Tetrahedron 64 (2008) 6711–6723

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An expedient, regioselective synthesis of novel 2-alkylamino- and 2-alkylthiothiazolo[5,4-*e*]- and -[4,5-*g*]indazoles and their anticancer potential

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ARTICLE INFO

Article history:
Received 18 February 2008
Received in revised form 30 April 2008
Accepted 1 May 2008
Available online 3 May 2008

Keywords:
Thiazolo[5,4-*e*]- and -[4,5-*g*]indazoles
Anticancer
Regioselective synthesis
Thioureidoindazoles
Indazolyl dithiocarbamates
Bromine in acetic acid

ABSTRACT

Several novel 2-alkylamino- and 2-alkylthiothiazolo[5,4-*e*]- and -[4,5-*g*]indazoles and their 6-alkyl and 8-alkyl derivatives have been synthesised in high overall yields starting from 5-nitro and 6-nitroindazoles in a three-step route involving the regioselective cyclisation of thioureidoindazoles and indazolyl dithiocarbamates as the key steps. Some assorted thiazoloindazoles have been screened for anticancer properties, which demonstrated the anticancer potential of at least one product, justifying its further follow-up.

1. Introduction

Heterocyclic compounds are extensively used as drugs, pharmaceuticals, agrochemicals, fine chemicals, etc. as well as lead molecules in these areas.[1] During the last few years, we have been actively engaged in developing novel syntheses of potentially bioactive condensed nitrogen heterocycles. Because of the importance of 1,3-azoles[2] in general and thiazoles[3] in particular, we have recently developed new syntheses of condensed thiazoles, viz. thiazolocarbazoles[4] and thiazoloindoles.[5a] In view of the reported diverse bioactivities of condensed thiazoles,[5b] we were on the look out for newer thiazoloheteroarenes with bioactive potential as our synthetic targets. We chose the thiazoloindazole skeleton as our target since indazoles too display diverse biological activities and are common components of drugs and pharmaceuticals.[6]

In fact, substituted and condensed indazoles are recently being increasingly reported as bioactive molecules. Some recent examples of substituted indazoles are granisetron used in CNS disorder,[7a] 7-substituted indazoles developed as neuronal-NOS inhibitors,[7b] antiinflammatory bendazac and benzydamine,[8] platelet aggregation inhibitor as well as anticancer YC-1,[9] the antidepressant drug candidate FS-32,[10a] a promising NSAID WAY-169916,[10b] *c*-ABL inhibitory 3-benzimidazol-2-yl-1*H*-indazoles for curing Gleevec™-resistant chronic myelogenous leukaemia,[11] 3-(indol-2-yl)indazoles as potent inhibitors of Chek1 kinase[12] and 3-substituted (indazol-5-yl)- and (indazol-7-yl)benzenesulfonamides as inhibitors of SAH/MTA nucleosidase[13a] and L1210 murine leukaemia cell cycle,[13b] respectively.

Recent examples of bioactive condensed indazoles are pyrimido[1,2-*b*]indazoles, showing promising anticancer activity against human carcinoma A549 cell lines,[14a] and the PI3 kinase modulatory thiazolo[4,5-*g*]dihydroindazoles with therapeutic potential for inflammatory and allergic diseases.[14b,c]

This ambience motivated us to try to develop an efficient synthesis of thiazoloindazoles because of their bioactive potential. The recent reports on the synthesis of other bioactive condensed thiazoles, viz. anticancer (against human carcinoma cell lines A549) 2-aminothiazolonapthalimides,[15a] HIV-integrase inhibitory thiazolo[5,4-*b*]pyridin-5(4*H*)-ones[15b] and GSK-3 inhibitory thiazolo[5,4-*f*]quinazolin-9-ones[15c] prompt us to report herein our recent success on the development of a short, expedient and regioselective synthesis of 2-alkylamino- and 2-alkylthiothiazolo[5,4-*e*]- and -[4,5-*g*]indazoles and their (indazolic) *N*-alkyl and *N*-benzenesulfonyl derivatives. The results of cytotoxic (A549) evaluation of some of the synthesised thiazoloindazoles are also presented herein.

2. Results and discussion

Our plan was to construct the thiazole nucleus on the indazole framework starting from 5-nitro and 6-nitroindazoles. The thiazole

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0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.05.009

ring can be built up from an arylamine either (i) by treatment with thiocyanogen, usually generated in situ from thiocyanates and bromine alone[16a] or bromine in acetic acid[16b] or 1,3-dichlorothiourea[16c] or (ii) by the oxidative cyclisation of derived thioureides using bromine in acetic acid (Hugershoff reaction),[17a–c] *para*-toluenesulfonic acid-on-clay,[4b] NBS-DBU[5a] or *N*-benzyl-DABCO tribromide.[17d] Alternatively, the derived thioamides may be made to undergo oxidative cyclisation by oxidants like potassium ferricyanide (Jacobson reaction),[18a,b] manganese(III) acetate,[18c] Dess–Martin periodinane[18d] or DDQ.[18e] A third option is by condensing the arylamine with Appel's salt,[19a] followed by cyclisation of the resulting 5-arylamino-4-chloro-1,2,3-dithiazole by conventional heating[19b] or by microwave irradiation.[15c,19c]

Of the aforesaid, we adopted the protocol involving thioureides as intermediates. Like indoles, indazoles are also susceptible to halogenation at C-3, especially under basic conditions.[20] Therefore, we decided to start with *N*-protected indazoles. Accordingly, 5-nitroindazole (**1**) was successively protected as its 1-benzenesulfonyl derivative (**2**), reduced to the corresponding amine (**3**) and condensed separately with methyl, ethyl and benzyl isothiocyanates to furnish in excellent yields the corresponding thioureidoindazoles (**4a**–**c**). The thiocarbonyl carbons of **4a**–**c** appearing at δ 181–182 and their mass spectral peaks at *m*/*z* 315 [M−RNH_2] and *m*/*z* 273 [M−RNCS] lent support to the formation of thioureide moieties.

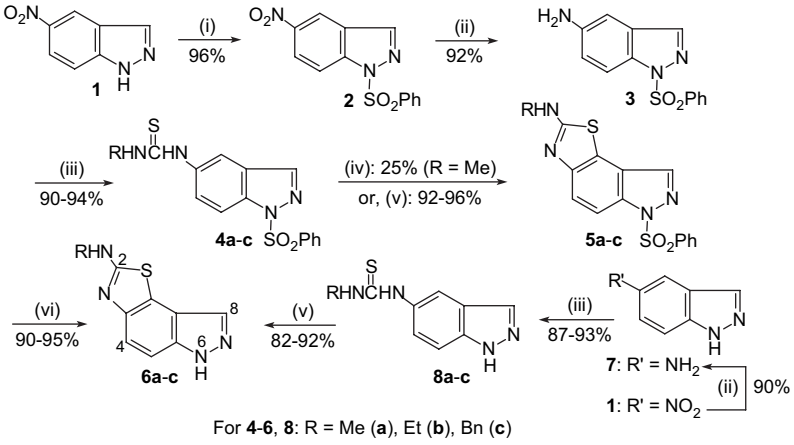
For the cyclisation of **4a**–**c**, we first tried tosic acid-on-clay and NBS–DBU since we had earlier successfully used these reagents for the regioselective synthesis of thiazolocarbazoles[4b] and thiazoloindoles,[5a] respectively. Since, in the thiazolocarbazole series, tosic acid-on-clay proved to be more efficient for the *N*-benzylthioureidocarbazole, the *N*-benzylthioureidoindazole (**4c**) was tried with this cyclising agent. Thus, **4c** was uniformly adsorbed on tosic acid (1 equiv)-doped montmorillonite K10 clay and heated at 60–70 °C. But even after 8 h, no reaction took place at all. The reagent NBS–DBU was next tried, this time on **4a**. The reaction was quite fast, and the sole product, isolated in a mere 25% yield, was identified as the corresponding angularly cyclised product, i.e., the thiazolo[5,4-*e*]indazole (**5a**) (Scheme 1). The conspicuous appearance of two one-proton doublets at δ 7.98 (H-4) and δ 7.70 (H-5) with *ortho*-coupling (*J*=9 Hz) supported angular cyclisation, since in the alternative linearly cyclised product, a thiazolo[4,5-*f*]indazole, each of the two corresponding protons (H-4 and H-8) would have appeared as a doublet with *para*-coupling.

We could trace the low yield of **5a** to its poor solubility in dichloromethane, which was used for extracting it. We, therefore, resorted to the Hugerschoff reaction since it does not involve any extractive work-up. Each of **4a**–**c** was, therefore, treated separately with bromine in acetic acid at room temperature, which expeditiously furnished the respective 2-alkylamino-6-benzenesulfonylthiazolo[5,4-*e*]indazoles (**5a**–**c**) in high yields. The cleavage of the protecting group by mild alkaline hydrolysis smoothly afforded the unprotected thiazoloindazoles (**6a**–**c**) in excellent yields (Scheme 1).

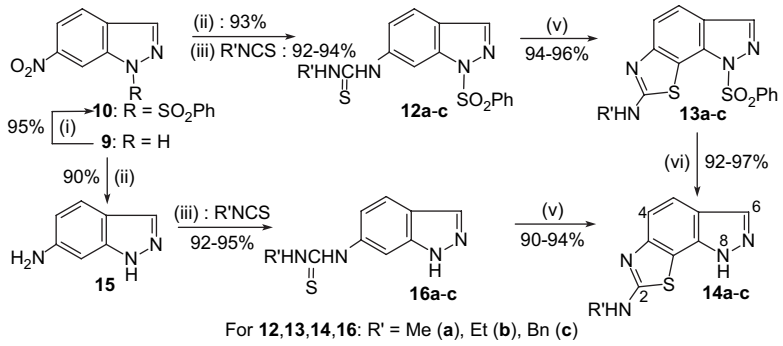
We initially anticipated, based on our previous experience,[4a] that the use of bromine in acetic acid as the cyclising agent in the unprotected indazole nucleus may additionally cause bromination in the products. That is why we started with the *N*-benzensulfonyl derivative (**2**). However, when the unprotected 5-aminoindazole itself (**7**) was subjected to a similar sequence of reactions, the parent thiazoloindazoles (**6a**–**c**) were formed efficiently via the underivatised thioureidoindazoles (**8a**–**c**) (also shown in Scheme 1). Our initial concern thus turned out to be unfounded. The structures of **8a**–**c** received similar ^{13}C NMR ($\delta_{C=S}$ 180–182.5) and mass spectrometric [*m*/*z* 175: M−RNH_2; *m*/*z* 133: M−RNCS] support. The individual ^1H and ^{13}C chemical shifts of **5a**–**c** and **6a**–**c** (ascertained from HMQC and HMBC spectra for **5a** and **6a** and by comparison for the rest) immediately revealed that the carbon chemical shifts of CH-4 (ca. δ 119), CH-5 (δ 108) and CH-8 (δ 131) together can be considered as a marker for identifying this particular thiazoloindazole skeleton.

As planned, the methodology was extended to 6-nitroindazole (**9**) and its 1-benzenesulfonyl derivative (**10**). Each of **9** and **10** was subjected to the same sequence of reactions, leading to the isolation of again only the angularly cyclised products, viz. 2-alkylamino-8-benzenesulfonylthiazolo[4,5-*g*]indazoles (**13a**–**c**) and the related deprotected thiazoloindazoles (**14a**–**c**) in excellent yields in each step (Scheme 2). In this series too, the individual NMR assignments of at least one member, viz. **13c** and **14b**, were determined from their HMQC and HMBC spectra, and the same for the rest were ascertained by comparison. Pertinently, initially we tried to cyclise **12a** by NBS–DBU, but unlike its 5-thioureido isomer (**4a**), it did not react at all, even at 50 °C.

Two more extensions of the present methodology were then aimed at. One was to try to synthesise 2-alkylthiothiazoloindazoles, and the other was to check if the observations made for the 2-alkylamino derivatives of both [5,4-*e*]- and [4,5-*g*]-isomers also hold good for their indazolic 1-alkyl derivatives. The first target was achieved by the cyclisation (by bromine in acetic acid) of methyl and ethyl 1*H*-indazol-5/6-yl dithiocarbamates (**17a**,**b**/**19a**,**b**). The latter, were prepared by condensing 5/6-aminoindazoles (**7**/**15**)

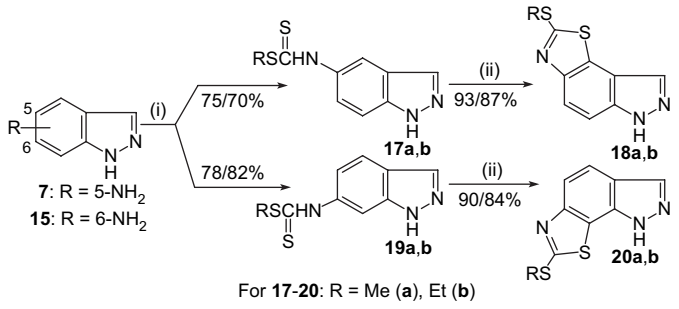


Scheme 1. Reagents and conditions: (i) NaOH (2.5 equiv), *n*-$Bu_4N^+HSO_4^-$ (1.5 mol %), THF, 1 h; $PhSO_2Cl$ (1.2 equiv), 2–3 h; (ii) 10% Pd–C (10% w/w), $NH_2NH_2{\cdot}H_2O$, MeOH, reflux, 3 h; (iii) RNCS (1.5 equiv), dry THF, reflux, 2–3 h; (iv) NBS (1.1 equiv), DBU (2 equiv), −10 °C; CC, *n*·Al_2O_3; (v) Br_2–AcOH (1:10), THF, rt, 30–45 min; (vi) K_2CO_3 (4 equiv), MeOH–H_2O (3:1), reflux, 1–1.5 h.



Scheme 2. Reagents and conditions: as in Scheme 1.

with carbon disulfide in the presence of pyridine and triethylamine, followed by treatment with methyl/ethyl iodides. Pertinently, this protocol had earlier been used for the preparation of indolyl dithiocarbamates[21a] for their subsequent cyclisation by NBS–DBU[21b] or NBS–Et_3N[21c] to indolic phytoalexins. Our experiments led to the formation of both 2-alkylthiothiazolo[5,4-*e*]indazoles (**18a**,**b** from **7**) and 2-alkylthiothiazolo[4,5-*g*]indazoles (**20a**,**b** from **15**) in quite good yields (Scheme 3). The occurrence of angular cyclisation in both the isomeric classes was, as before, evident from the appearance of two *ortho*-coupled protons in their ^{1}H NMR spectra (see Section 4).

