR (potassium bromide): (–C–H) 2954–2835 cm^{-1}; ^1H nmr (deuteriochloroform) δ: 0.91 (t, 3H, CH_3), 1.11–1.86 (m, 4H, CH_2CH_2), 3.28 (t, 2H, SCH_2), 3.91 (s, 3H, OCH_3), 7.16 (d, 2H, Ar–H), 7.65 (d, 2H, Ar–H), 7.83 (s, 1H, CH-pyridazine); ms: m/z 346 (M^{-2}); *Anal.* Cald for $C_{16}H_{17}ClN_4OS$: C, 55.09; H, 4.91; N, 16.06; S, 9.19. Found: C, 55.03; H, 4.77; N, 15.99; S, 9.01.

3-(Benzylthio)-6-chloro-7-(4-methoxyphenyl)-[1,2,4]triazolo [4,3-b]pyridazine (10j). This compound was obtained as a pale yellow powder 50% yield, mp 280°C (dec); IR (potassium bromide): (–C–H) 2995–2835 cm^{-1}; ^1H nmr (deuteriochloroform, DMSO-d_6) δ: 3.81 (s, 3H, OCH_3), 4.44 (s, 2H, SCH_2), 7.05 (d, 2H, Ar-H), 7.17–7.36 (m, 5H, Ar–H), 7.55 (d, 2H, Ar–H), 7.7 (s, 1H, CH-pyridazine); ms: m/z 382 (M^{+1}); *Anal*. Cald for $C_{19}H_{15}ClN_4OS$: C, 59.60; H, 3.95; N, 14.63; S, 8.37. Found: C, 59.55; H, 3.85; N, 14.53; S, 8.27.

6-Chloro-7-(4-methylphenyl)-3-(methylthio)-[1,2,4]triazolo [4,3-b]pyridazine (10k). This compound was obtained as a yellow powder 31% yield, mp 249–250°C; IR (potassium bromide): (–C–H) 2925–2851 cm^{-1}; ^1H nmr (deuteriochloroform) δ: 2.55 (s, 3H, CH_3), 2.75 (s, 3H, SCH_3), 7.29–7.56 (m, 4H, Ar–H), 7.85 (s, 1H, CH-pyridazine); ms: m/z 290 (M^{-2}); *Anal.* Cald for $C_{13}H_{11}ClN_4S$: C, 53.70; H, 3.81; N, 19.27; S, 11.03. Found: C, 53.55; H, 3.80; N, 19.01; S, 11.92.

6-Chloro-3-(ethylthio)-7-(4-methylphenyl)-[1,2,4]triazolo[4,3-b] pyridazine (10l). This compound was obtained as a yellow powder 56% yield, mp 284–285°C; IR (potassium bromide): (–C–H) 2917–2729 cm^{-1}; ^1H nmr (deuteriochloroform) δ: 1.10 (t, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.25 (q, 2H, SCH_2), 7.36–7.58 (m, 4H, Ar–H), 7.92 (s, 1H, CH-pyridazine); ms: m/z 298 (M^{-6}); *Anal*. Cald for $C_{14}H_{13}ClN_4S$: C, 55.17; H, 4.30; N, 18.38; S, 10.52. Found: C, 55.01; H, 4.23; N, 18.23; S, 10.47.

6-Chloro-7-(4-methylphenyl)-3-(propylthio)-[1,2,4]triazolo [4,3-b]pyridazine (10m). This compound was obtained as a yellow powder 40% yield, mp 197–198°C; IR (potassium bromide): (–C–H) 2949–2880 cm^{-1}; ^1H nmr (deuteriochloroform) δ: 0.91 (t, 3H, CH_3), 1.64 (q, 2H, CH_2), 2.35 (s, 3H, CH_3), 3.34 (t, 2H, SCH_2), 7.34–7.55 (m, 4H, Ar–H), 7.93 (s, 1H, CH-pyridazine); ms: m/z 217 (M–N=CSC_3H_7); *Anal*. Cald for $C_{15}H_{15}ClN_4S$: C, 56.51; H, 4.74; N, 17.57; S, 10.06. Found: C, 56.30; H, 4.53; N, 17.48; S, 10.08.

3-(Butylthio)-6-chloro-7-(4-methylphenyl)-[1,2,4]triazolo [4,3-b]pyridazine (10n). This compound was obtained as a pale yellow powder 20% yield, mp 232°C (dec); IR (potassium bromide): (–C–H) 2953–2859 cm^{-1}; ^1H nmr (deuteriochloroform) δ: 0.92 (t, 3H, CH_3), 1.15–1.86 (m, 4H, CH_2CH_2), 2.43 (s, 3H, CH_3), 3.24 (t, 2H, SCH_2), 7.43–7.64 (m, 4H, Ar–H), 7.85 (s, 1H, CH-pyridazine); ms: m/z 330 (M^{-2}); *Anal.* Cald for $C_{16}H_{17}ClN_4S$: C, 57.73; H, 5.15; N, 16.83; S, 9.63. Found: C, 57.61; H, 5.05; N, 16.73; S, 9.54.

