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Target-oriented synthesis of functionalized pyrazolo-fused medium-sized N,S-heterocycles *via* Friedel–Crafts ring closure approach

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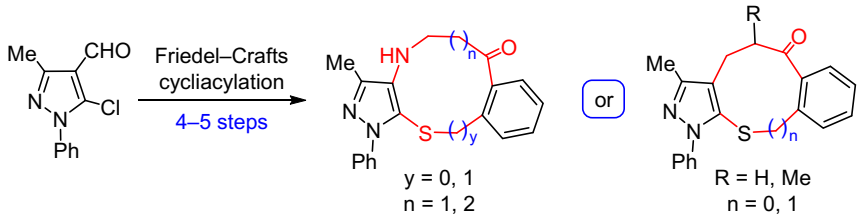


Efficient and concise synthetic protocol to benzo- and pyrazolo-fused medium-sized N,S-heterocycles (e.g,. thiazocinones, thiazoninones, thiazecinones, thiecinones, and thioninones) is developed. The process involves the $AlCl_3/MeNO_2$, TfOH or polyphosphoric acid mediated cyclization of pyrazole-based carboxylic acids or esters into tricyclic ketones under mild conditions. The designed protocol offers easy access to biologically and pharmaceutically promising pyrazoles in good yields. The structure elucidation of all new compounds without stereochemical assignments has been carried out by spectral and elemental analysis.

Keywords: polycycles, pyrazoles, thiazocinones, thiecinones, Friedel–Crafts cycliacylation.

Condensed polycycles containing medium-ring N,S-heterocycles are common structural motifs in many naturally occurring alkaloids[1] displaying wide range of pharmacological activities (Fig.1).[2] The alliance of great structural diversity and versatile pharmaceutical applicability of these heterocycles have maintained the interest of both organic and medicinal researchers toward the discovery of novel bioactive architectures.[3] Interestingly, numerous strategies have been successfully applied to construct fused six- and seven-membered heterocycles, including olefin metathesis,[4] Cope rearrangement,[5] Mizoroki–Heck reaction,[6] Diels–Alder reaction,[7] ring expansion,[8] Friedel–Crafts reaction,[9] cycloadditions,[10] transition metal catalized cycloaddition,[11] Heck-type coupling,[12] sigmatropic cyclization,[13] Baylis–Hillman reaction,[14] domino[15] and cascade[16] strategies.

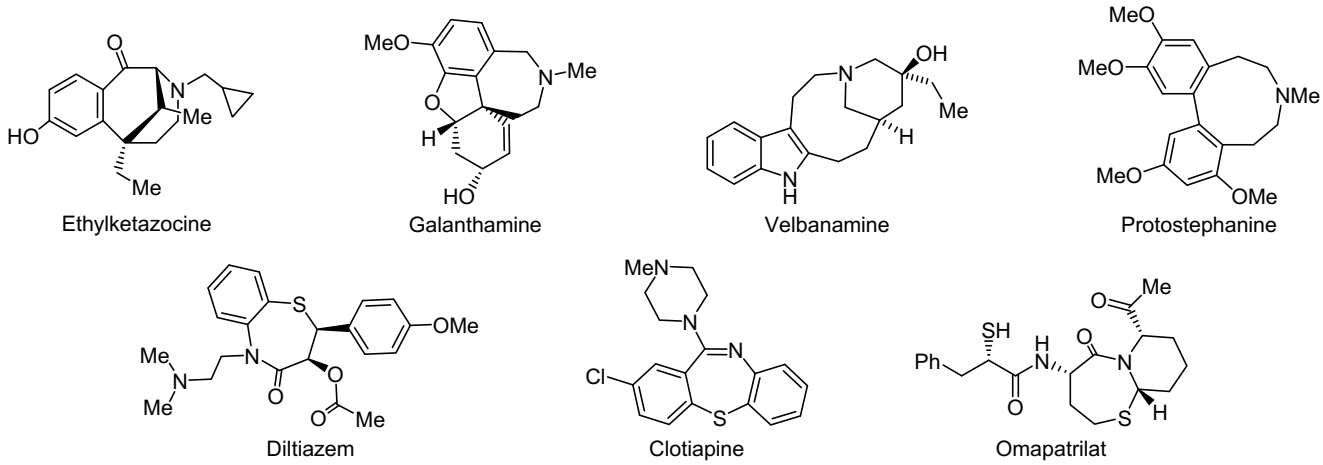


Figure 1. Examples of biologically active medium-sized N,S-heterocycles.