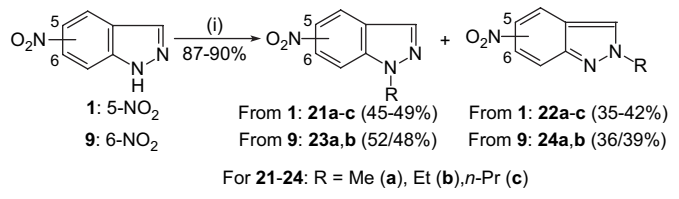


Scheme 3. Reagents and conditions: (i) CS_2 (2–3 equiv), Py–Et_3N (3:1), RI (1.5 equiv); (ii) Br_2–AcOH (1:10), THF, rt, 30–45 min.

The NMR spectroscopic data of both **18** and **20** further revealed that these two isomeric classes can be distinguished from each other by the appearance of the ^{13}C chemical shift of CH-5, which was ca. δ 110 for **18a**,**b** and ca. δ 116 for **20a**,**b**.

In order to materialise the second target, each of 5-nitroindazole (**1**) and 6-nitroindazole (**9**) was separately *N*-alkylated to furnish both *N*(1)-alkyl (**21a–c** from **1**; and **23a**,**b** from **9**) and *N*(2)-alkyl (**22a–c** from **1**; **24a**,**b** from **9**) derivatives in around 90% overall yields in both the isomeric classes (Scheme 4).

The 1-alkyl and 2-alkyl isomers could be differentiated from each other by some of their ^{1}H and/or ^{13}C chemical shifts. For the 5-nitro series, only the ^{13}C chemical shifts were critical. Thus, the chemical shifts for CH-3 (ca. δ 136) and for CH-7 (ca. δ 110) were



Scheme 4. Reagents and conditions: (i) (a) NaOH (2.5 equiv), n-$Bu_4N^+HSO_4^-$ (1.5 mol %), THF, rt, 1 h; RI (1.2 equiv), 3 h; (b) CC, silica gel.

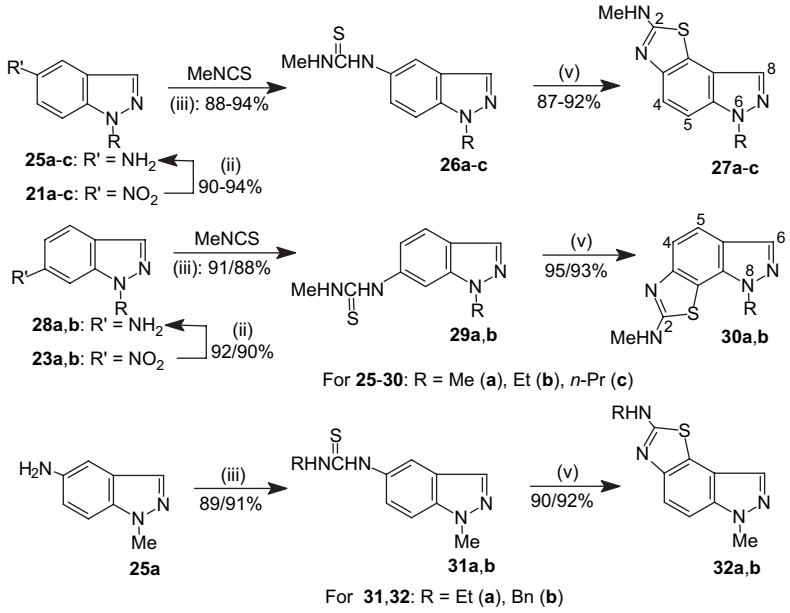
indicative of the 1-alkyl derivatives, whereas the CH-3 signal at ca. δ 127 and, more importantly, the C-7a signal at ca. δ 150 were suggestive of the 2-alkyl isomers (**22a–c**). In the case of the 6-nitro series, the chemical shifts of H-3 and CH-3 could differentiate between the two alkyl isomeric classes. Thus, the related signals appeared at ca. δ 8.1 (s) and ca. δ 133, respectively, for the 1-alkyl isomers (**23a**,**b**), whereas the respective values were ca. δ 8.7 (d, 1 Hz) and ca. δ 124 for the 2-alkyl derivatives (**24a**,**b**).

Once properly identified, each of the 1-alkyl-5-nitroindazoles (**21a–c**) and 1-alkyl-6-nitroindazoles (**23a**,**b**) was separately and successively reduced to the corresponding amines (**25a–c**; **28a**,**b**), condensed with methyl isothiocynate, and the resulting 1-alkyl-5/6-(*N*′-methylthioureido)indazoles (**26a–c**; **29a**,**b**) were cyclised by bromine in acetic acid to furnish the respective 2-methylamino derivatives of 6-alkylthiazolo[5,4-*e*]indazoles (**27a–c** from **26a–c**) and 8-alkylthiazolo[4,5-*g*]indazoles (**30a**,**b** from **29a**,**b**) in around 90% yield in each step (Scheme 5).

For diversification, 5-amino-1-methylindazole (**25a**) was additionally converted, following the same protocol, to 2-ethylamino- and 2-benzylamino-6-methylthiazolo[5,4-*e*]indazoles (**32a**,**b**) via the intermediacy of the respective thioureidoindazoles (**31a**,**b**) (Scheme 5). On scrutiny, it transpired that the ^{1}H and ^{13}C NMR spectroscopic data of the 6/8-alkylthiazoloindazoles of both [5,4-*e*]-type (**27a**,**b**) and [4,5-*g*]-type (**30a**,**b**) were quite similar to those of the parent 6/8-desmethylthiazoloindazoles (**6a**,**b** and **14a**,**b**, respectively).

Thus, the cyclisations of both thioureidoindazoles and indazolyl dithiocarbamates, with or without alkyl substitution at the indazolic *N*(1), were regioselective, leading to the formation of only the angular thiazoloindazoles. Also, the use of bromine in acetic acid did not cause nuclear bromination, contrary to our concern, at any of the cyclisation steps. Most of the steps do not require any chromatographic separation, and the yields were excellent throughout. The method is thus well poised for scale-up.

In order to make a comparative evaluation of the present method with three extant syntheses of the thiazoloindazole skeleton (as such or modified) that we could trace in the literature, a comparison was necessitated. In the earliest reports,[22a–c] the synthesis of 2-methylthiazolo[5,4-*e*]- and -[4,5-*g*]indazoles was achieved starting from 5-amino- and 6-aminoindazoles, respectively, via the successive intermediacies of *ortho*-thiocyanato-aminoindazoles, followed by cyclisation of the derived thiophenoxides by acetic anhydride. The overall yields were merely ca. 19% and 26% in the three-step route. In contrast, ours was a two-step route, furnishing, for example, the 2-alkylaminothiazolo[5,4-*e*]- (**6a–c**) and -[4,5-*g*]indazoles (**16a–c**) in ca. 77–86% and 83–89% overall yields starting from the same aminoindazoles. Besides, in the previous route, the ready isomerisation of thiocyanates to isothiocyanates was cited as a major problem,[22a–c] and thiocyanation was reported not to be always *ortho*-oriented.[23] Later, the linear 2-aminothiazolo[5,4-*f*]indazole itself was prepared



Scheme 5. Reagents and conditions: as in Scheme 1.

directly from 6-aminoindazole by treatment with thiocyanogen, generated in situ from copper(II) thiocyanate and acetic acid.[24a,b] A comparison of our method with this route is inconsequential since it dealt with only one product, which was a linear thiazoloindazole. In the third and most recent report,[14b,c] a library of 2-alkylamino-8-arylthiazolo[4,5-*g*]-4,5-dihydroindazoles were prepared by the condensation–cyclisation of 2-alkylamino-thiazolocyclohexenone carboxylates with aryl hydrazines by heating in acetic acid. Since patented, the yields of the products, i.e., 4,5-dihydroindazoles could not be gathered. Moreover, the thiazolocyclohexenone carboxylates had to be preformed in a multi-step way. Our method is thus a better method on all counts.

Seven thiazoloindazoles, viz. **5a**, **14a–c**, **18a** and **30a**,**b** were tested at 25, 50 and 100 μmol solutions in DMSO for anticancer activity against human lung carcinoma A549 cell line at using the *m*ethyl *t*hiazolyl *t*etrazolium bromide assay (MTT).[25] The experiments were done in triplicate. The results (Table 1) revealed that at 25 μmol concentrations, the screened products showed weak to moderate (ca. 29–72%) inhibition with respect to control, i.e., DMSO. Of these, **14c** appeared to be more effective, warranting its further follow-up. Further investigation with few other cell lines is also underway, and the results will be published elsewhere in due course.

3. Conclusion

We have developed a short, expedient and highly efficient synthesis of 2-alkylamino- and 2-alkylthiothiazolo[5,4-*e*]- and -[4,5-*g*]indazoles as well as their (indazolic) *N*-benzenesulfonyl and *N*-alkyl derivatives. Since the cyclisations were regioselective in all the cases, furnishing only the angular products, our route is quite suitable for scale-up. Additionally, since some of the synthesised thiazoloindazoles, particularly **14c**, have shown worthwhile anticancer potential, the present work of ours becomes even more important.

Table 1
Growth inhibitory effects[a] of thiazoloindazoles on human lung carcinoma A549 cell line

Concentrations[b] (μmol)	Thiazoloindazoles						
	5a	**14a**	**14b**	**14c**	**18a**	**30a**	**30b**
25	52.7	29.5	47.1	72.1	67.6	62.2	55.7
50	56.2	56.3	75.9	N.D.[c]	73.2	68.1	70.2
100	70.4	71.4	72.0	76.8	58.7	63.5	77.2

[a] The growth inhibitions (%) of the treated carcinoma cells were calculated relative to growth of untreated (control) cells.
[b] Exponentially growing cells were treated with different micromolar concentrations of investigated thiazoloindazoles during a period of 72 h, and cytotoxicity was measured using MTT survival assay. All experiments were performed in triplicates.
[c] N. D.: not determined.

4. Experimental section

4.1. General

Solvents were purified and dried using standard techniques. Pet. ether refers to petroleum ether, bp 60–80 °C. Silica gel G (Merck, India) was used for analytical TLC, and silica gel (60–120 mesh; Qualigens, India) and neutral alumina (Brockmann standard; BDH, India) were used for column chromatography (CC). Melting points (in celsius) were recorded on a Toshniwal apparatus and are uncorrected. IR spectra were recorded in Nujol mull (unless stated otherwise) and also in neat or as KBr pellets on a Nicolet Impact 410, Nicolet Magnus 750 series II, Shimadzu FTIR-8300 or Perkin–Elmer 782 spectrophotometers. The ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectra of **4c**, **8b**, **12b**,**c**, **22c**, **24a** and **31a** were recorded on a Bruker AC-200 spectrometer. For all other compounds, the ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR (PND and DEPT 135) spectra, and 2D NMR (viz. HMQC and HMBC) spectra of **5a**, **6a**, **13c**, **14b** and **27a** were recorded in a Bruker DRX-500 spectrometer. LR EIMS as well as HR EIMS, FABMS (*m*-nitrobenzyl alcohol as liquid matrix) and ESI-MS (+ve; TOF) were recorded on JEOL JMS-AX505HA, JEOL JMS Mstaion 700 or Micromass Q-Tofmicro mass spectrometers. Elemental analyses were performed on a Dr. Hans Hoesli analyser. 5-Nitroindazole and 6-nitroindazole were procured commercially from Lancaster.

*4.1.1. 1-Benzenesulfonyl-5-nitro-1H-indazole (**2**)*

To a solution of 5-nitro-1*H*-indazole (**1**, 1.63 g, 10 mmol) in THF at room temperature were added powdered NaOH (1.0 g, 25 mmol) and *n*-Bu_4NHSO_4 (51 mg, 0.15 mmol, 1.5 mol %). The resulting mixture was stirred for 1 h and then cooled in an ice-bath. $PhSO_2Cl$ (1.4 mL, 11 mmol) was added dropwise to it and stirred at room temperature for another 2 h, when the reaction was complete

(TLC). The reaction mixture was then poured into water (50 mL), extracted with CH_2Cl_2 (3×50 mL). The organic layer was dried (Na_2SO_4) and solvent evaporated to furnish the crude product, which was crystallised from CH_2Cl_2 to furnish pure **2** (2.9 g; 96%) as white needles, mp 208–210 °C.

IR: 3119, 3070, 1523, 1375, 1348, 1296, 1173, 1089, 1069, 904, 783, 730 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.43 (2H, t, J=7.5 Hz), 7.56 (1H, t, J=7.5 Hz), 7.80 (2H, d, J=8 Hz), 8.14 (1H, d, J=9 Hz), 8.28 (1H, dd, J_1=9 Hz, J_2=2 Hz), 8.56 (1H, s) and 8.61 (1H, d, J=1.5 Hz); ^{13}C NMR: δ 114.3, 120.3, 125.4, 128.2 (×2), 130.9 (×2), 136.4, 144.3 (all Ar–CH), 126.3, 136.8, 142.6, 145.2 (all Ar–C); LR EIMS: m/z (%) 303 (M^+; 53), 239 (26), 141 (56), 77 (100); HR EIMS: Calcd for $C_{13}H_9N_3O_4S$ 303.0314, found 303.0312.

*4.1.2. 5-Amino-1-benzenesulfonyl-1H-indazole (**3**)*

To a solution of **2** (0.91 g, 3 mmol) in MeOH (30 mL) was added 10% Pd–C (ca. 90 mg, 10% w/w), followed by $NH_2NH_2\cdot H_2O$ (0.2 mL, 3.5 mmol). The resulting solution was refluxed until (3 h) the reaction was complete (TLC), filtered through a Celite bed, the solvent distilled off from the filtrate and the resulting residue crystallised from pet. ether.–CH_2Cl_2 to furnish pure **3** as white crystals, mp 208–210 °C (0.755 g, 92%).

