Palladium-catalyzed synthesis of novel tetra- and penta-cyclic biologically active benzopyran- and pyridopyran-containing heterocyclic systems

Tatjana Beresneva, Anatoly Mishnev, Elina Jaschenko, Irina Shestakova, Anita Gulbe, and Edgars Abele*

Latvian Institute of Organic Synthesis, 21 Aizkraukles Street, Riga, LV-1006, Latvia
E-mail: abele@osi.lv

Abstract

Syntheses of novel tetra- and penta-cyclic benzopyran and pyridopyran derivatives, *via* direct intramolecular arylation of 2-iodophenoxymethylhetarenes and 3-(2-bromo-pyridin-3-yloxymethyl)-benzo[4,5]imidazo[2,1-*b*]thiazole in the catalytic system $Pd(OAc)_2$ / Xantphos / Cs_2CO_3 / Ag_2CO_3 in toluene, and a one-pot bicatalytic method for 12*H*-[1]benzopyrano[3′,4′:4,5]thiazolo[3,2-*a*]benzimidazole directly from 3-chloro-methylbenzo[4,5]imidazo[2,1-*b*]thiazole and 2-iodophenol, are described. This latter compound exhibits high cytotoxicity (MG-22A**,** 6 μg/mL) on the mouse hepatoma cancer cell line and low toxicity (LD_{50}, 1058 mg/kg) on the mouse Swiss albino embryo fibroblasts 3T3.

Keywords: Palladium catalysis, intramolecular arylation, phase transfer catalysis, fused benzothiazoles, imidazoles, benzopyrans, pyridopyrans, cytotoxicity

Introduction

Pyrans and their benzo derivatives are of interest as biologically active compounds.[1-3] The synthesis and reactions of pyrans and benzopyrans have been well reviewed.[4-9] Recently the uses and properties of important natural and synthetic 2*H*-pyran-2-ones in organic synthesis were documented.[8, 9] One of the earliest works describing the synthesis of the pyranothiazole ring from 3,5-dibromopyran-4-one and a thioamide was published in 1948.[10] Some methods for the preparation of 2-substituted [1]benzopyrano[3,4-*d*]-thiazol-4-ones and -imidazol-4-ones are documented.[11] More recently, the palladium-catalyzed synthesis of thiazolobenzopyran-2-ones from methyl 5-(2-allyloxyphenyl)thiazole-4-carboxylates was reported.[12] Benzopyranothiazole and benzopyranothiophene ring systems were prepared by thermal intramolecular 1,3-dipolar cycloaddition of 2-(prop-2-ynyloxy- and cyanomethyloxy)-3,5-diphenyl-4-hydroxythiazolium hydroxides.[13] Benzopyranoimidazoles have been prepared by electrochemical reduction / rearr-

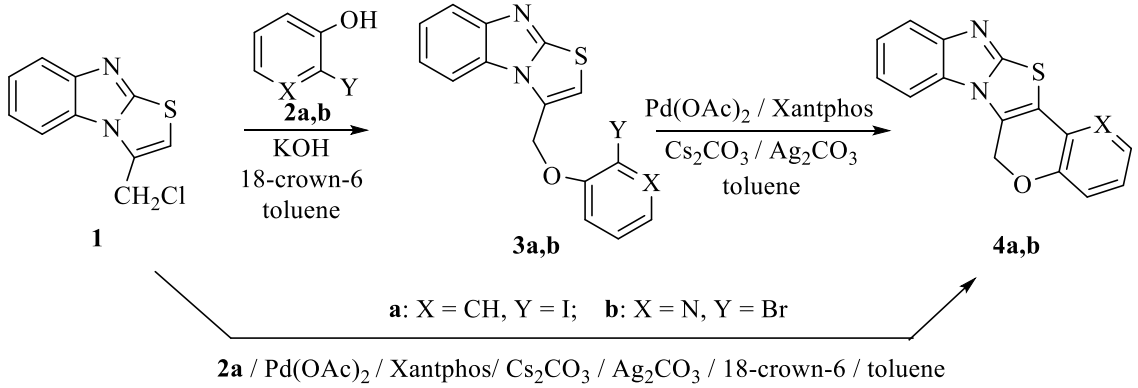
angement of benzopyranotriazines[14] or by condensation of hydrazine with 4-oxochroman-3-carbaldehyde[15].