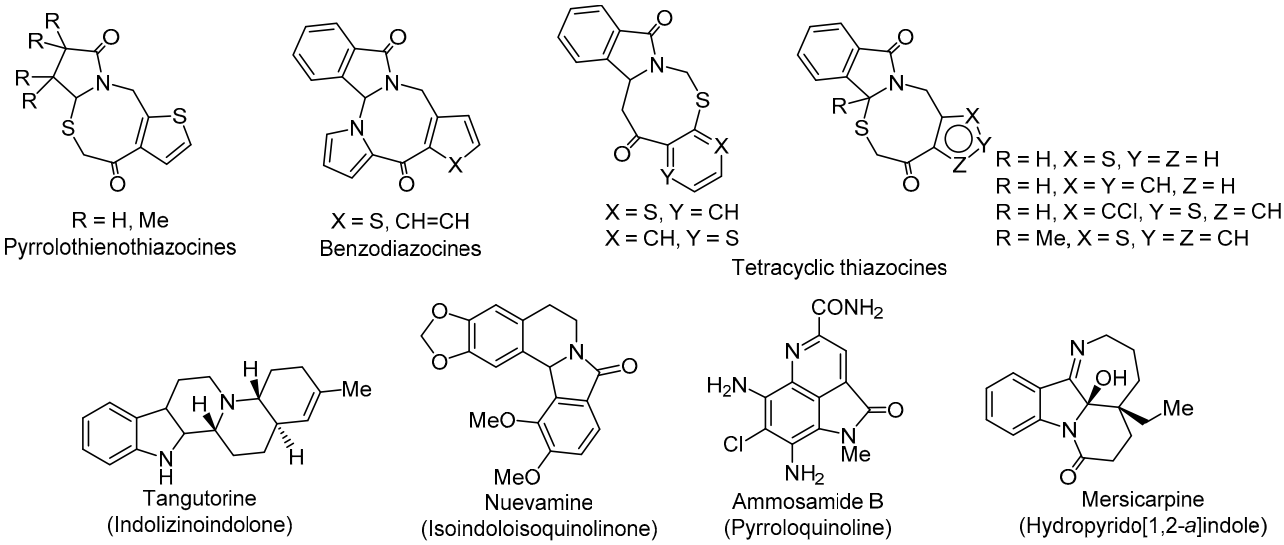


Figure 2. Some of polyheterocycles synthesized in the main step by Friedel–Crafts processes.

An examination of the literary precedents for the synthesis of medium-sized N,S-heterocycles revealed that several examples of benzo-annulated 1,3-, 1,4-, 1,5-thiazepine regio-isomers have been explored.[17] Interestingly, that synthesis of 1,2- and 1,3-thiazocines has been described only in few works.[18]

However, no information was found on the synthesis of nine-membered and larger rings, except for the few examples from some natural products families, e.g., erythrina, aspidosperma, and iboga alkaloids.[19] The lack of efficient protocols for the synthesis of eight-membered and larger strained rings were attributed to the transannular interactions[20] (nonbonded repulsions) especially severe in seven-membered and larger rings. Currently, several approaches to the synthesis of the medium-sized hetero-cycles[21] have been utilized to overcome these barriers.