IR: 3428, 3342, 1613, 1512, 1259, 1185, 1062, 824, 726 cm^{-1}; ^1H NMR (DMSO-d_6): δ 5.09 (2H, s), 6.59 (1H, d, J=1.5 Hz), 6.78 (1H, dd, J_1=9 Hz, J_2=2 Hz), 7.34 (2H, t, J=7.5 Hz), 7.46 (1H, t, J=7.5 Hz), 7.61 (1H, d, J=9 Hz), 7.62 (2H, d, J=9 Hz) and 8.07 (1H, s); ^{13}C NMR: δ 102.8, 114.0, 120.2, 127.7 (×2), 130.4 (×2), 135.3, 143.4 (all Ar–CH), 128.4, 133.7, 137.2, 147.3 (all Ar–C); LR EIMS: m/z (%) 273 (M^+; 73), 132 (100), 105 (17), 77 (15), 51 (10); HR EIMS: Calcd for $C_{13}H_{11}N_3O_2S$ 273.0572, found 273.0561.

4.2. Synthesis of thioureidoindazoles. General procedure

In a typical experiment, to a solution of the amine (**3**, 0.273 g, 1 mmol) in dry THF (20 mL) was added methyl, ethyl or benzyl isothiocyanate (1.5 mmol). The resulting solution was refluxed until the amine was fully consumed (TLC). The solvent was distilled off and the residue crystallised from MeOH–CH_2Cl_2 to furnish pure thioureidoindazoles (**4a**–**c**).

*4.2.1. 1-Benzenesulfonyl-5-(N-methylthioureido)-1H-indazole (**4a**)*

White needles; yield: 0.32 g (92%); mp 206–208 °C; IR: 3383, 3151, 1533, 1500, 1248, 1195, 1169, 1142, 1069, 824, 724 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.90 (3H, d, J=3.5 Hz), 7.56 (1H, br), 7.59 (2H, t, J=7.5 Hz), 7.70 (1H, d, J=8.5 Hz), 7.71 (1H, t, J=7.5 Hz), 7.88 (1H, br s), 8.05 (1H, dd, J_1=8.5 Hz, J_2=1.5 Hz), 8.51 (1H, s) and 9.68 (1H, s); ^{13}C NMR: δ 25.9 (NH*C*H$_3$), 113.4, 115.4, 126.9, 127.9 (×2), 130.7 (×2), 135.8, 143.5 (all Ar–CH), 116.2, 136.8, 137.2, 137.7 (all Ar–C), 182.6 (NH*C*SNH); LR EIMS: m/z (%) 346 (M^+; 39), 315 (82), 312 (83), 290 (19), 174 (17), 171 (100), 141 (20), 132 (66), 105 (12), 77 (65), 74 (16), 51 (16); HR EIMS: Calcd for $C_{15}H_{14}N_4O_2S_2$ 346.0558, found 346.0556.

*4.2.2. 1-Benzenesulfonyl-5-(N-ethylthioureido)-1H-indazole (**4b**)*

White needles; yield: 0.324 g (90%); mp 150–152 °C; IR: 3317, 3142, 3077, 1535, 1508, 1280, 1245, 1186, 1091, 837, 726 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.18 (3H, t, J=7 Hz), 3.65 (1H, br s), 6.07 (1H, br s), 7.43 (1H, dd, J_1=9 Hz, J_2=2 Hz), 7.48 (2H, t, J=7.5 Hz), 7.59 (1H, s), 7.59 (1H, tt, J_1=7.5 Hz, J_2=1 Hz), 7.97 (2H, dd, J_1=8.5 Hz, J_2 1 Hz), 8.15 (1H, s), 8.19 (1H, d, J=9 Hz) and 8.31 (1H, br); ^{13}C NMR: δ 14.6 (*C*H$_3$), 40.7 (N*C*H$_2$), 115.0, 118.6, 120.2, 127.9 (×2), 129.8 (×2), 134.9, 141.3 (all Ar–CH), 126.9, 133.2, 137.6, 139.0 (all Ar–C) and 181.2 (NH*C*SNH); LR EIMS: m/z (%) 360 (M^+; 2), 273 (87), 315 (11), 132 (100), 105 (23), 77 (23), 51 (13). Anal. Calcd for $C_{16}H_{16}N_4O_2S_2$: C, 53.33; H, 4.44; N, 15.55. Found: C, 53.37; H, 4.46; N, 15.57%.

*4.2.3. 1-Benzenesulfonyl-5-(N-benzylthioureido)-1H-indazole (**4c**)*

White needles; yield: 0.396 g (94%); mp 180–182 °C; IR: 3342, 3287, 1515, 1448, 1242, 1182, 1089, 1058, 726 cm^{-1}; ^1H NMR (200 MHz; DMSO-d_6): δ 4.72 (2H, d, J=6 Hz), 7.15–7.41 (5H, m), 7.58 (2H, t, J=7 Hz), 7.60 (1H, d, J=8 Hz), 7.71 (1H, t, J=7 Hz), 7.92 (2H, d, J=7 Hz), 7.95 (1H, s), 8.07 (1H, d, J=8 Hz), 8.26 (1H, t, J=6 Hz), 8.53 (1H, s) and 9.77 (1H, s); ^{13}C NMR (50 MHz): δ 47.2 (NH*C*H$_2$), 112.6, 116.2, 126.8, 127.0 (×2), 127.3 (×2), 128.2 (×2), 129.8 (×2), 134.9, 142.6 (all Ar–CH), 126.0, 136.0, 136.3, 136.9, 138.9 (all Ar–C), 181.2 (NH*C*SNH); LR EIMS: m/z (%) 422 (M^+; 11), 388 (20), 316 (25), 315 (100), 273 (54), 251 (38), 174 (40), 141 (35), 132 (68), 107 (65), 106 (47), 104 (21), 91 (84), 77 (85). Anal. Calcd for $C_{21}H_{18}N_4O_2S_2$: C, 59.71; H, 4.26; N, 13.27. Found: C, 59.68; H, 4.24; N, 13.29%.

4.3. Cyclisation of 4a using NBS–DBU

To a solution of **4a** (0.344 g, 1 mmol) in dry THF (20 mL) at −5 to −10 °C was gradually added NBS (0.198 g, 1.1 mmol). After 5 min DBU (0.1 mL, 2 mmol) was added to it and the resulting solution stirred for 45 min. The solution was poured into 10% aq $Na_2S_2O_3$ (30 mL), extracted with CH_2Cl_2 (4×25 mL), the pooled extracts washed with water and dried (Na_2SO_4). The solvent was removed in vacuo to furnish a residue, which was purified by CC over neutral Al_2O_3 and elution with pet. ether–EtOAc (1:1), followed by crystallisation from MeOH–CH_2Cl_2 to furnish pure **5a** as white needles (0.086 g, 25%; mp 226–228 °C).

4.4. Cyclisation using Br_2–AcOH. General procedure

A solution of bromine (0.1 mL, 2 mmol) in acetic acid (1 mL) was added dropwise with stirring to a solution of the thioureidoindazoles (**4a**/**b**/**c**) in THF (15–20 mL) at room temperature, stirred for 30–45 min, when the reaction became complete (TLC). The solution was poured into 10% aq $Na_2S_2O_3$ solution (50 mL) and neutralised with aq K_2CO_3 when a white precipitate appeared. It was filtered, washed with water and dried. The crude products was crystallised from MeOH–CH_2Cl_2 to furnish pure thiazoloindazoles (**5a**–**c**).

*4.4.1. 6-Benzenesulfonyl-2-methylaminothiazolo[5,4-e]-1H-indazole (**5a**)*

Yield: 0.316 g (92%); mp 226–228 °C; IR: 3204, 1599, 1566, 1275, 1170, 1124, 923, 726 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.93 (3H, d, J=4.5 Hz, NH*CH*$_3$), 7.56 (2H, t, J=7.5 Hz, H-3′), 7.67 (1H, t, J=7.5 Hz, H-4′), 7.70 (1H, d, J=9 Hz, H-4), 7.89 (2H, d, J=7.5 Hz, H-2′), 7.98 (1H, d, J=9 Hz, H-5), 8.06 (1H, q, J=4.5 Hz, N*H*CH$_3$) and 8.63 (1H, s, H-8); ^{13}C NMR: δ 31.5 (NH*C*H$_3$), 110.8 (CH-5), 121.5 (CH-4), 127.8 (×2, CH-2′), 130.6 (×2, CH-3′), 135.7 (CH-4′), 141.7 (CH-3), 120.7 (C-8a), 121.3 (C-8b), 137.0 (C-5a), 137.1 (C-1′), 151.0 (C-3a), 167.9 (C-2); LR EIMS: m/z (%) 344 (M^+; 82%), 313 (5), 203 (100), 176 (96), 126 (34), 98 (18), 77 (11); HR EIMS: Calcd for $C_{15}H_{12}N_4O_2S_2$ 344.0401, found 344.0397.

*4.4.2. 6-Benzenesulfonyl-2-ethylaminothiazolo[5,4-e]-1H-indazole (**5b**)*

White crystals; yield: 0.333 g (93%); mp 227–229 °C; IR (KBr): 3206, 3117, 1589, 1557, 1374, 1276, 1172, 1095, 914, 825, 814, 726 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.19 (3H, t, J=7 Hz), 3.38 (2H, dq, J_1=7 Hz, J_2=5 Hz), 7.56 (2H, t, J=7.5 Hz), 7.68 (1H, t, J=7.5 Hz), 7.70 (1H, d, J=9 Hz), 7.89 (2H, d, J=7.5 Hz), 7.98 (1H, d, J=9 Hz), 8.12 (1H, t J=5 Hz) and 8.64 (1H, s); ^{13}C NMR: δ 15.2 (CH$_3$), 39.8 (NH*C*H$_2$), 110.8, 121.5, 127.8 (×2), 130.6 (×2), 135.7, 141.7 (all Ar–CH), 120.7, 121.2, 137.0, 137.1, 151.1, 167.0 (all Ar–C); LR EIMS: m/z (%) 358 (M^+; 88%), 217 (100), 189 (21). HR EIMS: Calcd for $C_{16}H_{14}N_4O_2S_2$ 358.0558, found 358.0563.

*4.4.3. 6-Benzenesulfonyl-2-benzylaminothiazolo[5,4-e]-1H-indazole (**5c**)*

White crystals; yield: 0.403 g (96%); mp 210–212 °C; IR: 3217, 1619, 1560, 1278, 1169, 1095, 912, 726 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.06 (2H, d, J=5.5 Hz), 7.25 (1H, t, J=7.5 Hz), 7.33 (2H, t, J=7.5 Hz), 7.37 (2H, d, J=7.5 Hz), 7.56 (2H, t, J=7.5 Hz), 7.68 (1H, tt, J_1=7.5 Hz, J_2=1 Hz), 7.71 (1H, d, J=9 Hz), 7.79 (2H, dd, J_1=7.5 Hz, J_2=1 Hz), 7.98 (1H, d, J=9 Hz), 8.64 (1H, t, J=5.5 Hz) and 8.66 (1H, s); ^{13}C NMR: δ 48.3 ($NHCH_2$), 110.9, 121.6, 127.8 (×2), 127.9, 128.3 (×2), 129.2 (×2), 130.6 (×2), 135.7, 141.7 (all Ar–CH), 120.7, 121.5, 137.1, 139.5, 140.9, 150.8, 167.3 (all Ar–C); LR EIMS: m/z (%) 420 (M^+; 65), 316 (15), 315 (20), 279 (52), 106 (20), 91 (100); HR EIMS: Calcd for $C_{21}H_{16}N_4O_2S_2$ 420.0716, found 420.0714.

4.5. Deprotection of benzenesulfonyl group. General procedure

To a solution of **5a–c** (1 mmol) in MeOH (30 mL) was added an aq solution (10 mL) of K_2CO_3 (0.55 g, 4 mmol), and the solution was refluxed for 6–8 h until the reaction became complete (TLC). Water (40 mL) was added to this solution and MeOH distilled off. On cooling, crystals appeared, which were filtered, washed with water, dried and recrysatllised from CH_2Cl_2 to furnish pure **6a–c**.

*4.5.1. 2-Methylaminothiazolo[5,4-e]-1H-indazole (**6a**)*

White flakes; yield: 0.184 g (90%) from **5a**; 0.179 g (88%) from **8a**; mp 284–286 °C; IR: 3204, 1599, 1147, 1082, 935, 827 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.93 (3H, d, J=4.5 Hz, $NHCH_3$), 7.40 (1H, d, J=9 Hz, H-5), 7.48 (1H, d, J=9 Hz, H-4), 7.41 (1H, q, J=4.5 Hz, NH–CH_3), 8.04 (1H, s, H-8) and 13.13 (1H, s, H-6); ^{13}C NMR: δ 31.5 ($NHCH_3$), 108.7 (CH-5), 119.3 (CH-4), 131.8 (CH-8), 117.5 (C-8a), 119.1 (C-8b), 137.8 (C-5a), 147.6 (C-3a), 166.4 (C-2); LR FABMS: m/z 204 (M^+); HR FABMS: Calcd for $C_9H_8N_4S$ 204.0470, found: 204.0486.

*4.5.2. 2-Ethylaminothiazolo[5,4-e]-1H-indazole (**6b**)*

White needles; yield: 0.2 g (92%) from both **5b** and **8b**; mp 238–240 °C; IR: 3208, 1605, 1569, 1149, 1082, 930, 833 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.22 (3H, t, J=7.5 Hz), 3.39 (2H, dq, J_1=7.5 Hz, J_2=5 Hz), 7.41 (1H, d, J=9 Hz), 7.48 (1H, d, J=9 Hz), 7.78 (1H, t, J=5 Hz), 8.05 (1H, s) and 13.12 (1H, s); ^{13}C NMR: δ 15.3 (CH_3), 39.7 ($NHCH_2$), 108.6, 119.3, 131.8 (all Ar–CH), 117.5, 119.0, 137.8, 147.6, 165.4 (all Ar–C); LR EIMS: m/z (%) 218 (M^+; 100), 203 (63), 190 (43). HR EIMS: Calcd for $C_{10}H_{10}N_4S$ 218.0627, found 218.0618.