An important modern development in the palladium-catalyzed synthesis of heterocyclic compounds using an intramolecular Heck-type reaction was recently highlighted in some reviews.[16-19] Regioselective functionalization of the imidazole ring by transition metal-catalyzed C-N and C-C bond formation was reported in details by Rossi *et al*.[20] Interestingly, that the pyrano[3′,4′:4,5]imidazo[1,2-*a*]pyridin-1-one ring system has been constructed by Cu(I)-catalyzed cross-coupling and heterocyclization reactions of halogenated imidazopyridine-carboxylic acids in the presence of terminal alkynes.[21]

Our interest in polycyclic compounds containing imidazothiazole and related fragments was prompted by the wide range of biological activity of these heterocyclic systems.[22-24] Furthermore, the synthesis of tetra- and penta-cyclic imidazolo- and thiazolo-benzopyran derivatives has not been investigated until now and so is the main aim of the present work. Beside this, selected stable compounds (**4a, 10** and **13**) were tested as cytotoxic agents.

Results and Discussion

Synthesis of the novel polycyclic compounds **4a,b, 7, 10** and **13** was carried out in two steps. Alkylation of 2-iodophenol (**2a**) or 2-bromo-3-hydroxypyridine (**2b**) with chloromethylhetarenes **1, 5, 8, 11**[24] was successfully achieved under phase transfer catalytic conditions – solid KOH / 18-crown-6 / toluene. Intermediates **3a,b, 6, 9** and **12** were isolated in 21-87 % yields. (Schemes 1-4)



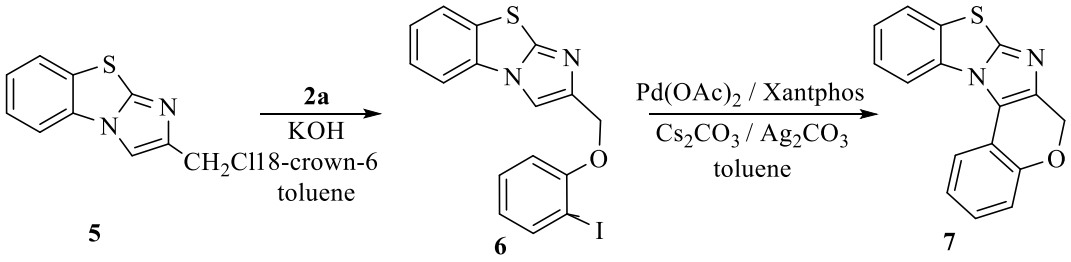
Scheme 1

The influence of catalyst, ligand and additive on the intramolecular Heck-type cyclization was studied in detail. Initially, we examined direct intramolecular arylation of 2-iodophenoxy-methylhetarene **3a** using 10 mol.% $Pd(PPh_3)_4$ as catalyst and 2 eq. Cs_2CO_3 as base. No product was found under these conditions. The use of the system 10 mol.% $Pd(OAc)_2$ / 20 mol.%

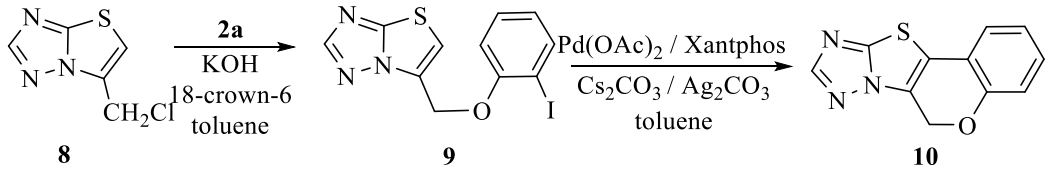
Xantphos / Cs_2CO_3 (2 eq.) / toluene provided the polycycle **4a** in a low (17%) yield with 55% conversion. The high activity of Ag_2CO_3 as an additive in Rh-catalyzed arylation of hetarenes was recently demonstrated.[25] The addition of 0.5 eq. Ag_2CO_3 to the system $Pd(OAc)_2$ (10 mol.%) / Xantphos (20 mol.%) / Cs_2CO_3 (2 eq.) / toluene furnished the desired product **4a** in improved (69 %) yield with full conversion of the starting material **3a**. All catalytic systems in the presence of Ag_2CO_3 were more active.