3-(Benzylthio)-6-chloro-7-(4-methylphenyl)-[1,2,4]triazolo [4,3-b]pyridazine (10o). This compound was obtained as a pale yellow powder 47% yield, mp 262–263°C; IR (potassium bromide): (–C–H) 2921–2733 cm^{-1}; ^1H nmr (deuteriochloroform) δ: 2.44 (s, 3H, CH_3), 4.45 (s, 2H, SCH_2), 7.03–7.65 (m, 9H, Ar–H), 7.71 (s, 1H, CH-pyridazine); ms: m/z 363 (M^{-3}); *Anal.* Cald for $C_{19}H_{15}ClN_4S$: C, 62.20; H, 4.12; N, 15.27; S, 8.74. Found: C, 62.15; H, 4.05; N, 15.23; S, 8.67.

CHEMOTHERAPEUTIC ACTIVITIES

The screening of all the synthesized compounds for their antibacterial activity (Gram positive and Gram negative bacteria) and also inhibitory activity against soybean 15-lipoxygenase (15-LO) enzyme is underway, and the results will be published elsewhere.

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REFERENCES AND NOTES

[1] Rashad, A. E.; Shamroukh, A. H.; Ali, M. A.; Abdel Motti, F. M. Heteroatom Chem 2007, 18, 274.

[2] Rakib, E. M.; Abouricha, S.; Hannioui, A.; Benchat, N. J Iran Chem Soc 2006, 3, 272.

[3] Barnett, S. F.; Defeo-Jones, D.; Haskell, K. M.; Huber, H. E.; Nahas, D. D. PCT Int Appl WO 02 83,064 (Cl. A61K) 24 Oct. 2002, US Appl. Pv 282, 783, 10 Apr. 2001. Chem Abstr 2002, 137, P333127c.

[4] Noguchi, H.; Kitazumi, K.; Mori, M.; Shiba, T. Eur J Pharmacol 2002, 434, 21.

[5] Polsky–Fisher, S. L.; Vickers, S.; Cui, D.; Subramanian, R. Drug Metab Dispos 2006, 34, 1004.

[6] McMahon, L. R.; France, C. P. Br J Pharmacol 2006, 147, 260.

[7] Carling, R. W.; Madin, A.; Guibin, A.; Russell, M. G. N. J Med Chem 2005, 48, 7089.

[8] Albright, J. D.; Moran, D. P.; Wright, W. B.; Collins, J. P. J Med Chem 1981, 24, 592.

[9] Biziere, K.; Bourguignon, J. J.; Chambon, J. P.; Heaulme, M. Br J Pharmacol 1987, 90, 183.

[10] Katrusiak, A.; Melzer, E.; Baloniak, S.; Bobkiewicz, T.; Polcyn, P. Acta Pol Pharm 2001, 58, 217. (Chem. Abstr. 2002, 136, 350111q).

[11] Alig, B.; Marhold, A.; Mueller, P.; Wolfrum, P. PCT Int Appl WO 02 12,236 (Cl. CO7D 471/04) 14 Feb. 2002, DE Appl. 10,038,019, 4 Aug. 2000. (Chem Abstr 2000, 136, P183832s).

[12] Mohamed, M. I.; Zaky, H. T.; Mohamed, H. M.; Kandile, N. G. Afinidad 2005, 62, 48. (Chem Abstr 2006, 144, 254075a).

[13] Shamroukh, A. H.; Ali, M. A. Arch Pharm Chem Life Sci 2008, 341, 223.

[14] Bakavoli, M.; Nikpour, M.; Rahimizadeh, M.; Saberi, M. R.; Sadeghian, H. Bioorg Med Chem 2007, 15, 2120.

[15] Bakavoli, M.; Sadeghian, H.; Tabatabaei, Z.; Rezaei, E.; Rahimizadeh, M.; Nikpour, M. J Mol Model 2008, 14, 471.

[16] Bakavoli, M.; Seyedi, S. M.; Shiri, A.; Saberi, S.; Gholami, M.; Sadeghian, H. J Chem Res 2013, 37, 48.

[17] Roshchin, A. I. Tetrahedron Lett 2010, 51, 3633.

[18] Yassin, F. A. Chem Heterocycl Comp 2009, 45, 8, 997.

[19] Deeb, A.; Hassaneen, M.; Kotb, M. Heteroatom Chem 2005, 16, 4, 278.

[20] Razvi, M.; Ramalingam, T.; Sattur, P. B.; Indian J Chem 1989, 28B, 987.

[21] Carling, R. W.; Madin, A.; Guiblin, A.; et al., J Med Chem 2005, 48, 23,7089.

[22] Fluran, A.; Fluran, M.; Stanovink, B.; Tisler, M.; Monatsh Chem 1974, 105, 834.