*4.5.3. 2-Benzylaminothiazolo[5,4-e]-1H-indazole (**6c**)*

White needles; yield: 0.266 g (95%) from **5c**; 0.257 g (92%) from **8c**; mp 226–228 °C; IR: 3178, 3124, 1597, 1570, 1473, 1449, 1354, 1183, 926 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.59 (2H, d, J=5.5 Hz), 7.25 (1H, t, J=7.5 Hz), 7.34 (2H, t, J=7.5 Hz), 7.34 (2H, d, J=7.5 Hz), 7.41 (1H, d, J=8.5 Hz), 7.47 (1H, d, J=8.5 Hz), 8.05 (1H, s), 8.33 (1H, t, J 5.5 Hz) and 13.14 (1H, s); ^{13}C NMR: δ 48.3 ($NHCH_2$), 108.7, 119.4, 127.8, 128.3 (×2), 129.2 (×2), 131.8 (all Ar–CH), 117.5, 119.3, 137.9, 139.9, 147.3, 165.6 (all Ar–C); LR EIMS: m/z (%) 280 (M^+; 100), 279 (18), 189 (35), 176 (14), 106 (12), 91 (71); HR EIMS: Calcd for $C_{15}H_{12}N_4S$ 280.0782, found 280.0774.

4.6. Preparation of 5-amino-1*H*-indazole (7)

Following the procedure described for the reduction of **2** to **3**, 5-nitro-1*H*-indazole (**1**, 0.49 g, 3 mmol) was reduced to 5-Amino-1*H*-indazole as colourless cubes; yield: 0.36 g (90%); lit. mp 175–178 °C; CAS No. 19335-11-6; Sigma-Aldrich Catalogue item no. A59557.

4.7. Preparation of thioureidoindazoles 8a–c

Following the general procedure described for the conversion of **3** to **4a–c**, except that refluxing was carried out in dry methanol, the thioureidoindazoles **8a–c** were synthesised by the condensation of the amine **7** (1 mmol) with the respective alkyl isothiocyanates. The crude products were crystallised from CH_2Cl_2 to furnish pure **8a–c**.

*4.7.1. 5-(N-Methyl)thioureido-1H-indazole (**8a**)*

Off-white crystals; yield: 0.18 g (87%); mp 233–235 °C; IR: 3222, 1629, 1548, 1301, 1161, 1070 and 839 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.83 (3H, d, J=4.5 Hz), 7.15 (1H, d, J=8.5 Hz), 7.39 (1H, br), 7.43 (1H, d, J=8.5 Hz), 7.58 (1H, d, J=1 Hz), 7.98 (1H, s), 9.39 (1H, br s) and 12.98 (1H, s); ^{13}C NMR: δ 32.2 ($NHCH_3$), 111.2, 116.9, 125.8, 134.4 (all Ar–CH), 123.7, 132.2, 138.8 (all Ar–C), 182.5 (NH*C*SNH); LR EIMS: m/z (%) 206 (M^+; 90), 175 (34), 172 (100), 157 (31), 145 (27), 133 (80), 105 (17), 74 (16); HR EIMS: Calcd for $C_9H_{10}N_4S$ 206.0626, found 206.0626.

*4.7.2. 5-(N-Ethyl)thioureido-1H-indazole (**8b**)*

White crystals; yield: 0.2 g (91%); mp 204–206 °C; IR: 3235, 1549, 1333, 1299, 704 cm^{-1}; ^1H NMR (200 MHz; DMSO-d_6): δ 1.09 (3H, t, J=6 Hz), 3.48 (2H, q, J=6 Hz), 7.22 (1H, dd, J_1=9 Hz, J_2=1.5 Hz), 7.49 (1H, d, J=9 Hz), 7.54 (1H, t, J=6 Hz), 7.65, 8.03 and 9.36 (1H, s each) and 13.04 (1H, br s); ^{13}C NMR (50 MHz): δ 14.3 (CH_3), 38.2 ($NHCH_2$), 110.2, 115.8, 125.0 and 133.4 (all Ar–CH), 122.8, 131.5 and 137.9 (all Ar–CH) and 180.6 (NH*C*SNH); LR EIMS: m/z (%) 220 (M^+; 73), 187 (22), 186 (50), 175 (45), 158 (40), 133 (100), 105 (15). Anal. Calcd for $C_{10}H_{12}N_4S$ C, 54.54; H, 5.45; N, 25.45. Found: C, 54.59; H, 5.43; N, 25.48%.

*4.7.3. 5-(N-Benzyl)thioureido-1H-indazole (**8c**)*

White needles; yield: 0.26 g (93%); mp 224–226 °C; IR: 3367, 1544, 1337, 1315, 1160, 961, 740 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.68 (2H, d, J=5.5 Hz), 7.16–7.19 (1H, m), 7.20 (1H, d, J=8.5 Hz), 7.23–7.30 (4H, m), 7.49 (1H, d, J=8.5 Hz), 7.65 (1H, s), 7.94 (1H, br s), 7.99, 9.50 and 12.99 (1H, s each); ^{13}C NMR: δ 48.1 ($NHCH_2$), 111.1, 117.0, 125.9, 127.6, 128.1 (×2), 129.0 (×2) and 134.4 (all Ar–CH), 123.7, 132.3, 138.8 and 140.1 (all Ar–C), 182.3 (NH*C*SNH); LR EIMS: m/z (%) 282 (M^+; 22), 248 (23), 175 (64), 133 (33), 107 (16), 91 (100); HR EIMS: Calcd for $C_{15}H_{14}N_4S$ 282.0939, found 282.0932.

4.8. Preparation of 1-benzenesulfonyl-6-nitro-1*H*-indazole (10)

Following the procedure described for the preparation of **2** from **1**, 1.63 g (10 mmol) of 6-nitro-1*H*-indazole (**9**) was treated with benzenesulfonyl chloride to furnish the crude product, which was crystallised from CH_2Cl_2 to furnish pure **10**.

*4.8.1. 1-Benzenesulfonyl-6-nitro-1H-indazole (**10**)*

Pale yellow needles; yield: 2.88 g (95%); mp 176–178 °C; IR: 3106, 1532, 1379, 1351, 1314, 1263, 1172, 1092, 1062, 898, 844, 742 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.55 (2H, t, J=7.5 Hz), 7.71 (1H, t, J=7.5 Hz), 7.97 (2H, d, J=7.5 Hz), 8.09 (1H, d, J=8.5 Hz), 8.18 (1H, dd, J_1=8.5 Hz, J_2=2 Hz), 8.77 (1H, s) and 8.84 (1H, s); ^{13}C NMR: δ 109.3, 120.2, 124.6, 128.2 (×2), 130.9 (×2), 136.3, 143.3 (all Ar–CH), 129.9, 136.8, 139.5, 148.9 (all Ar–C); LR EIMS: m/z (%) 303 (M^+; 46), 239 (24), 141 (59), 77 (100), 51 (15); HR EIMS: Calcd for $C_{13}H_9N_3O_4S$ 303.0313, found 303.0305.

4.9. Reduction of 10 to 6-amino-1-benzenesulfonyl-1*H*-indazole (11)

Following the same procedure described for reduction of **2** to **3**, 1-benzenesulfonyl-6-nitro-1*H*-indazole (**10**, 0.91 g, 3 mmol)

was reduced by $NH_2NH_2 \cdot H_2O$/Pd–C to 6-amino-1-benzenesulfonyl-1*H*-indazole (**11**), which was crystallised from pet. ether–CH_2Cl_2.

*4.9.1. 6-Amino-1-benzenesulfonyl-1H-indazole (**11**)*

Colourless cubes; yield: 0.76 g (93%); mp 132–134 °C; IR: 3437, 3348, 1617, 1486, 1331, 1225, 1192, 1139, 1089, 824, 764, 725 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.16 (2H, s), 6.66 (1H, dd, J_1=8.5 Hz, J_2=2 Hz), 7.39 (1H, d, J=8.5 Hz), 7.39 (1H, s), 7.43 (2H, t, J=7.5 Hz), 7.54 (1H, t, J=7.5 Hz), 7.95 (1H, d, J=2 Hz) and 7.94–7.98 (2H, m); ^{13}C NMR: δ 96.8, 114.9, 122.5, 127.8 (×2), 134.3, 142.1 (all Ar–CH), 119.0, 138.1, 142.9, 148.9 (all Ar–C); LR EIMS: *m*/*z* (%) 273 (M^+; 80), 132 (100), 104 (37), 77 (24), 51 (12); HR EIMS: Calcd for $C_{13}H_{11}N_3O_2S$ 273.0572, found 273.0571.

4.10. Preparation of thioureidoindazoles 12a–c

Each of the thioureidoindazoles **12a–c** was prepared by condensation of the amine **11** (273 mg, 1 mmol) with the respective alkyl isothiocyanates, following the general procedure described for the syntheses of **4a–c**. The crude products were crystallised from MeOH–CH_2Cl_2 to furnish pure **12a–c**.

*4.10.1. 1-Benzenesulfonyl-6-(N-methylthioureido)-1H-indazole (**12a**)*

White needles; yield 0.32 g (92%); mp 210–212 °C; IR: 3311, 3143, 1619, 1553, 1520, 1343, 1293, 1248, 1171, 725 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.97 (3H, d, J=4.5 Hz), 7.39 (1H, d, J=8.5 Hz), 7.58 (2H, t, J=7.5 Hz), 7.69 (1H, tt, J_1=8 Hz, J_2=1 Hz), 7.73 (1H, d, J=8.5 Hz), 7.93 (2H, dd, J_1=8.5 Hz, J_2=1 Hz), 7.98 (1H, br), 8.43 (1H, s), 8.49 (1H, br s) and 9.98 (1H, br s); ^{13}C NMR: δ 32.0 (NH*C*H_3), 122.6, 127.9 (×2), 130.6 (×2), 135.7, 143.4 (all Ar–CH), 137.2, 141.1 (all Ar–C), 180.2 (NH*C*SNH); LR EIMS: *m*/*z* (%) 346 (M^+; 38), 315 (95), 312 (90), 273 (36), 205 (10), 174 (33), 171 (100), 146 (22), 143 (44), 141 (24), 132 (60), 104 (19), 77 (87), 74 (13); HR EIMS: Calcd for $C_{15}H_{14}N_4O_2S_2$ 346.0559, found 346.0554.

*4.10.2. 1-Benzenesulfonyl-6-(N-ethylthioureido)-1H-indazole (**12b**)*

White crystals; yield: 0.33 g (92%); mp 208–210 °C; IR: 3349, 1619, 1541, 1348, 1304, 1187, 1089, 1069, 725 cm^{-1}; ^1H NMR (200 MHz; DMSO-d_6): δ 1.16 (3H, t, J=7 Hz), 3.49 (2H, quintet, J=7 Hz), 7.37 (1H, d, J=8.5 Hz), 7.57 (2H, t, J=7 Hz), 7.70 (1H, t, J=7.5 Hz), 7.72 (1H, d, J=8.5 Hz), 7.93 (2H, d, J=7.5 Hz), 8.07 (1H, br s), 8.43 (1H, s) and 9.87 (1H, s); ^{13}C NMR (50 MHz): δ 14.0 (CH_3), 40.7 (NH*C*H_2), 104.7, 120.3, 121.9, 127.1 (×2), 129.8 (×2), 134.9 and 142.5 (all Ar–CH), 121.7, 136.4, 140.3, 141.3 (all Ar–C), 180.2 (NH*C*SNH); LR EIMS: *m*/*z* (%) 360 (M^+; 52), 327 (32), 326 (92), 315 (45), 273 (41), 251 (11), 219 (16), 186 (14), 185 (100), 174 (18), 157 (32), 141 (15), 132 (80), 104 (18), 88 (15), 77 (66), 51 (18); HR EIMS: Calcd for $C_{16}H_{15}N_4O_2S_2$ 360.0714, found 360.0704.

*4.10.3. 1-Benzenesulfonyl-6-(N-benzylthioureido)-1H-indazole (**12c**)*

White needles; yield: 0.395 g (94%); mp 202–204 °C; IR: 3363, 3151, 1619, 1540, 1301, 1222, 1169, 1096, 724 cm^{-1}; ^1H NMR (200 MHz; DMSO-d_6): δ 4.78 (2H, d, J=4 Hz), 7.12–7.55 (6H, m), 7.57 (2H, t, J=8 Hz), 7.70 (1H, m), 7.72 (1H, t, J=8 Hz), 7.93 (2H, d, J=8 Hz), 8.44 (1H, s), 8.48 (1H, t, J=4 Hz), 8.59 (1H, s) and 10.06 (1H, s); ^{13}C NMR (50 MHz): δ 47.2 (CH_2), 105.1, 120.1, 121.8, 127.09 (×3), 127.5 (×2), 128.3 (×2), 129.7 (×2), 134.8, 142.5 (all Ar–CH), 127.03, 136.3, 138.6, 140.2, 141.1 (all Ar–C), 180.8 (NH*C*SNH); LR EIMS: *m*/*z* (%) 422 (M^+; 9), 388 (17), 316 (27), 315 (100), 273 (52), 251 (38), 174 (45), 146 (24), 141 (31), 132 (65), 107 (65), 106 (49), 104 (20), 91 (86), 79 (17), 77 (88); HR EIMS: Calcd for $C_{21}H_{18}N_4O_2S_2$ 422.0871, found 422.0871.

4.11. Cyclisation of 12a–c to 2-alkylamino-8-benzenesulfonylthiazolo[4,5-g]indazoles (13a–c)

Following the general procedure described for the cyclisation of **4a–c** to **5a–c**, each of the thioureidoindazoles **12a–c** (1 mmol) was cyclised by Br_2–AcOH to furnish the thiazolo[4,5-*g*]indazoles (**13a–c**). All the crude products were purified by crystallisation from MeOH–CH_2Cl_2.

*4.11.1. 8-Benzenesulfonyl-2-methylaminothiazolo[4,5-g]-1H-indazole (**13a**)*

White crystals; yield: 0.33 g (95%); mp 262–264 °C; IR (KBr): 3209, 1592, 1410, 1378, 1307, 1221, 1175, 1051, 726 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.99 (3H, d, J=4.5 Hz), 7.48 (1H, d, J=8.5 Hz), 7.57 (2H, t, J=7.5 Hz), 7.65 (1H, d, J=8.5 Hz), 7.67 (1H, t, J=7.5 Hz), 7.81 (2H, d, J=7.5 Hz), 8.26 (1H, d, J=4.5 Hz) and 8.50 (1H, s); ^{13}C NMR: δ 31.3 (NHCH_3), 118.1, 120.0, 128.0 (×2), 130.7 (×2), 135.6, 144.9 (all Ar–CH), 113.3, 122.5, 136.1, 137.0, 156.0, 170.3 (all Ar–C); LR EIMS: *m*/*z* (%) 344 (M^+; 90), 203 (100), 175 (25), 134 (18), 77 (11); HR EIMS: Calcd for $C_{15}H_{12}N_4O_2S_2$ 344.0402, found 344.0403.