The polycycle **4a** was also obtained directly from 3-chloromethylbenzo[4,5]imidazo[2,1-*b*]thiazole (**1**) and 2-iodophenol (**2a**) in a *one-pot* synthesis using the bicatalytic system $Pd(OAc)_2$ (10 mol.%) / Xantphos (20 mol.%) / Cs_2CO_3 (3 eq.) / Ag_2CO_3 (0,5 eq.) / 18-crown-6 (10 mol.%), but in lower yield (25%) than the two step synthesis provided.

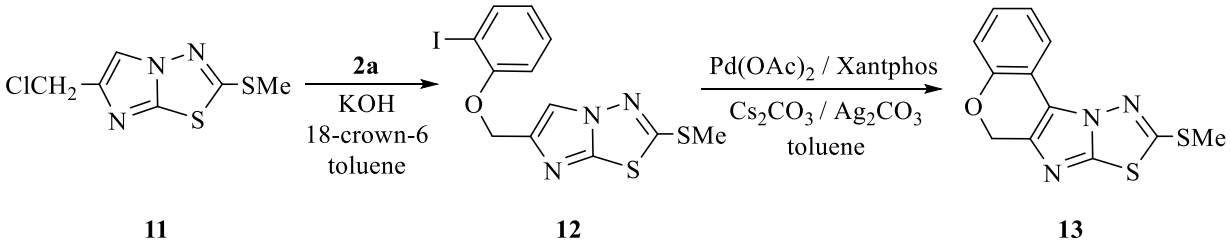
The catalytic system $Pd(OAc)_2$ (10 mol.%) / Xantphos (20 mol.%) / Cs_2CO_3 (2 eq.) / Ag_2CO_3 (0,5 eq.) / toluene, as the most active, was used for the preparation of the polycyclic compounds **4b** (Scheme 1), **7** (Scheme 2), **10** (Scheme 3) and **13** (Scheme 4). The products **4a,b, 7, 10** and **13** were isolated by column chromatography in 31-63% yields.



Scheme 2



Scheme 3



Scheme 4

The structure of compound **13** was confirmed by X-ray structural data. Needle like crystals of compound **13** suitable for intensity measurement were grown from chloroform. The entire molecule of polycycle **13** is essentially planar (Figure 1). The maximal deviation from the least squares mean plane drawn through all non-hydrogen atoms of the molecule is 0.398(2) Å for the O5 atom. The molecule contains four condensed rings, the 1,3,4-thiadiazole (A), imidazole (B), pyran (C) and benzene (D). Rings A, B and D are planar within 0.002Å, 0.002 Å and 0.01Å respectively. The pyran ring (C) adopts a twist-half-chair conformation where atoms C6, C6a, C10b and C10c form a strict plane (±0.005Å), while the O5 and C4a atoms deviate from this plane by 0.564(4)Å and 0.258(4)Å respectively. The thiadiazolo-imidazole system (A+B) forms a dihedral angle of 9.5(1)º with the benzene ring (D).

Bond lengths in compound **13** are in good agreement with the crystal structure of methyl 2-chloro-8-oxo-6*H*,8*H*-[1]benzopyrano[4′,3′:4,5]imidazo[2,1-*b*][1,3]thiazine-10-carboxylate[26] having three similar condensed rings (B+C+D fragment), and of 6-(4-chlorophenyl)imidazo-[2,1-b][1,3,4]thiadiazole-2-sulfonamide[27] with a similar thiadiazolo-imidazole system (A+B). Intermolecular contacts are all of the van der Waals type.

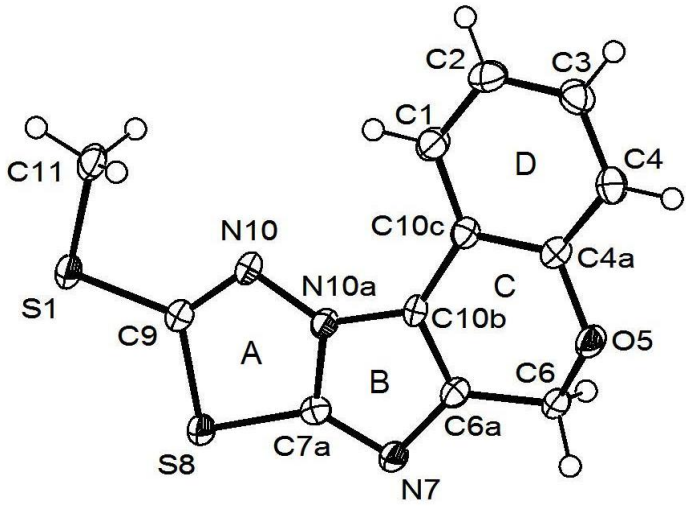


Figure 1. View of the molecule **13** with atomic numbering and ring labels.