Among the most worthwhile strategies for accessing 1,4- and 1,5-thiazocines described in the literature are ring-closing metathesis of olefinic sulfones and sulfoxides using Grubbs catalyst in CH_2Cl_2,[22] Pd-catalyzed carbonylation/ cyclization of 2-(2-iodobenzylsulfanyl)-5-alkylbenzenamines,[23] cyclization of aryl thioesters using LiHMDS in THF,[24] cyclization of bromosulfanyl arenes in the presence of LDA,[25] ring expansion of the thiazolium salts,[26] photo-induced cyclization of phthalimidoalkylsulfanyl-based carboxylic acids or esters,[27] $SnCl_2$-mediated cyclizations of thiopyran hemiacetals,[28] cyclization of iminoethers using Amberlyst ion exchange resin,[29] intramolecular Ugi reaction of bifunctional oxoacids,[30] cyclization of thiophenol-based carboxylic acid using PCl_5,[31] cyclization of 1-amino-8-bromonaphthalene thioethers using *p*-TsCl in pyridine,[32] and cyclization of 3-(benzhydrylsulfanyl)propanoic acids using EDC in the presence of Hünig's base.[24] Nevertheless, a few methods have been reported for the synthesis of thiazonines or larger ring systems including ring expansion of ω-bromoalkyl benzothiazolium salts,[33] 2,3-sigmatropic rearrangements of chloramine-T based S-imides,[34] and ring expansion of S-lactams using $NaIO_4$.[35]

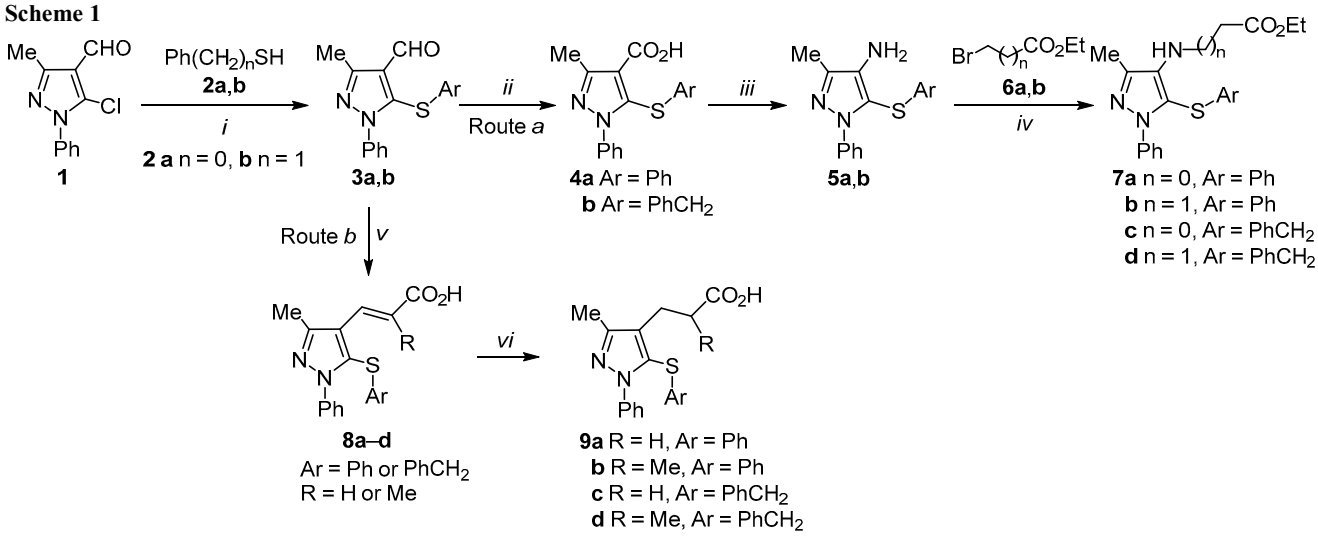
In this context, it is worth highlighting the great importance of Friedel–Crafts reactions in the area of medium-ring synthesis.[36] Precedents in the literature have shown that this type of processes is considered as macrocyclization methodology[37] and often adopted for the construction of several homo- and heterocyclic skeletons, e.g., thiazocines, pyrrolothienothiazocines, and benzo-diazocines (Fig. 2).[38]

As an extension of our research program focused on synthesizing drug-like heterocycles[39] using Friedel–Crafts cyclization,[40] herein, we wish to report our attempts toward the construction of pyrazole polycycles incorporating pyrazole and medium-sized N-heterocycles in the new molecular design, in particular, benzo- and pyrazolo-fused 8-, 9-, and 10-membered N,S-heterocycles utilizing Brønsted and Lewis acids mediated Friedel–Crafts cyclizations of presynthesized heterocyclic acids or esters.