*4.11.2. 8-Benzenesulfonyl-2-ethylaminothiazolo[4,5-g]-1H-indazole (**13b**)*

White flakes; yield: 0.336 g (94%); mp 214–216 °C; IR: 3212, 1614, 1599, 1375, 1172, 1020, 725 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.24 (3H, t, J=7 Hz), 3.45 (2H, dq, J_1=7 Hz, J_2=5.5 Hz), 7.48 (1H, d, J=8.5 Hz), 7.59 (2H, t, J=8 Hz), 7.66 (1H, d, J=8.5 Hz), 7.68 (1H, t, J=8 Hz), 7.87 (2H, dd, J_1=8 Hz, J_2=1 Hz), 8.32 (1H, t, J=5.5 Hz) and 8.51 (1H, s); ^{13}C NMR: δ 15.2 (*C*H_3), 39.6 (NH*C*H_2), 118.1, 120.0, 128.0 (×2), 130.7 (×2), 135.6, 144.9 (all Ar–CH), 113.1, 122.5, 136.1, 137.0, 156.1, 169.7 (all Ar–C); LR EIMS: *m*/*z* (%) 358 (M^+; 78), 217 (100), 189 (30). HR EIMS: Calcd for $C_{16}H_{14}N_4O_2S_2$ 358.0558, found 358.0554.

*4.11.3. 8-Benzenesulfonyl-2-benzylaminothiazolo[4,5-g]-1H-indazole (**13c**)*

White needles; yield: 0.405 g (96%); mp 211–213 °C; IR (KBr): 3222, 1614, 1586, 1564, 1373, 1173, 804, 727 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.66 (2H, d, J=5.5 Hz, NH*C*H_2), 7.27 (1H, t, J=7.5 Hz, H-4′), 7.36 (2H, t, J=7.5 Hz, H-3′), 7.41 (2H, d, J=7.5 Hz, H-2′), 7.48 (1H, d, J=8.5 Hz, H-4), 7.57 (2H, t, J=7.5 Hz, H-3″), 7.65 (1H, d, J=8.5 Hz, H-5), 7.67 (1H, t, J=7.5 Hz, H-4″), 7.81 (2H, d, J=8 Hz, H-2″), 8.51 (1H, s, H-6) and 8.82 (1H, t, J=5.5 Hz, N*H*CH_2); ^{13}C NMR: δ 48.0 (NH*C*H_2), 118.2 (CH-4), 120.0 (CH-5), 128.02 (CH-4′), 128.07 (×2, CH-2″), 128.3 (×2, CH-2′), 129.3 (×2, CH-3′), 130.7 (×2, CH-3″), 135.6 (CH-4″), 144.9 (CH-6), 113.4 (C-5a), 122.6 (C-8b), 136.1 (C-8a), 137.0 (C-1″), 139.4 (C-1′), 155.8 (C-3a), 169.7 (C-2); LR EIMS: *m*/*z* (%) 420 (M^+; 67), 419 (7), 315 (19), 280 (35), 273 (17), 132 (23), 106 (20), 91 (100); HR EIMS: Calcd for $C_{21}H_{16}N_4O_2S_2$ 420.0714, found 420.0718.

4.12. Deprotection of benzenesulfonyl group of 13a–c to 14a–c

Following the same procedure described for the deprotection of **5a–c** to **6a–c**, each of the 8-benzenesulfonylthiazoloindazoles (**13a–c**, 1 mmol) was deprotected using aq methanolic potassium carbonate under reflux to furnish 2-alkyl/benzylaminothiazolo[4,5-*g*]indazoles (**14a–c**). The products were crystallised from CH_2Cl_2.

*4.12.1. 2-Methylaminothiazolo[4,5-g]-1H-indazole (**14a**)*

White needles; yield 0.19 g (92%); mp 310–312 °C; IR (KBr): 3216, 3023, 1586, 1556, 1371, 1239, 1045, 848, 748 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.95 (3H, d, J=5 Hz), 7.25 (1H, d, J=9 Hz), 7.56 (1H, d, J=9 Hz), 7.94 (1H, q, J=4 Hz) and 8.02 (1H, s); ^{13}C NMR: δ 31.5 (NHCH_3), 114.5, 118.5, 135.4 (all Ar–CH), 108.1, 119.5, 135.6, 152.6, 168.0 (all Ar–C); LR EIMS: *m*/*z* (%) 204 (M^+; 100), 175 (38). HR EIMS: Calcd for $C_9H_8N_4S$ 204.0470, found 204.0473.

*4.12.2. 2-Ethylaminothiazolo[4,5-g]-1H-indazole (**14b**)*

White flakes; yield 0.203 g (93%); mp 276–278 °C; IR (KBr): 3222, 3009, 1625, 1577, 1556, 1349, 1209, 915, 852, 787 cm^{-1}; ^1H NMR: δ 1.22 (3H, t, J=7 Hz, CH_3), 3.41 (2H, q, J=7 Hz, $NHCH_2$), 7.25 (1H, d, J=8.5 Hz, H-5), 7.57 (1H, d, J=8.5 Hz, H-4), 7.99 (1H, t, J=5.5 Hz, $NHCH_2$), 8.08 (1H, s, H-6) and 13.05 (1H, s, H-8); ^{13}C NMR: δ 15.3 (CH_3), 39.8 ($NHCH_2$), 114.5 (CH-5), 118.5 (CH-4), 135.4 (CH-6), 109.0 (C-5a), 119.5 (C-8b), 135.6 (C-8a), 152.6 (C-3a), 167.0 (C-2); LR EIMS: m/z (%) 218 (M^+; 100), 203 (58), 190 (43). HR EIMS: Calcd for $C_{10}H_{10}N_4S$ 218.0627, found 218.0619.

*4.12.3. 2-Benzylaminothiazolo[4,5-g]-1H-indazole (**14c**)*

White needles; yield 0.27 g (97%); mp 246–248 °C; IR: 3209, 1629, 1599, 1070, 979, 918, 839, 797 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.63 (2H, d, J=5.5 Hz), 7.26 (1H, d, J=8.5 Hz), 7.28 (1H, t, J=7.5 Hz), 7.36 (2H, t, J=7.5 Hz), 7.42 (2H, d, J=7.5 Hz), 7.59 (1H, d, J=8.5 Hz), 8.05 (1H, s), 8.52 (1H, t, J=5.5 Hz) and 13.07 (1H, s); ^{13}C NMR: δ 48.4 ($NHCH_2$), 114.6, 118.6, 128.3 (×2), 129.2 (×2), 135.4 (all Ar–CH), 109.3, 119.6, 135.6, 139.7, 152.3, 167.3 (all Ar–C); LR EIMS: m/z (%) 280 (M^+; 100), 279 (19), 189 (42), 176 (14), 106 (12), 91 (79). Anal. Calcd for $C_{15}H_{12}N_4S$: C, 64.28; H, 4.28; N, 20.00. Found: C, 64.20; H, 4.29; N, 19.98%.

4.13. Preparation of 6-amino-1*H*-indazole (15)

Following the procedure described for reduction of **2** to **3**, 6-nitro-1*H*-indazole (**9**, 0.49 g, 3 mmol) was reduced to 6-amino-1*H*-indazole (**15**); colourless needles; yield: 0.36 g (95%); mp 204–206 °C (dec); lit. mp 204–206 °C (dec); CAS No. 6967-12-0; Sigma–Aldrich Catalogue no. A59565.

4.14. Preparation of thioureidoindazoles 16a–c

The thioureidoindazoles **16a**–**c** were synthesised by the condensation of the amine **15** (1 mmol) with the respective alkyl isothiocyanates, following the general procedure described earlier for the preparation of **8a**–**c**. The crude products were purified by crystallisation from CH_2Cl_2.

*4.14.1. 6-(N-Methyl)thioureido-1H-indazole (**16a**)*

Off-white prisms; yield 0.19 g (92%); mp 204–206 °C; IR: 3234, 1629, 1569, 1240, 1052, 948, 860, 777 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.93 (3H, d, J=4.5 Hz), 6.97 (1H, d, J=7.5 Hz), 7.67 (1H, d, J=8.5 Hz), 7.73 (1H, s), 7.99, 9.67 and 12.94 (1H, s each); ^{13}C NMR: δ 32.1 ($NHCH_3$), 104.1, 118.5, 121.5 and 134.2 (all Ar–CH), 120.8, 138.0 and 141.8 (all Ar–C), 181.9 (NHCSNH); LR EIMS: m/z (%) 206 (M^+; 100), 175 (34), 172 (78), 133 (95), 105 (15); HR EIMS: Calcd for $C_9H_{10}N_4S$ 206.0626, found 206.0627.

*4.14.2. 6-(N-Ethyl)thioureido-1H-indazole (**16b**)*

White flakes; yield 0.204 g (93%); mp 182–184 °C; IR: 3171, 1626, 1546, 1507, 1341, 1241, 1049, 943, 777 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.13 (3H, t, J=7 Hz), 3.51 (2H, quintet, J=7 Hz), 6.98 (1H, d, J=8.5 Hz), 7.67 (1H, d, J=8.5 Hz), 7.80 (2H, s), 7.99, 9.56 and 12.97 (1H, s each); ^{13}C NMR: δ 15.0 (CH_3), 39.5 ($NHCH_2$), 103.9, 118.4, 121.3, 134.1 (all Ar–CH), 120.7, 138.1, 141.0 (all Ar–C), 180.9 (NHCSNH); LR EIMS: m/z (%) 220 (M^+; 76), 187 (19), 186 (50), 175 (42), 159 (12), 158 (42), 150 (13), 133 (100), 117 (13), 105 (16), 90 (17); HR EIMS: Calcd for $C_{10}H_{12}N_4S$ 220.0783, found 220.0781.

*4.14.3. 6-(N-Benzyl)thioureido-1H-indazole (**16c**)*

Off-white plates; yield 0.27 g (95%); mp 193–195 °C; IR: 3170, 1525, 1458, 1376, 1202, 1069, 943, 744 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.74 (2H, d, J=5.5 Hz), 6.98 (1H, dd, J_1=8.5 Hz, J_2=1.5 Hz), 7.22–7.26 (1H, m), 7.31–7.34 (4H, m), 7.67 (1H, d, J=8.5 Hz), 7.85 (1H, s), 7.98 (1H, s), 8.22 (1H, t, J=5.5 Hz), 9.78 (1H, s) and 12.94 (1H, s); ^{13}C NMR: δ 48.0 ($NHCH_2$), 104.3, 118.5, 121.4, 127.7, 128.3 (×2), 129.1 (×2), 134.2 (all Ar–CH), 120.8, 138.0, 139.8, 140.9 (all Ar–C), 181.6 (NHCSNH); LR EIMS: m/z (%) 282 (M^+; 22), 248 (18), 175 (38), 133 (28), 106 (22), 91 (100); HR EIMS: Calcd for $C_{15}H_{14}N_4S$ 282.0939, found 282.0935.

4.15. Preparation of indazolyl dithiocarbamates. General procedure

To a mixture of the amine **7** (0.133 g, 1 mmol), dry triethylamine (0.5 mL) and dry pyridine (1.5 mL) was added carbon disulfide (0.1 mL, 1.2 mmol) at 0 °C and the solution kept at room temperature for 1 h. The reaction mixture was then treated with methyl or ethyl iodide (1.2 mmol) at 0 °C, stirred for another 2–3 h and then the mixture was poured into 2 N H_2SO_4 (30 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined extracts were washed successively with water (50 mL), saturated aq Na_2CO_3 and water, dried (Na_2SO_4) and the solvent evaporated to furnish the crude products (**17a**,**b**), which were purified by crystallisation from pet. ether–CH_2Cl_2.

*4.15.1. Methyl 1H-indazol-5-yl dithiocarbamate (**17a**)*

White flakes; yield: 0.174 g (78%); mp 186–188 °C (dec); IR: 3223, 1597, 1522, 1147, 1028, 935, 806 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.51 (3H, s), 7.32 (1H, br d, J=8.5 Hz), 7.41 (1H, br), 7.49 (1H, d, J=8.5 Hz), 8.03, 11.58 and 13.08 (1H, s each); ^{13}C NMR: δ 18.7 (SCH_3), 110.9, 116.1, 124.8 and 134.7 (all Ar–CH), 119.0, 123.3, 138.9 (all Ar–C), 198.1 (NHCSSEt); LR EIMS: m/z (%) 223 (M^+; 12%), 176 (18), 175 (100), 143 (11), 117 (9), 90 (10); HR EIMS: Calcd for $C_9H_9N_3S_2$ 223.0328, found 223.0326.

*4.15.2. Ethyl 1H-indazol-5-yl dithiocarbamate (**17b**)*

Pale yellow crystals; yield: 0.17 g (72%); mp 250–252 °C (dec); IR: 3230, 1593, 1507, 1149, 1036, 930, 804 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.24 (3H, t, J=7 Hz), 3.25 (2H, q, J=7 Hz), 7.46 (1H, br), 7.53 (1H, d, J=8.5 Hz), 7.60 (1H, d, J=8.5 Hz), 8.08 (1H, s) and 13.12 (1H, s); ^{13}C NMR: δ 15.2 (CH_3), 29.8 (SCH_2), 108.3, 117.3, 123.1, 134.5 (all Ar–CH), 120.0, 122.5, 138.6 (all Ar–C), 197.9 (NHCSSEt). Anal. Calcd for $C_{10}H_{11}N_3S_2$: C, 50.63; H, 4.64; N, 17.72. Found: C, 50.57; H, 4.62; N, 17.69%.

4.16. Cyclisation of 17a,b to 2-alkylthiothiazolo[5,4-*e*]-indazoles (18a,b)

Following the general procedure described earlier for the cyclisation of **4a**–**c** to **5a**–**c**, the indazolyl dithiocarbamates (**17a**,**b**) were cyclised by Br_2–AcOH to furnish regioselectively the 2-alkylthiothiazolo[5,4-*e*]indazoles (**18a**,**b**), which were purified by crystallisation from CH_2Cl_2.