Table 1. Crystal data of the compound **13**

Empirical formula	$C_{12}H_9N_3OS_2$
Formula weight	275.34
Temperature (K)	180(2)
Crystal system	orthorombic
Space group	$P2_12_12_1$
a (Å)	3.9926(1)
b (Å)	10.2615(3)
c (Å)	27.847(1)
Volume (Å^3)	1140.88(6)
Z	4
Calc. density (Mg/m^{-3})	1.603
Crystal size (mm)=	0.4 ×□0.1 ×□0.1
Crystal colour	Colorless
θ□ range (°)	2.12 - 27.10
Index ranges	*h* -5 →□5
	k -12 →□13
	l -34 →□35
Data / Restraints / Parameters	2279 / 0 / 163
Final *R* indices [I>2σ□(I)]	0.0326 / 0.0670
R indices (all data)	0.0417 / 0.0707
Hydrogen atoms treatment	Constrained
Largest diff. peak and hole (e.Å^{-3})	0. 274 and -0.248

Table 2. Cytotoxicity of polycyclic compounds **4a**, **10** and **13** IC_{50} (μg/mL)

Compound	HT-1080, IC_{50}	MG-22A, IC_{50}	3T3, LD_{50}, mg/kg
4a	40	6	1058
10	20	28	1100
13	50	78	1487

Cytotoxic activity of compounds **19** and **23** was tested *in vitro* on two monolayer tumor cell lines: MG-22A and HT-1080 (Table 2). Compound **4a** exhibit high activity on the mouse hepatoma (MG-22A**,** 6 μg/mL) cancer cell line. However, on the human fibrosarcoma cell line this compound is essentially inactive. Polycyclic compound **10** exhibit middle activity on both cancer cell lines. Compound **13** is inactive on the MG-22A and HT-1080 cancer cell lines.
Interestingly, that toxicity of compounds **4a**, **10** and **13** (LD_{50}, 1058-1487 mg/kg) detected on the mouse normal fibroblasts is not high.

Conclusions

In summary, we have developed a facile method for synthesis of novel imidazole and thiazole containing benzopyran and pyridopyran derivatives *via* intramolecular cyclization of corresponding 2-iodophenoxy(or bromopyridin-3-yloxy)methylhetarenes in the catalytic system $Pd(OAc)_2$ / Xantphos / Cs_2CO_3 / Ag_2CO_3 / toluene. 12*H*-[1]Benzopyrano[3′,4′:4,5]thiazolo[3,2-*a*]benzimidazole (**4a**) exhibit high cytotoxicity on the mouse hepatoma (MG-22A**,** 6 μg/mL) cancer cell line and low toxicity on mouse Swiss Albino embryo fibroblasts (3T3, LD_{50} 1058 mg/kg).

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury BB 400 MHz in $CDCl_3$ using HMDSO as internal standard. LC-MS spectra were recorded on Alliance Waters 2695 instrument and Waters 3100 mass detector. Column chromatography was performed with silica gel 0,035-0,070 nm (Acros). X-Ray diffraction data was collected using Nonius KappaCCD single crystal diffractometer (Bruker AXS) (MoKα_1 - radiation, graphite monochromator). The structure was solved by SIR2004 [28] and refined by SHELXL97 [29] programs. Rms deviation of fitted atoms = 0.0066. 3-Chloromethylbenzo[4,5]imidazo[2,1-*b*]thiazole (**1**), 2-chloromethylbenzo[d]imidazo[2,1-*b*]thiazole (**5**), 6-chloromethylthiazolo[3,2-*b*][1,2,4]triazole (**8**), 6-chloromethyl-2-methylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazole (**11**) were obtained by the procedure described in article.[24] All prepared compounds are new and were characterized by melting point, LC-MS, HRMS, ^1H NMR and ^{13}C NMR spectra.