The reaction sequences employed for the synthesis of pyrazole-based ester **7a**–**d** and acid **9a**–**d** precursors starting from pyrazole-4-carbaldehyde **1**,[41a] are illustrated in Scheme 1. Initially, the proposed synthetic pathway involved the reaction of pyrazole-4-carbaldehyde **1** with thiophenol or benzylmercaptan **2a**,**b**[41b] in DMF to produce substituted aldehydes **3a**,**b**. The initial route (route *a*) toward precursors **7a**–**d** was started from aldehydes **3a**,**b**. This synthesis involved oxidation of aldehydes **3a**,**b** using $KMnO_4$ to afford carboxylic acids **4a**,**b**. Acids **4a**,**b** underwent the Schmidt[42] reaction by treatment with NaN_3/ H_2SO_4 to give aminopyrazoles **5a**,**b** in good yields. Alkylation of amines **5a**,**b** with ethyl α- or β-bromo-alkanoate **6a**,**b** using K_2CO_3/DMF subsequently yields ester precursors **7a**–**d**.

The second route (route *b*) encompassed the formation of heterocyclic acids **9a**–**d** *via* the condensation of substrates **3a**,**b** with AcONa or $EtCO_2Na$ and their corresponding acid anhydrides followed by reduction of the resulting acrylic acids **8a**–**d** with sodium amalgam (Na/Hg, 2.5%), which resulted in acid precursors **9a**–**d** in good yields. With starting compounds in hand, our further studies were devoted to the development of facile and readily scalable procedures to pyrazolo- and benzo-fused medium-sized 8–

Scheme 1



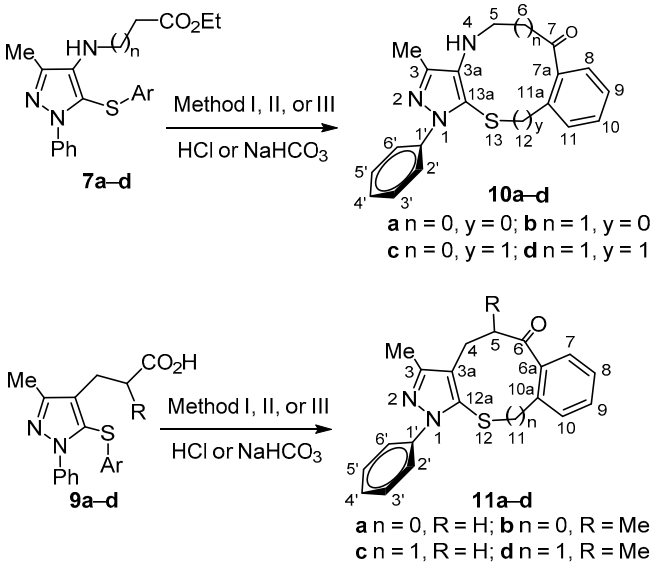
i: **2a** or **2b**, K_2CO_3, DMF, 90–100°C, 5–6 h (77–88%); *ii*: $KMnO_4$, H_2O, Me_2CO, 0°C–rt, 1 h, then 70–80°C, 3 h (84–86%);
iii: NaN_3, H_2SO_4, 0–5°C, 1 h, then 60–70°C, 4 h, then NaOH, H_2O (74–77%); *iv*: **6a**,**b**, K_2CO_3, DMF, 90–100°C, 4–6 h (78–85%);
v: Ac_2O/AcONa or $(EtCO)_2O$/$EtCO_2Na$, Et_3N, 120–130°C, 4–5 h, Na_2CO_3, HCl (74–81%);
vi: 2.5% Na/Hg,1 N NaOH, 40–50°C, 2 h, HCl (87–90%)

10-membered N,S-heterocyclic systems proceeding *via* Friedel–Crafts cyclization of precursors **7**, **9 a**–**d**.