*4.16.1. 2-Methylthiothiazolo[5,4-e]-1H-indazole (**18a**)*

White flakes; yield: 0.19 g (90%); mp 211–213 °C (dec); IR: 3204, 1601, 1580, 1442, 1376, 1045, 965, 919, 858 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.79 (3H, s), 7.62 (1H, d, J=9 Hz), 7.82 (1H, d, J=9 Hz), 8.28 (1H, s) and 13.46 (1H, s); ^{13}C NMR: δ 16.7 (S–CH_3), 110.4, 120.9, 133.1 (all Ar–CH), 116.8, 125.8, 138.6, 149.0, 164.2 (all Ar–C); LR EIMS: m/z (%) 221 (M^+; 100), 206 (11), 189 (11), 188 (92), 162 (17), 148 (10); HR EIMS: Calcd for $C_9H_7N_3S_2$ 221.0081, found 221.0072.

*4.16.2. 2-Ethylthiothiazolo[5,4-e]-1H-indazole (**18b**)*

Pale yellow crystals; yield: 0.2 g (84%); mp 188–190 °C (dec); IR (KBr): 3179, 3125, 1608, 1479, 1440, 1422, 1073, 1046, 1007, 921 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.41 (3H, t, J=7.5 Hz), 3.34 (2H, q, J=7.5 Hz), 7.62 (1H, d, J=9 Hz), 7.84 (1H, d, J=9 Hz), 8.29 (1H, s) and 13.46 (1H, s); ^{13}C NMR: δ 15.5 (CH_3), 28.7 (SCH_2), 110.4, 121.0, 133.2 (all Ar–CH), 116.7, 125.9, 138.6, 148.9, 162.7 (all Ar–C); HR ESI-MS: Calcd for $C_{10}H_9N_3S_2$ ($M+H^+$) 236.0311, found 236.0318.

4.17. Alkyl 1*H*-indazol-6-yl dithiocarbamates (19a,b)

Following the general method described before for the preparation of **17a**,**b** from **7**, the alkyl (1*H*-indazol-6-yl)dithiocarbamates **19a**,**b** were prepared from **15** and purified by crystallisation from pet. ether–CH_2Cl_2.

*4.17.1. Methyl 1H-indazol-6-yl dithiocarbamate (**19a**)*

White flakes; yield: 0.167 g (75%); mp 134–136 °C; IR: 3151, 1633, 1533, 1334, 1029, 950, 864, 731 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.57 (3H, s), 7.21 (1H, ill-split d), 7.72 (1H, d, J=8.5 Hz), 8.03 (1H, s), 8.11 (1H, br) and 13.06 (1H, s); ^{13}C NMR: δ 18.8 (S*C*H_3), 105.0, 118.5, 121.5, 134.3 (all Ar–CH), 121.5, 138.6, 140.4 (all Ar–C), 197.9 (NHCSSCH$_3$); LR EIMS: m/z (%) 223 (M^+; 15), 176 (25), 175 (100), 143 (9), 117 (15), 90 (12). Anal. Calcd for $C_9H_9N_3S_2$: C, 48.43; H, 4.04; N, 18.83. Found: C, 48.47; H, 4.05; N, 18.86%.

*4.17.2. Ethyl 1H-indazol-6-yl dithiocarbamate (**19b**)*

Pale yellow crystals; yield: 0.165 g (70%); mp 98–100 °C; IR: 3124, 1633, 1527, 1334, 1023, 950, 837, 771, 724 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.26 (3H, t, J=7.5 Hz), 3.22 (2H, q, J=7.5 Hz), 7.21 (1H, ill-split d), 7.73 (1H, d, J=8.5 Hz), 8.04 (1H, s), 8.12 (1H, br), 11.72 (1H, s) and 13.07 (1H, s); ^{13}C NMR: δ 14.9 (CH_3), 29.7 (S*C*H_2), 105.7, 118.6, 121.4, 134.3 (all Ar–CH), 121.7, 138.3, 140.4 (all Ar–C), 197.8 (NHCSSEt). Anal. Calcd for $C_{10}H_{11}N_3S_2$: C, 50.63; H, 4.64; N, 17.72. Found: C, 50.60; H, 4.66; N, 17.75%.

4.18. Cyclisation of 19a,b to 2-alkylthiothiazolo[4,5-*g*]-indazoles (20a,b)

The indazolyl dithiocarbamates (**19a**,**b**) were cyclised by Br_2–AcOH to furnish regioselectively the 2-alkylthiothiazolo[4,5-*g*]indazoles (**20a**,**b**), following the general procedure described earlier for the cyclisation of **17a**,**b** to **18a**,**b**. The products were crystallised from CH_2Cl_2.

*4.18.1. 2-Methylthiothiazolo[4,5-g]-1H-indazole (**20a**)*

White flakes; yield: 0.205 g (93%); mp 227–229 °C; IR (KBr): 3153, 3078, 1628, 1484, 1377, 1238, 1052, 1004, 930, 838, 797, 752 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.82 (3H, s), 7.60 (1H, d, J=9 Hz), 7.79 (1H, d, J=9 Hz), 8.19 (1H, s) and 13.56 (1H, s); ^{13}C NMR: δ 16.7 (S*C*H_3), 115.9, 119.9, 135.7 (all Ar–CH), 120.6, 134.8, 153.4, 167.3 (all Ar–C); LR EIMS: m/z (%) 221 (M^+; 100), 220 (7), 206 (13), 189 (10), 188 (76), 179 (7), 175 (7), 142 (9). Anal. Calcd for $C_9H_7N_3S_2$: C, 48.87; H, 3.17; N, 19.0. Found: C, 48.84; H, 3.16; N, 18.98%.

*4.18.2. 2-Ethylthiothiazolo[4,5-g]-1H-indazole (**20b**)*

Pale yellow crystals; yield: 0.204 g (87%); mp 207–209 °C; IR: 3150, 1628, 1445, 1242, 1048, 930, 804, 746 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.45 (3H, t, J=7.5 Hz), 3.40 (2H, q, J=7.5 Hz), 7.63 (1H, d, J=9 Hz), 7.82 (1H, d, J=9 Hz), 8.23 (1H, s) and 13.56 (1H, s); ^{13}C NMR: δ 15.4 (CH_3), 28.6 (S*C*H_2), 116.0, 119.9, 135.7 (all Ar–CH), 120.6, 134.9, 153.2, 167.6 (all Ar–C); HR ESI-MS: Calcd for $C_{10}H_{10}N_3S_2$ ($M+H^+$) 236.0311, found 236.0317.

4.19. Alkylations of 5/6-nitro-1*H*-indazole (1/9). General procedure

To a solution of 5-nitro-1*H*-indazole (**1**) or 6-nitroindazole (**9**) (1.63 g, 10 mmol) in THF (50 mL) were added the PTC (n-$Bu_4NH^+SO_4^-$, 51 mg, 0.15 mmol) and powdered NaOH (1.0 g, 25 mmol). The solution was stirred for 1 h and then cooled in an ice-bath, and the alkyl iodide (1.2 mmol) was added dropwise to this solution, which was stirred at room temperature for another 3 h until the reaction was complete (TLC). The reaction mixture was then poured into water (50 mL) and extracted with CH_2Cl_2 (3×30 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated to furnish a mixture of *N*(1)-alkyl and *N*(2)-alkylnitroindazoles, which were separated by CC over silica gel and purified by crystallisation from pet. ether–CH_2Cl_2.

*4.19.1. 1-Methyl-5-nitro-1H-indazole (**21a**)*

Eluted with pet. ether–EtOAc (4:1); yellow needles; yield: 0.98 g (55%); mp 162–164 °C (lit.[26a] mp 158–162 °C); IR: 1613, 1513, 1493, 1332, 1202, 1066, 791, 747 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.15 (3H, s), 7.46 (1H, d, J=9 Hz), 8.19 (1H, s), 8.28 (1H, dd, J_1=9 Hz, J_2=2 Hz) and 8.73 (1H, d, J=2 Hz); ^{13}C NMR: δ 36.4 (N*C*H_3), 109.6, 119.3, 121.7, 135.9 (all Ar–CH), 123.4, 141.9, 142.7 (all Ar–C). Anal. Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.95; N, 23.73. Found: C, 54.29; H, 3.97; N, 23.70%.

*4.19.2. 1-Ethyl-5-nitro-1H-indazole (**21b**)*

Eluted with pet. ether–EtOAc (7:1); yellow needles; yield: 0.94 g (49%); mp 155–157 °C; IR: 1613, 1586, 1513, 1334, 1195, 1069, 738 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.56 (3H, t, J=7 Hz), 4.49 (2H, q, J=7 Hz), 7.48 (1H, d, J=9 Hz), 8.20 (1H, d, J=0.5 Hz), 8.26 (1H, dd, J_1=9 Hz, J_2=2 Hz) and 8.72 (1H, d, J=2 Hz); ^{13}C NMR: δ 15.2 (CH_3), 44.7 (N*C*H_2), 109.5, 119.4, 121.6, 136.0 (all Ar–CH), 123.5, 141.0, 142.6 (all Ar–C); LR EIMS: m/z (%) 191 (M^+; 100), 176 (67), 161 (11), 145 (10), 130 (42), 105 (15), 90 (24), 76 (19), 63 (21). Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.71; N, 21.99. Found: C, 56.58; H, 4.69; N, 21.96%.

*4.19.3. 5-Nitro-1-n-propyl-1H-indazole (**21c**)*

Eluted with pet. ether–EtOAc (9:1); yellow needles; yield: 0.92 g (45%); mp 61–63 °C; IR: 1610, 1586, 1511, 1186, 1151, 1067, 913, 787, 758 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.99 (3H, t, J=7 Hz), 1.99 (2H, sextet, J=7 Hz), 4.41 (2H, t, J=7 Hz), 7.47 (1H, d, J=9 Hz), 8.21 (1H, d, J=0.5 Hz), 8.26 (1H, dd, J_1=9 Hz, J_2=2 Hz) and 8.72 (1H, d, J=2 Hz); ^{13}C NMR: δ 11.7 (CH_3), 23.5 (CH_2), 51.4 (N*C*H_2), 109.6, 119.4, 121.6, 136.0 (all Ar–CH), 123.4, 141.6, 142.6 (all Ar–C). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.54; H, 5.36; N, 20.49. Found: C, 58.58; H, 5.38; N, 20.46%.

*4.19.4. 2-Methyl-5-nitro-2H-indazole (**22a**)*

Eluted with pet. ether–EtOAc (7:3); ochre yellow flakes; yield: 0.62 g (35%); mp 128–130 °C (lit.[26b] mp 129–131 °C); IR: 1613, 1513, 1493, 1456, 1332, 1202, 1066, 791, 744 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.29 (3H, s), 7.74 (1H, d, J=9.5 Hz), 8.09 (1H, dd, J_1=9.5 Hz, J_2=2 Hz), 8.20 (1H, s) and 8.72 (1H, d, J=2 Hz); ^{13}C NMR: δ 41.3 (N*C*H_3), 118.5, 119.6, 120.6, 128.1 (all Ar–CH), 120.7, 143.4, 150.4 (all Ar–C). Anal. Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.95; N, 23.73. Found: C, 54.29; H, 3.94; N, 23.76%.

*4.19.5. 2-Ethyl-5-nitro-2H-indazole (**22b**)*

Eluted with pet. ether–EtOAc (4:1); ochre yellow flakes; yield: 0.725 g (38%); mp 73–75 °C; IR: 1619, 1566, 1334, 1149, 1062, 1003, 910, 758 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.72 (3H, t, J=7.5 Hz), 4.58 (2H, q, J=7.5 Hz), 7.76 (1H, d, J=9.5 Hz), 8.10 (1H, dd, J_1=9.5 Hz, J_2=2 Hz), 8.28 (1H, s) and 8.74 (1H, d, J=2 Hz); ^{13}C NMR: δ 15.9 (CH_3), 49.6 (N*C*H_2), 118.6, 119.7, 120.4, 126.6 (all Ar–CH), 120.5, 143.3, 150.1 (all Ar–C). Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.71; N, 21.99. Found: C, 56.57; H, 4.70; N, 22.02%.

*4.19.6. 5-Nitro-2-n-propyl-2H-indazole (**22c**)*

Eluted with pet. ether–EtOAc (6:1); ochre yellow flakes; yield: 0.86 g (42%); mp 116–118 °C; IR: 1610, 1586, 1511, 1186, 1151, 1067, 913, 787, 758 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$): δ 0.97 (3H, t, J=7 Hz), 2.08 (2H, sextet, J=7 Hz), 4.43 (2H, t, J=7 Hz), 7.74 (1H, d, J=9.5 Hz), 8.09 (1H, dd, J_1=9.5 Hz, J_2=2 Hz), 8.20 (1H, s) and 8.73 (1H, s); ^{13}C NMR (50 MHz): δ 11.0 (CH_3), 23.7 (CH_2), 55.9 (N*C*H_2), 118.2, 119.2, 120, 126.8 (all Ar–CH), 119.9, 142.9, 149.7 (all Ar–C). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.54; H, 5.36; N, 20.49. Found: C, 58.50; H, 5.34; N, 20.53%.

*4.19.7. 1-Methyl-6-nitro-1H-indazole (**23a**)*

Eluted with pet. ether–EtOAc (6:1); yellow needles; yield: 0.92 g (52%); mp 125–126 °C (lit.[26c] mp 125 °C); IR: 1580, 1527, 1348, 1222, 943, 844, 731, 731 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.13 (3H, s), 7.82 (1H, d, J=8.5 Hz), 7.99 (1H, dd, J_1=8.5 Hz, J_2=2 Hz), 8.09 (1H, s) and 8.36 (1H, s); ^{13}C NMR: δ 36.5 (NCH_3), 106.1, 115.7, 122.2, and 133.5 (all Ar–CH), 127.4, 139.0, 146.8 (all Ar–C). Anal. Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.95; N, 23.73. Found: C, 54.20; H, 3.96; N, 23.70%.

*4.19.8. 1-Ethyl-6-nitro-1H-indazole (**23b**)*

Eluted with pet. ether–EtOAc (9:1); yellow needles; yield 0.92 g (48%); mp 99–100 °C (lit.[26d] mp 98–99 °C); IR: 1507, 1348, 1314, 1202, 1062, 970, 837, 738 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.58 (3H, t, J=7 Hz), 4.54 (2H, q, J=7 Hz), 7.84 (1H, d, J=9 Hz), 8.01 (1H, dd, J_1=9 Hz, J_2=2 Hz), 8.12 (1H, d, J=1 Hz) and 8.40 (1H, d, J=1 Hz); ^{13}C NMR: δ 15.4 (CH_3), 44.7 (NCH_2), 106.1, 115.6, 122.2, 133.1 (all Ar–CH), 127.5, 138.1, 146.7 (all Ar–C); LR EIMS: m/z (%) 191 (M^+; 81), 176 (100), 130 (45). HR EIMS: Calcd for $C_9H_9N_3O_2$ 191.0695, found 191.0695.