General procedure for synthesis of 2-iodophenoxymethylhetarenes 3a, 6, 9, 12 and 3-(2-bromopyridin-3-yloxymethyl)-benzo[4,5]imidazo[2,1-*b*]thiazole (3b)
Solid pulverized KOH (0.98 g, 4.5 mmol) was added to solution of chloromethyl derivatives **1**, **5**, **8** or **11** (4 mmol), 2-iodophenol (**2a**) (0.88 g, 4 mmol) or 2-bromo-3-hydroxypyridine (**2b**) (0.87 g, 4 mmol), 18-crown-6 (0.1g, 0.4 mmol) in toluene (20 mL). Reaction mixture was refluxed for 2 h, cooled to room temperature, filtered and solvent was removed under reduced pressure. The products were purified using flash chromatography (silica, ethyl acetate). Spectroscopic characteristics.

3-(2-Iodophenoxymethyl)-benzo[4,5]imidazo[2,1-*b*]thiazole (3a). 66% yield; mp 165-166 ºC; LC-MS, 407 (M^++1); ^1H NMR δ (□ppm□): 5.40 (s, 2H, CH_2), 6.82 (t, 1H, *J* = 7.6 Hz, 4'-H), 6.86 (s, 1H, 2-H), 6.96 (d, 1H, *J* = 8.4 Hz, 6'-H), 7.26 (t, 1H, *J* = 8.0 Hz, 5'-H), 7.32-7.41 (m, 2H, 6-H and 7-H), 7.80-7.84 (m, 3H, 5-H, 8-H and 3'-H); ^{13}C NMR δ (□ppm□): 63.80 (CH_2), 86.97, 109.97, 111.95, 113.15, 119.17, 121.19, 123.61, 124.15, 128.48, 129.55, 129.78, 140.09, 148.40, 156.20, 156.81.

3-(2-Bromopyridin-3-yloxymethyl)-benzo[4,5]imidazo[2,1-*b*]thiazole (3b). 44% yield; mp 204-205 ºC; LC-MS, 361 (M^++1); ^{1}H NMR δ (□ppm□): 5.75 (s, 2H, CH_2), 7.26 and 7.35 (both t, 2H, *J* = 7 Hz, 6-H and 7-H), 7.50 (m, 1H, 5'-H), 7.52 (s, 1H, 2-H), 7.70 (d, 1H, *J* = 8 Hz, 4'-H), 7.85-7.90 (m, 2H, 5-H and 8-H), 8.05 (d, 1H, *J* = 5 Hz, 6-H'); ^{13}C NMR δ (□ppm□): 62.57 (CH_2), 112.50, 112.60, 118.38, 120.73, 121.86, 123.27, 124.28, 127.94, 129.41, 131.72, 142.22, 147.77, 150.59, 156.29.

2-(2-Iodophenoxymethyl)-benzo[d]imidazo[2,1-*b*]thiazole (6). 21% yield; mp 175-177 ºC; LC-MS, 407 (M^++1); ^{1}H NMR δ (□ppm□): 5.27 (s, 2H, CH_2), 6.74 (t, 1H, *J* = 7.2 Hz, 4'-H), 7.03 (d, 1H, *J* = 8.4 Hz, 6'-H), 7.26-7.46 (m, 3H, 5'-H, 6-H and 7-H), 7.60, 7.69 and 7.79 (all d, 3H, *J* = 8.0 Hz, 3'-H, 5-H, 8-H), 7.85 (s, 1H, 3-H); ^{13}C NMR δ (□ppm□): 66.37 (CH_2), 86.73, 110.07, 112.80, 112.97, 115.19, 122.94, 124.33, 124.91, 126.14, 129.53, 138.40, 139.45, 143.99, 147.47, 157.11.