Gratifyingly, with initial extensive investigations of mild catalysts, solvents, and temperatures, the ring closures of substrate **7a** were demonstrated to be possible. At this stage, a few attempts toward the formation of medium-sized compound **10a** were tried on substrate **7a** using low stoichiometric loadings of mild $AlCl_3/MeNO_2$, PPA, or TfOH catalysts for 30 min at a certain temperature, which afforded product **10a** in poor yields. So we started adjusting the reaction conditions by increasing the reaction time at elevated temperatures with more than stoichiometric loadings of acid promoters. Out of several modifications tried, the conditions outlined in Table 1 seemed satisfactory to achieve the desired products **10**, **11 a**–**d** in 70–90% yields. With suitable conditions for this reaction, Friedel–Crafts cycliacylation of functionalized precursors containing more reactive arenes was feasible. The crude products were purified several times by flash column chromatography and crystallization.

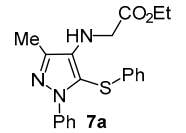
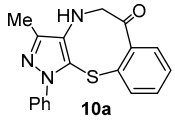
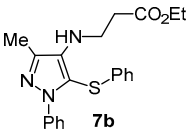
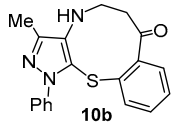
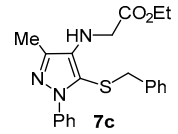
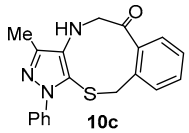
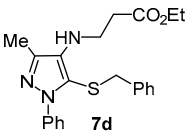
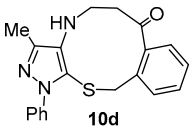
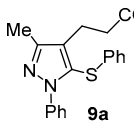
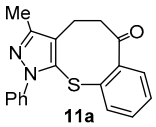
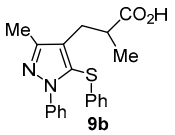
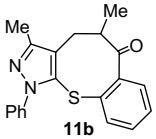
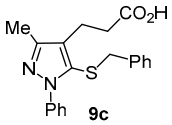
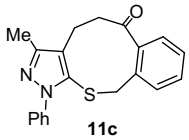
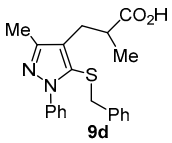
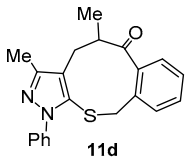
These results demanded an explanation of the significant role of catalysts in Friedel–Crafts cycliacylations in heterocyclic system. First of all and after a literature search, we found that the catalytic inhibitions[43] of Lewis or Brønsted acids are considered a major problem encountered with inter- and intramolecular Friedel–Crafts processes in heteroaromatics synthesis. This suggested that the rate of the ring closure process is strongly dependent on the catalyst strength. Conceivably, the ease of the cyclization process depends mainly on the binding activity of acidic catalysts on heteroatoms present in the substrate. Since the stronger catalyst is the more it is complexed with heteroatoms and, hence, leads to the deactivation of a nucleophilic substrate and consequent retard the cyclization process fully. Conversely, the mild catalyst is the less coordinated with substrate heteroatoms.

Scheme 2



Regarding the role of catalyst inhibition on slowing or inhibiting ring closure of electron-rich arenes, we presume that the weakly acidic catalysts are unable to coordinate effectively with the heteroatoms. The result highlights the utility of cyclization procedures which lies in the mildness of selected catalysts, operating conditions, and functional group compatibility in order to bring ring closure to completion. The most important finding of cyclization studies was the proposed mechanism[44] for Friedel–Crafts cycliacylations in heteroarenes. Mechanistically, we proposed that acylation process would take place *via* an initial treatment with acidic catalysts. This could result in an acyl carbocation,[45] either free or as an ion pair, by loss of H_2O or EtOH molecules. The acyl carbocation would undergo cycliacylation into tricyclic scaffolds.