*4.19.9. 2-Methyl-6-nitro-2H-indazole (**24a**)*

Eluted with pet. ether–EtOAc (3:1); ochre yellow plates; yield 0.64 g (36%); mp 160–162 °C (lit.[26c,e] mp 159–160 °C); IR: 1619, 1560, 1527, 1341, 1301, 1162, 1062, 824, 731 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$): δ 4.31 (3H, d, J=3.5 Hz), 7.75 (1H, dd, J_1=9 Hz, J_2=3.5 Hz), 7.91 (1H, d, J=9 Hz), 8.03 (1H, d, J=3.5 Hz) and 8.68 (1H, s); ^{13}C NMR: δ 41.0 (NCH_3), 115.2, 115.6, 121.2, 124.5 (all Ar–CH), 124.5, 146.4, 146.8 (all Ar–C). Anal. Calcd for $C_9H_9N_3O_2$: C, 54.24; H, 3.95; N, 23.73. Found: C, 54.29; H, 3.97; N, 23.70%.

*4.19.10. 2-Ethyl-6-nitro-2H-indazole (**24b**)*

Eluted with pet. ether–EtOAc (4:1); ochre yellow plates; yield 0.745 g (39%); mp 88–90 °C (lit.[26d] mp 89–90 °C); IR: 1619, 1560, 1527, 1334, 1308, 1142, 1016, 744 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.68 (3H, t, J=7 Hz), 4.56 (2H, q, J=7 Hz), 7.75 (1H, d, J=9 Hz), 7.88 (1H, dd, J_1=9 Hz, J_2=2 Hz), 8.07 (1H, s) and 8.68 (1H, d, J=1 Hz); ^{13}C NMR: δ 16.0 (CH_3), 49.8 (NCH_2), 115.8, 116.0, 121.7, 123.3 (all Ar–CH), 124.7, 146.8, 147.1 (all Ar–C). Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.71; N, 21.99. Found: C, 56.51; H, 4.69; N, 22.01%.

4.20. Reduction of 21a–c to 1-alkyl-5-aminoindazoles (25a–c)

Following the procedure described for the preparation of **3** from **2**, 1-alkyl-5-nitro-1*H*-indazoles (**21a–c**, 3 mmol each) were reduced by $NH_2NH_2 \cdot H_2O$/Pd–C to the corresponding amines (**25a–c**), which were purified by crystallisation from pet. ether–CH_2Cl_2.

*4.20.1. 5-Amino-1-methyl-1H-indazole (**25a**)*

Colourless needles; yield: 0.415 g (94%); mp 156–158 °C; IR: 3373, 3204, 3098, 1646, 1301, 1222, 1149, 870, 804, 744 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.60 (2H, s), 3.99 (3H, s), 6.86 (1H, dd, J_1=8.5 Hz, J_2=2 Hz), 6.91 (1H, d, J=1 Hz), 7.19 (1H, d, J=8.5 Hz) and 7.76 (1H, s); ^{13}C NMR: δ 35.9 (NCH_3), 103.8, 110.0, 118.8, 131.4 (all Ar–CH), 125.3, 136.0, 140.5 (all Ar–C); LR EIMS: m/z (%) 147 (M^+; 100), 146 (40), 119 (25). Anal. Calcd for $C_8H_9N_3$: C, 65.31; H, 6.12; N, 28.57. Found: C, 65.28; H, 6.10; N, 28.60%.

*4.20.2. 5-Amino-1-ethyl-1H-indazole (**25b**)*

Colurless needles; yield: 0.44 g (91%); mp 100–102 °C; IR: 3378, 3319, 3214, 1647, 1624, 1508, 1321, 1232, 1202, 1023, 847, 811 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.47 (3H, t, J=7 Hz), 3.60 (2H, br s), 4.35 (2H, q, J=7 Hz), 6.84 (1H, dd, J_1=9 Hz, J_2=2 Hz), 6.90 (1H, s), 7.21 (1H, d, J=8.5 Hz) and 7.77 (1H, s); ^{13}C NMR: δ 15.3 (CH_3), 44.1 (NCH_2), 103.9, 110.0, 118.7, 131.4 (all Ar–CH), 125.4, 135.1, 140.5 (all Ar–C); LR EIMS: m/z (%) 161 (M^+; 100), 146 (76), 133 (16), 119 (15), 105 (7). Anal. Calcd for $C_9H_{11}N_3$: C, 67.08; H, 6.83; N, 26.09. Found: C, 67.05; H, 6.82; N, 26.12%.

*4.20.3. 5-Amino-1-n-propyl-1H-indazole (**25c**)*

Colourless needles; yield: 0.47 g (90%); mp 167–169 °C; IR: 3315, 3204, 1684, 1571, 1508, 1322, 1234, 1187, 857, 804 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (3H, t, J=7 Hz), 1.92 (2H, sextet, J=7 Hz), 3.30 (2H, br s), 4.26 (2H, t, J=7 Hz), 6.84 (1H, dd, J_1=9 Hz, J_2=2 Hz), 6.91 (1H, d, J=1.5 Hz), 7.20 (1H, d, J=9 Hz) and 7.77 (1H, d, J=1 Hz); ^{13}C NMR: δ 11.8 (CH_3), 23.6 (CH_2), 50.9 (NCH_2), 103.9, 110.1, 118.7, 131.4 (all Ar–CH), 125.2, 135.6, 140.4 (all Ar–C); LR EIMS: m/z (%) 175 (M^+; 80), 147 (12), 146 (100), 133 (16), 119 (20), 105 (8), 92 (10); HR EIMS: Calcd for $C_{10}H_{13}N_3$ 175.1110, found 175.1108.

4.21. Preparation of 1(*N*)-alkyl-5-(*N*-methylthioureido)-indazoles (26a–c) from 25a–c

Following the general procedure described earlier for the preparation of **8a–c**, the thioureidoindazoles **26a–c** were synthesised by the condensation of the amines **25a–c** (1 mmol) with methyl isothiocyanate and purified by crystallisation from CH_2Cl_2.

*4.21.1. 1-Methyl-5-(N-methylthioureido)-1H-indazole (**26a**)*

Colourless prisms; yield: 0.207 g (94%); mp 198–200 °C; IR: 3217, 3164, 1546, 1500, 1255, 1056, 990, 771, 711 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.88 (3H, d, J=4.5 Hz), 4.0 (3H, s), 7.25 (1H, d, J=8.5 Hz), 7.45 (1H, br), 7.56 (1H, d, J=8.5 Hz), 7.62 (1H, d, J=1 Hz), 7.99 (1H, s) and 9.46 (1H, s); ^{13}C NMR: δ 32.1 ($NHCH_3$), 36.2 (NCH_3), 110.7, 117.1, 125.9, 133.2 (all Ar–CH), 124.3, 132.4, 138.5 (all Ar–C), 182.5 (NH*C*SNH); LR EIMS: m/z (%) 220 (M^+; 79), 187 (30), 186 (100), 171 (40), 164 (32), 147 (60), 146 (27), 132 (16); HR EIMS: Calcd for $C_{10}H_{12}N_4S$ 220.0783, found 220.0779.

*4.21.2. 1-Ethyl-5-(N-methylthioureido)-1H-indazole (**26b**)*

White needles; yield: 0.2 g (90%); mp 177–179 °C; IR: 3270, 3161, 1541, 1522, 1506, 1244, 1193, 1051, 958, 887, 765 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.38 (3H, t, J=7 Hz), 2.89 (3H, d, J=4.5 Hz), 4.41 (2H, q, J=7 Hz), 7.25 (1H, d, J=8.5 Hz), 7.47 (1H, br s), 7.61 (1H, d, J=9 Hz), 7.63 (1H, d, J=1.5 Hz), 8.01 (1H, d, J=0.5 Hz) and 9.47 (1H, br s); ^{13}C NMR: δ 15.8 (CH_3), 32.2 ($NHCH_3$), 44.0 (NCH_2), 110.6, 117.1, 125.7, 133.2 (all Ar–CH), 124.4, 132.4, 137.6 (all Ar–C), 182.5 (NH*C*SNH); LR EIMS: m/z (%) 234 (M^+; 100), 201 (38), 200 (90), 185 (54), 178 (35), 161 (42), 146 (53), 133 (10), 105 (11); HR EIMS: Calcd for $C_{11}H_{14}N_4S$ 234.0939, found 234.0932.

*4.21.3. 5-(N-Methylthioureido)-1-n-propyl-1H-indazole (**26c**)*

White prisms; yield: 0.22 g (88%); mp 167–169 °C; IR: 3250, 3177, 1540, 1507, 1248, 1056, 1023, 897, 824, 744 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.81 (3H, t, J=7 Hz), 1.82 (2H, sextet, J=7 Hz), 2.89 (3H, d, J=4.5 Hz), 4.38 (2H, t, J=7 Hz), 7.28 (1H, d, J=8 Hz), 7.47 (1H, br s), 7.61 (1H, d, J=8 Hz), 7.62 (1H, s), 8.0 (1H, d, J=0.5 Hz) and 9.46 (1H, s); ^{13}C NMR: δ 12.0 (CH_3), 23.7 (CH_2), 32.2 ($NHCH_3$), 50.5 (NCH_2), 110.6, 117.0, 125.7, 133.2 (all Ar–CH), 124.3, 132.4, 138.2 (all Ar–C), 182.5 (NH*C*SNH); LR EIMS: m/z (%) 248 (M^+; 100), 217 (19), 215 (47), 214 (64), 192 (48), 188 (24), 185 (68), 175 (45), 172 (11), 170 (16), 163 (15), 147 (11), 146 (88), 133 (13), 105 (10); HR EIMS: Calcd for $C_{12}H_{16}N_4S$ 248.1095, found 248.1098.

4.22. Cyclisation of 26a–c to 2-methylamino-6-alkylthiazolo[5,4-*e*]indazoles (27a–c)

The thioureidoindazoles (**26a–c**) were cyclised by Br_2–AcOH, as described earlier, to furnish regioselectively the thiazolo[5,4-*e*]indazoles, **27a–c**, which were crystallised from pet. ether–CH_2Cl_2.

*4.22.1. 6-Methyl-2-methylaminothiazolo[5,4-e]-1H-indazole (**27a**)*

Colourless needles; yield: 0.2 g (92%); mp 214–216 °C; IR (KBr): 3230, 3134, 3103, 1625, 1557, 1476, 1305, 1230, 1149, 1059, 928, 813, 783 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.93 (3H, d, J=4.5 Hz, NHCH_3), 4.03 (3H, s, NCH_3), 7.48 (1H, d, J=9 Hz, H-5), 7.51 (1H, d, J=9 Hz, H-4), 7.78 (1H, q, J=4.5 Hz, NH–CH_3) and 8.0 (1H, s, H-3); ^{13}C NMR: δ 31.5 (NHCH_3), 36.5 (NCH_3), 108.3 (CH-5), 119.2 (CH-4), 130.4 (CH-8), 118.1 (×2, C-8a, C-8b), 137.5 (C-5a), 147.7 (C-3a), 166.5 (C-2); LR EIMS: m/z (%) 218 (M^+; 100), 203 (14), 190 (19), 189 (21); HR EIMS: Calcd for $C_{10}H_{10}N_4S$ 218.0627, found 218.0621.

*4.22.2. 6-Ethyl-2-methylaminothiazolo[5,4-e]-1H-indazole (**27b**)*

Colourless needles; yield 0.21 g (90%); mp 191–193 °C; IR (KBr): 3204, 1606, 1555, 1407, 1207, 1188, 1142, 1062, 930, 824, 797 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.44 (3H, t, J=7 Hz), 3.0 (3H, d, J=4.5 Hz), 4.49 (2H, q, J=7 Hz), 7.56 (1H, d, J=9 Hz), 7.58 (1H, d, J=9 Hz), 7.84 (1H, q, J=4.5 Hz) and 8.08 (1H, s); ^{13}C NMR: δ 15.7 (CH_3), 31.5 (NHCH_3), 44.2 (NHCH_2), 108.2, 119.2 and 130.5 (all Ar–CH), 118.2, 119.4, 136.6, 147.8, 166.4 (all Ar–C); LR EIMS: m/z (%) 232 (M^+; 100), 217 (60), 204 (33), 203 (30), 176 (35), 175 (21), 162 (16), 149 (16), 120 (14), 69 (17); HR EIMS: Calcd for $C_{11}H_{12}N_4S$ 232.0782, found 232.0779.

*4.22.3. 2-Methylamino-6-n-propylthiazolo[5,4-e]-1H-indazole (**27c**)*

White crystals; yield: 0.214 g (87%); mp 157–159 °C; IR (KBr): 3253, 1581, 1550, 1471, 1438, 1409, 1187, 794 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.93 (3H, t, J=7 Hz), 1.97 (2H, sextet, J=7 Hz), 3.13 (3H, s), 4.36 (2H, t, J=7 Hz), 5.89 (1H, br s), 7.33 (1H, d, J=9 Hz), 7.61 (1H, d, J=9 Hz) and 7.93 (1H, s); ^{13}C NMR: δ 11.8 (CH_3), 23.6 (CH_2), 32.2 (NHCH_3), 51.3 (NCH_2), 107.7, 119.3, 130.3 (all Ar–CH), 118.1, 119.9, 137.1, 147.3, 167.6 (all Ar–C); LR EIMS: m/z (%) 246 (M^+; 100), 218 (15), 217 (74), 204 (10), 189 (22), 175 (7), 149 (7); HR EIMS: Calcd for $C_{12}H_{14}N_4S$ 246.0940, found 246.0939.

4.23. Reduction of 23a,b to 1-alkyl-6-aminoindazoles (28a,b)

Following the procedure described earlier for the reduction of **2** to **3**, 1-alkyl-6-nitro-1*H*-indazoles (**23a**,**b** 2 mmol each) were reduced by $NH_2NH_2 \cdot H_2O$/Pd–C to the corresponding amines (**28a**,**b**), which were crystallised from pet. ether–CH_2Cl_2.