6-(2-Iodophenoxymethyl)-thiazolo[3,2-*b*][1,2,4]triazole (9). 87% yield; mp 121-122 ºC; LC-MS, 358 (M^++1); ^{1}H NMR δ (□ppm□): 5.38 (s, 2H, CH_2), 6.80 (t, 1H, *J* = 8.0 Hz, 4'-H), 6.96 (d, 1H, *J* = 8.4 Hz, 6'-H), 7.24 (d, 1H, *J* = 1.6 Hz, 5-H), 7.34 (t, 1H, *J* = 8.0 Hz, 5'-H), 7.82 (d, 1H, *J* = 8.0 Hz, 3'-H), 8.19 (d, 1H, *J*= 1.2 Hz, 2-H); ^{13}C NMR δ (□ppm□): 63.39 (CH_2), 86.67, 111.40, 112.87, 123.97, 128.48, 129.72, 139.76, 156.30, 156.35, 156.84.

6-(2-Iodophenoxymethyl)-2-methylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazole (12). 42% yield; mp 124-125 ºC; LC-MS, 404 (M^++1); ^{1}H NMR δ (□ppm□): 2.73 (s, 3H, CH_3), 5.19 (s, 2H, CH_2), 6.72 (t, 1H, *J* = 8.8 Hz, 5'-H), 6.99 (d, 1H, *J* = 8.4 Hz, 6'-H), 7.29 (t, 1H, *J*= 8.4 Hz, 4'-H) 7.78 (d, 1H, *J* = 7.6 Hz, 3'-H), 7.83 (s, 1H, 5-H); ^{13}C NMR δ (□ppm□): 16.07 (Me), 66.80 (CH_2), 86.80, 112.54, 112.95, 122.82, 129.44, 139.46, 142.00, 144.21, 157.06, 161.44.

General procedure for synthesis of polycyclic compounds 4a,b, 7, 10 and 13

Mixture of 2-iodophenoxymethylhetarenes **3a, 6, 9, 12** or 3-(2-bromo-pyridin-3-yloxymethyl)-benzo[4,5]imidazo[2,1-*b*]thiazole **3b** (0.49 mmol), $Pd(OAc)_2$ (0.011 g, 0.049 mmol), Xantphos (0.057 g, 0.098 mmol), anhydrous Cs_2CO_3 (0.32 g, 0.98 mmol) and Ag_2CO_3 (0.068 g, 0.25mmol) in dry toluene (10 mL) was heated at 120ºC for 24 h in glass reactor under argon. Reaction mixture was filtered and solvent was removed under reduced pressure. The products were purified using flash chromatography (silica, ethyl acetate : hexane (1:1)). Spectroscopic characteristics:

12*H*-[1]Benzopyrano[3′,4′:4,5]thiazolo[3,2-*a*]benzimidazole (4a). 69% yield; mp >230 ºC; LC-MS, 279 (M^++1); ^{1}H NMR δ (□ppm□): 5.80 (s, 2H, CH_2), 6.96 (d, 1H, *J* = 8.0 Hz, 4-H), 7.02 (t, 1H, *J* = 8.0 Hz, 2-H), 7.10 (d, 1H, *J* = 7.6 Hz, 1-H), 7.18 (t, 1H, *J* = 7.6 Hz, 3-H), 7.26 and 7.36 (both t, 2H, *J* = 8.0 Hz, 8-H and 9-H), 7.53 and 7.79 (both d, 2H, *J* = 8.0 Hz, 7-H and 10H); ^{13}C NMR δ (□ppm□): 63.24 (CH_2), 110.14, 116.26, 116.28, 116.38, 118.13, 119.72, 121.57, 121.79, 122.61, 122.81, 122.83, 123.75, 123.77, 129.25, 129.38; HRMS: *m/z* $[M+H]^+$ calcd for $C_{16}H_{11}N_2OS$: 279.0592; found 279.0603.

6*H*-Pyrido[3″,2″:2′,3′]pyrano[4′,5′:5,4]thiazolo[3,2-*a*]benzimidazole (4b). 49% yield; mp >230 ºC; LC-MS, 280 (M^++1); ^{1}H NMR δ (□ppm□): 5.85 (s, 2H, 6-H), 7.03 (m, 1H, 3-H), 7.15

(d, 1H, *J* = 8.4 Hz, 4-H), 7.24 and 7.34 (both t, 2H, *J* = 8.0 Hz, 8-H and 9-H), 7.47 and 7.76 (both d, 2H, *J* = 8.0 Hz, 7-H and 10H), 9.09 (d, 1H, *J* = 4.8 Hz, 2-H); ^{13}C NMR δ (□ppm□): 63.87 (CH_2), 110.08, 117.63, 119.75, 121.69, 122.26, 123.47, 124.04, 124.84, 129.17, 119.97, 137.87, 143.00, 147.99, 156.76; HRMS: *m/z* $[M+H]^+$ calcd for $C_{15}H_{10}N_2OS$: 280.0545; found 280.0531.

6*H*-[1]Benzopyrano[3′,4′:4,5]imidazo[2,1-*b*]benzothiazole (7). 63% yield; mp 153-155 °C; LC-MS, 279 (M^++1); ^{1}H NMR δ (□ppm□): 5.29 (s, 2H, 6-H), 7.07-7.21 and 7.26-7.49 (m, 5H, 2-H, 3-H, 4-H, 10-H and 11-H), 7.72 (m, 2H, 1-H, 12-H), 8.14 (t, 1H, *J* = 8.4 Hz, 9-H); ^{13}C NMR δ (□ppm□): 60.36 (CH_2), 114.16, 114.80, 117.98, 118.09, 121.80, 122.29, 124.49, 124.79, 125.93, 127.61, 130.00, 132.79, 142.08, 149.43, 152.51; HRMS: *m/z* $[M+H]^+$ calcd for $C_{16}H_{11}N_2OS$: 279.0592; found 279.0584.

6*H*-[1]Benzopyrano[3′,4′:4,5]thiazolo[3,2-*b*][1,2,4]triazole (10). 31% yield; mp 131-132 °C; LC-MS, 230 (M^++1); ^{1}H NMR δ (□ppm□): □5.58 (s, 2H, 6-H), 6.97 (d, 1H, *J* = 8.4 Hz, 4-H), 7.01 (t, 1H, *J* = 7.6 Hz, 2-H), 7.16 (d, 1H, *J* = 8.0 Hz, 1-H), 7.22 (t, 1H, *J* = 8.0 Hz, 3-H), 8.13 (s, 1H, 8-H); ^{13}C NMR δ (□ppm□): 62.73 (CH_2), 116.75, 117.54, 120.59, 121.53, 122.58, 122.81, 130.07, 151.90, 155.87, 156.18; HRMS: *m/z* $[M+H]^+$ calcd for $C_{11}H_8N_3OS$: 230.0388; found 230.0399.

9-Methylsulfanyl-6*H*-[1]Benzopyrano[3′,4′:4,5]imidazo[2,1-*b*][1,3,4]thiadiazole (**13**). 47% yield; mp 153-155 °C; LC-MS, 276 (M^++1); ^{1}H NMR δ (□ppm□): 2.82 (s, 3H, CH_3), 5.47 (s, 2H, CH_2), 6.93 (d, 1H, *J* = 8.0 Hz, 4-H), 7.00 and 7.73 (both t, 2H, *J* = 7.6 Hz, 2-H and 3-H), 7.73 (d, 1H, *J* = 7.6 Hz, 1-H); ^{13}C NMR δ (□ppm□): 16.24 (CH_3), 67.72 (CH_2), 115.70, 116.50, 120.73, 121.64, 121.65, 128.11, 136.09, 145.30, 151.56, 161.82; HRMS: *m/z* $[M+H]^+$ calcd for $C_{12}H_{10}N_3OS_2$: 276.0265; found 276.0256.

□**In vitro cytotoxicity assay.** Monolayer tumor cell lines –HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma), 3T3 (mouse Swiss Albino embryo fibroblasts), - were cultured in standard medium (Dulbecco`s modified Eagle`s medium; DMEM) and supplemented with 10% fetal bovine serum (“Sigma”). Tumor cell lines were obtained from the ATCC. About 10 x10^4 cells ml^{-1} were placed in 96-well plates immediately after compounds were added to the wells; the volume of each plate was 200 µl. The control cells without test compounds were cultured on separate plate. The plates were incubated for 72h, 37 °C, 5% CO_2. The number of surviving cells was determined using tri(4-dimethylaminophenyl)methyl chloride (crystal violet: CV) or 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolinium bromide (MTT)[30, 31]. LD_{50} was tested according ”Alternative Toxicological Methods”.[32] The program Graph Pad Prism® 3.0 was used for calculations (r□< 0.05.).