*4.23.1. 6-Amino-1-methyl-1H-indazole (**28a**)*

Colurless needles; yield: 0.27 g (92%); mp 174–176 °C (lit.[26f] mp 173–174 °C); IR: 3434, 3333, 3223, 1627, 1573, 1281, 864, 817 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.88 (2H, br s), 3.91 (3H, s), 6.49 (1H, d, J=1 Hz), 6.55 (1H, dd, J_1=8.5 Hz, J_2=2 Hz), 7.46 (1H, d, J=8.5 Hz) and 7.79 (1H, d, J=0.5 Hz); ^{13}C NMR: δ 35.5 (NCH_3), 91.9, 112.8, 122.2, 133.1 (all Ar–CH), 118.3, 141.9, 146.1 (all Ar–C); LR EIMS: m/z (%) 147 (M^+; 100), 146 (34), 119 (18); HR EIMS: Calcd for $C_8H_9N_3$ 147.0796, found 147.0792.

*4.23.2. 6-Amino-1-ethyl-1H-indazole (**28b**)*

Colourless needles; yield: 0.29 g (90%); mp 120–122 °C; IR: 3375, 3323, 3191, 1626, 1314, 1281, 1241, 1182, 1109, 817 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.47 (3H, t, J=7 Hz), 3.88 (2H, br s), 4.29 (2H, q, J=7 Hz), 6.54 (1H, s), 6.56 (1H, dd, J_1=8.5 Hz, J_2=2 Hz), 7.48 (1H, d, J=8.5 Hz) and 7.82 (1H, s); ^{13}C NMR: δ 15.1 (CH_3), 43.7 (NCH_2), 92.0, 112.8, 122.3, 133.2 (all Ar–CH), 118.5, 140.9, 145.9 (all Ar–C); LR EIMS: m/z (%) 161 (M^+; 100), 146 (71), 133 (28), 119 (14), 92 (10); HR EIMS: Calcd for $C_9H_{11}N_3$ 161.0953, found 161.0952.

4.24. Preparation of 1-alkyl-6-(*N*-methylthioureido)indazoles (29a,b) from 28a,b

Following the general procedure described earlier for the preparation of **8a**–**c**, the thioureidoindazoles **29a**,**b** were synthesised by the condensation of the amines **28a**,**b** (1 mmol each) with methyl isothiocyanate and purified by crystallisation from CH_2Cl_2.

*4.24.1. 1-Methyl-6-(N-methylthioureido)-1H-indazole (**29a**)*

White prisms; yield: 0.2 g (91%); mp 211–213 °C; IR: 3228, 3163, 1619, 1553, 1248, 1054, 992, 844, 771, 712 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.92 (3H, d, J=4.5 Hz), 3.97 (3H, s), 6.99 (1H, d, J=7 Hz), 7.66 (1H, d, J=9 Hz), 7.68 (1H, s), 7.74 (1H, br s), 7.96 (1H, s) and 9.69 (1H, s); ^{13}C NMR: δ 32.2 (NHCH_3), 36.1 (NCH_3), 104.3, 118.9, 121.8, 133.1 (all Ar–CH), 121.5, 137.9, 140.7 (all Ar–C), 182.0 (NHCSNH); LR EIMS: m/z (%) 220 (M^+; 78), 189 (20), 288 (13), 187 (29), 186 (100), 185 (18), 172 (10), 171 (17), 147 (73), 146 (26), 119 (20); HR EIMS: Calcd for $C_{10}H_{12}N_4S$ 220.0783, found 220.0780.

*4.24.2. 1-Ethyl-6-(N-methylthioureido)-1H-indazole (**29b**)*

White crystals; yield: 0.205 g (88%); mp 188–190 °C; IR: 3255, 3156, 1623, 1544, 1312, 1242, 1055, 1015, 963, 850, 711 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.37 (3H, t, J=7 Hz), 2.97 (3H, d, J=4.5 Hz), 4.35 (2H, q, J=7 Hz), 6.99 (1H, d, J=8.5 Hz), 7.66 (1H, d, J=8.5 Hz), 7.72 (1H, s), 7.77 (1H, br s), 7.97 (1H, d, J=0.5 Hz) and 9.68 (1H, s); ^{13}C NMR: δ 15.7 (CH_3), 32.2 (NHCH_3), 43.9 (NCH_2), 104.2, 118.9, 121.8, 133.1 (all Ar–CH), 121.7, 137.9, 139.8 (all Ar–C), 182.0 (NHCSNH); LR EIMS: m/z (%) 234 (M^+; 100), 203 (10), 201 (32), 200 (47), 185 (34), 178 (34), 161 (43), 146 (50), 133 (24), 74 (13); HR EIMS: Calcd for $C_{11}H_{14}N_4S$ 234.0939, found 234.0943.

4.25. Cyclisation of 29a,b to 2-methylamino-8-alkylthiazolo-[4,5-*g*]indazoles (30a,b)

The thioureidoindazoles (**29a**,**b**; 1 mmol each) were regioselectively cyclised by Br_2–AcOH, as described earlier for **5a**–**c**, to furnish the thiazolo[4,5-*g*]indazoles, **30a**,**b**. The crude products were purified by crystallisation from CH_2Cl_2.

*4.25.1. 8-Methyl-2-methylaminothiazolo[4,5-g]-1H-indazole (**30a**)*

White needles; yield: 0.207 g (95%); mp 238–240 °C; IR (KBr): 3159, 3122, 1606, 1556, 1408, 1276, 1057, 846, 799, 722 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.97 (3H, d, J=4.5 Hz), 4.09 (3H, s), 7.26 (1H, d, J=9 Hz), 7.56 (1H, d, J=9 Hz), 7.98 (1H, s) and 8.04 (1H, q, J=4.5 Hz); ^{13}C NMR: δ 31.6 (NHCH_3), 37.4 (NCH_3), 114.7, 119.1, 134.1 (all Ar–CH), 108.9, 120.3, 136.0, 152.8, 168.1 (all Ar–C); LR EIMS: m/z (%) 218 (M^+; 100), 217 (14), 190 (18), 189 (30), 188 (16), 176 (13); HR EIMS: Calcd for $C_{10}H_{10}N_4S$ 218.0627, found 218.0625.

*4.25.2. 8-Ethyl-2-methylaminothiazolo[4,5-g]-1H-indazole (**30b**)*

White needles; yield: 0.215 g (93%); mp 183–185 °C; IR: 3226, 3097, 1606, 1556, 1410, 1274, 1037, 836, 788 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.39 (3H, t, J=7 Hz), 2.97 (3H, d, J=4.5 Hz), 4.41 (2H, q, J=7 Hz), 7.28 (1H, d, J=8.5 Hz), 7.57 (1H, d, J=8.5 Hz), 8.01 (1H, s) and 8.04 (1H, q, J=4.5 Hz); ^{13}C NMR: δ 16.8 (CH_3), 31.6 (NHCH_3), 45.2 (NCH_2), 114.8, 119.1, 134.4 (all Ar–CH), 108.5, 120.4, 135.1, 152.7, 168.0 (all Ar–C); LR EIMS: m/z (%) 232 (M^+; 100), 217 (33), 204 (15), 203 (7), 176 (26), 175 (10). Anal. Calcd for $C_{11}H_{12}N_4S$: C, 56.90; H, 5.17; N, 24.14. Found: C, 56.85; H, 5.15; N, 24.16%.

4.26. Preparation of 1-methyl-5-(*N*-ethyl/benzylthioureido)-indazoles (31a,b) from 25a

Following the general procedure described previously for the preparation of **8a**–**c**, the thioureidoindazoles **31a**,**b** were synthesised by the condensation of the amine **25a** (1 mmol) with ethyl or benzyl isothiocyanates and purified by crystallisation from CH_2Cl_2.

*4.26.1. 5-(N-Ethylthioureido)-1-methyl-1H-indazole (**31a**)*

White needles; yield: 0.21 g (89%); mp 184–186 °C; IR: 3244, 3149, 1542, 1508, 1241, 1051, 765, 706 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$): δ 1.18 (3H, t, J=8 Hz), 3.63 (2H, q, J=8 Hz), 4.07 (3H, s), 7.28 (1H, d, J=9 Hz), 7.40 (1H, d, J=9 Hz), 7.62 (1H, s), 8.01 (1H, s) and 8.03 (1H, br s); ^{13}C NMR (50 MHz): δ 14.2 (CH_3), 35.7 (NCH_3), 40.2 ($NHCH_2$), 110.6, 118.8, 125.4, 132.8 (all Ar–CH), 124.1, 128.8, 138.6 (all Ar–C), 180.7 (NHCSNH); LR EIMS: m/z (%) 234 (M^+; 92), 221 (15), 201 (31), 200 (100), 189 (21), 188 (22), 185 (14), 173 (15), 172 (73), 171 (45), 164 (30), 159 (14), 147 (93), 146 (32), 132 (16), 119 (13); HR EIMS: Calcd for $C_{11}H_{14}N_4S$ 234.0939, found 234.0943.

*4.26.2. 5-(N-Benzylthioureido)-1-methyl-1H-indazole (**31b**)*

White prisms; yield: 0.27 g (91%); mp 182–184 °C; IR: 3237, 3184, 1540, 1520, 1222, 1188, 1069, 963, 738, 704 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.01 (3H, s), 4.72 (2H, d, J=5.5 Hz), 7.23 (1H, t, further-split, J=9 Hz), 7.30 (1H, dd, J_1=9 Hz, J_2=2 Hz), 7.31–7.32 (4H, m), 7.58 (1H, d, J=9 Hz), 7.70 (1H, br s), 8.0 (1H, d, J=1 Hz), 8.01 (1H, br s) and 9.56 (1H, s); ^{13}C NMR: δ 36.3 (NCH_3), 48.1 (NCH_2), 110.6, 117.1, 125.9, 127.6, 128.2 (×2), 129.0 (×2), 133.2 (all Ar–CH), 124.3, 132.5, 138.5, 140.1 (all Ar–C), 182.4 (NHCSNH); LR EIMS: m/z (%) 296 (M^+; 29), 263 (10), 262 (33), 221 (18), 189 (23), 188 (8), 147 (38), 146 (13), 106 (10), 91 (100); HR EIMS: Calcd for $C_{16}H_{16}N_4S$ 296.1096, found 296.1089.

4.27. Cyclisation of 31a,b to 2-ethylamino/benzylamino-6-methylthiazolo[5,4-*e*]indazoles (32a,b)

The thioureidoindazoles (**31a**,**b**) were cyclised by Br_2–AcOH, as described earlier, to furnish regioselectively the thiazolo[5,4-*e*]indazoles, **32a**,**b**, which were crystallised from CH_2Cl_2.

*4.27.1. 2-Ethylamino-6-methylthiazolo[5,4-e]-1H-indazole (**32a**)*

White needles; yield: 0.21 g (90%); mp 217–219 °C; IR (KBr): 3207, 1600, 1553, 1453, 1228, 1157, 929, 796 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.20 (3H, t, J=7 Hz), 3.32–3.41 (2H, m), 4.03 (3H, s), 7.47 (1H, d, J=8.5 Hz), 7.51 (1H, d, J=8.5 Hz), 7.82 (1H, t, J=5.5 Hz) and 8.0 (1H, s); ^{13}C NMR: δ 15.3 (CH_3), 36.5 (NCH_3), 39.7 (NCH_2), 108.2, 119.27, 130.4 (all Ar–CH), 118.1, 119.20, 137.5, 147.8, 165.5 (all Ar–C); LR EIMS: m/z (%) 232 (M^+; 100), 231 (8), 217 (63), 204 (32), 203 (18), 190 (17), 189 (21), 176 (8); HR EIMS: Calcd for $C_{11}H_{12}N_4S$ 232.0782, found 232.0775.

*4.27.2. 2-Benzylamino-6-methylthiazolo[5,4-e]-1H-indazole (**32b**)*

White flakes; yield: 0.27 g (92%); mp 194–196 °C; IR (KBr): 3201, 3085, 1590, 1553, 1448, 1345, 1224, 930, 793, 759, 702 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.05 (3H, s), 4.61 (2H, d, J=5.5 Hz), 7.27 (1H, t, J=7.5 Hz), 7.33 (2H, t, J=7.5 Hz), 7.41 (2H, d, J=7.5 Hz), 7.49 (1H, d, J=9 Hz), 7.53 (1H, d, J=9 Hz), 8.03 (1H, s) and 8.37 (1H, t, J=5.5 Hz); ^{13}C NMR: δ 36.5 (NCH_3), 48.3 ($NHCH_2$), 108.3, 119.3, 127.8, 128.3 (×2), 129.2 (×2), 130.5 (all Ar–CH), 118.1, 119.5, 137.6, 139.9, 147.5, 165.7 (all Ar–C); LR EIMS: m/z (%) 294 (M^+; 100), 293 (12), 205 (10), 204 (11), 203 (76), 190 (15), 189 (7), 176 (6), 159 (5), 106 (9), 91 (43). Anal. Calcd for $C_{16}H_{14}N_4S$: C, 65.31; H, 4.76; N, 19.05. Found: C, 65.26; H, 4.77; N, 19.07%.

4.28. Cytotoxicity assay

The human lung carcinoma cell line (A549) was cultured in RPMI medium supplemented with 10% FCS at 37 °C in a 5% CO_2 atmosphere. Cells were plated overnight prior to the treatment with **5a**, **14a–c**, **18a** and **30a**,**b**. Unsynchronised cells were treated with different micromole concentrations of the investigated compounds in DMSO for 72 h. The medium was then removed by aspiration, the cells washed once with PBS, and 100 μL of PBS containing MTT (0.5 mg/mL) was added to each well. After 4 h, 100 μL of SDS solution (10% SDS in 0.01 M HCl) was added and kept at 37 °C for another 12 h. Then the absorbance at 560 nm was recorded with a spectrophotometric plate reader (Bio-Tek, USA). For results, see Table 1.

Acknowledgements

The authors express their sincere thanks to the Director, Bose Institute for providing laboratory facilities, the C.S.I.R., Govt. of India for a fellowship (T.K.), Mr. B. Majumder and Mr. P. Dey, both of B.I., for recording the NMR and IR spectra, respectively. The authors are immensely thankful to Prof. S. Chattopadhyay, Head, Bioorganic Division, B.A.R.C., Mumbai, India for recording the NMR spectra of some of the compounds and mainly for the biological screening of the thiazoloindazoles.

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