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References

1. Rocha, D. F. O.; Hamilton, K.; Goncalves, C. C. S.; Machado, G.; Marsaioli, A. J. *J. Nat. Prod.* **2011**, *74*, 658.
2. Mulwad, V. V.; Langi, B. P.; Chaskar, A. C. *Acta. Poloniae Pharm.-Drug Res.* **2011**, *68*, 39.
3. Agata, N.; Nogi, H.; Milhollen, M.; Kharbanda, S.; Kufe, D. *Cancer Res.* **2004**, *64*, 8512.
4. Ghosh, C. K.; Patra, A. *J. Heterocycl. Chem.* **2008**, *45*, 1529.
5. Ghosh, C. K. *J. Heterocycl. Chem.* **2006**, *43*, 813.
6. Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K. Six-membered rings with one heteroatom, and their fused carbocyclic derivatives. *Comprehensive Heterocyclic Chemistry III*, **2008**, *7*, 1-1066.
7. Hepworth, J. D.; Heron, B. M. *Progr. Heterocycl. Chem.* **2009**, *21*, 455.
8. Goel, A.; Ram, V. J. *Tetrahedron* **2009**, *65*, 7865.
9. Ram, V. J.; Srivastava, P. *Curr. Org. Chem.* **2001**, *5*, 571.
10. Sorkin, E.; Krähenbühl, W.; Erlenmeyer, H. *Helv. Chim. Acta* **1948**, *31*, 65.
11. Colotta, V.; Catarzi, D.; Varano, F.; Cecchi, L.; Filacchioni, G.; Martini, C.; Giusti, L.; Lucacchini, A. *Farmaco* **1998**, *53*, 375.
12. Che, Q.; Vo, N. H.; Chen, S. US Patent 0132513A1, 2008.
13. Potts, K. T.; Dery, M. O. *J. Chem. Soc., Chem. Commun.* **1986**, 561.
14. Bellec, C.; Vinot, N.; Maitte, P. *J. Heterocycl. Chem.* **1986**, *23*, 491.
15. Chiodini, L.; Di Ciommo, M.; Merlini, L. *J. Heterocycl. Chem.* **1981**, *18*, 23.
16. Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173.
17. Majumdar, K.; Chattopadhyay, B. *Curr. Org. Chem.* **2009**, *13*, 731.
18. Heravi, M. M.; Fazeli, A. *Heterocycles* **2010**, *81*, 1979.
19. Majumdar, K. C.; Chattopadhyay, B.; Maji, P. K.; Chattopadhyay, S. K.; Samanta, S. *Heterocycles* **2010**, *81*, 517.
20. Bellina, F.; Rossi, R. *Adv. Synth. Catal.* **2010**, *352*, 1223.
21. Bahlaouan, Z.; Abarbri, M.; Duchene, A.; Thibonnet, J.; Henry, N.; Enguehard-Gueiffier, C.; Gueiffier, A. *Org. Biomol. Chem.* **2011**, *9*, 1212.
22. Beresņeva, T.; Ābele, E.; Šestakova, I.; Jaschenko, E.; Bridane, V.; Kalviņš, I. *Latv. J. Chem.* **2009**, 133.
23. Chimirri, A.; Grasso, S.; Romeo, G.; Zappala, M. *Heterocycles* **1988**, *27*, 1975.
24. Beresneva, T.; Abele, E. *Heterocyclic Lett.* **2011**, *1*, 73.
25. Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748.
26. Van der Helm, D.; Powell, D. R.; Berlin, K. D.; Spruce, L. W.; Shyamasundar, N.; Radhakrishna, A. S. *Acta Cryst.* **1987**, *C43*, 1723.

27. Anilkumar, G. N.; Kokila, M. K.; Puttaraja; Karki, S. S.; Kulkarni, M. V. *Acta Cryst.* **2006**, *E62*, 2014.
28. Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **2005**, *38*, 381.
29. Sheldrick, G.M. *SHELXL97*. University of Göttingen, Germany, 1997.
30. Fast, D. J.; Lynch, R. C.; Leu, R. W. *J. Leuckocyt. Biol*. **1992**, *52*, 255.
31. Freshney, P. J. *Culture of Animal Cells (A Manual of Basic Technique*), Wiley-Liss, New York, 1994, pp. 296-297.
32. http://iccvam.niehs.nih.gov/methods/invidocs/guidance/iv_guide.htm [2004.01.10].