Table 1. Cyclization conditions of esters **7a**–**d** and acids **9a**–**d** and yields of products **10**, **11 a**–**d**

Substrate	Method	Time, h	Product	Yield, %
 **7a**	I*	15	 **10a**	81
	II**	6		78
	III***	4		73
 **7b**	I	12	 **10b**	84
	II	5		80
	III	4		75
 **7c**	I	20	 **10c**	78
	II	10		72
	III	8		70
 **7d**	I	17	 **10d**	79
	II	10		81
	III	8		75
 **9a**	I	17	 **11a**	83
	II	8		74
	III	5		75
 **9b**	I	18	 **11b**	79
	II	10		82
	III	7		80
 **9c**	I	20	 **11c**	81
	II	8		77
	III	6		75
 **9d**	I	16	 **11d**	85
	II	9		80
	III	6		73

* Method I: esters **7a**–**d** or acids **9a**–**d** (2 mmol) in CH_2Cl_2 (10 ml), $AlCl_3$ (10 mmol), $MeNO_2$ (100 mmol), room temperature.
** Method II: esters **7a**–**d** or acids **9a**–**d** (3 mmol), TfOH (1 ml, 12 mmol), 1,2-DCE (20 ml), reflux.
*** Method III: esters **7a**–**d** or acids **9a**–**d** (3 mmol), PPA (15 g), 160–180°C.

The formation of cyclic products **10**, **11 a**–**d** was proven on the basis of ^{1}H NMR, ^{13}C NMR, and IR spectra. For example, a comparison of the spectroscopic data of acid **9d** and ketone **11d** has clearly shown the disappearance of the characteristic CO_2H stretch found at 2630 cm^{-1} in the IR spectrum of acid **9d**, and the ^{1}H NMR spectrum of ketone **11d** indicates the absence of the diagnostic carboxylic acid signal shown at 10.09 ppm in the ^{1}H NMR spectrum of acid **9d**. Further, the characteristic changes in the ^{13}C NMR spectra proved that the cyclization process had occurred. For example, the disappearance of the CO_2H signal at 181.2 ppm in the ^{13}C NMR spectrum of compound **9d** and the appearance of the new carbonyl group signal at 199.9 ppm in the ^{13}C NMR spectrum of compound **11d**. Protons of the methylene groups in compounds **10**, **11 a**–**d** are unequivalent and are represented as unresolved signals. Thus, the direct inspection of the ^{1}H NMR spectrum of ketones **11b**,**d** displayed well-resolved two distinct shielded and upfielded signals assigned to diastereotopic protons of CH_2 group.

In conclusion, we have designed an unprecedented and concise catalytic protocol for the synthesis of tricyclic benzo- and pyrazolo-fused medium-sized N,S-heterocyclic ring systems incorporating 8-, 9-, and 10-membered rings from simple starting materials *via* Friedel–Crafts cyclacylations of acyclic acids or esters precursors. Encouraging results confirmed our assumption that it should be possible to synthesize polycyclic pyrazoles of promising medicinal interest from the corresponding acyclic precursors using mild acidic catalysts that would be beneficial to the synthetic community.

Experimental

IR spectra were obtained on a PerkinElmer 1600 FT-IR spectrophotometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL LA-400 FT-NMR (400 and 100 MHz, respectively) in $CDCl_3$ with TMS as internal standard. Elemental analyses were carried out by a vario EL III 2400 CHNOS elemental analyzer. Melting points were determined on a digital Gallenkamp capillary melting point apparatus and are uncorrected. The progress of the reactions was monitored by TLC on Silufol UV-254 silica gel plates, visualized with UV light (at 254 and/or 360 nm). Flash column chromatography was performed on Merck silica gel (230–400 mesh).

All chemicals used were of reagent grade and solvents were freshly distilled and dried by standard procedures before use. 5-Chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**1**) was prepared according to the literature procedure.[41]

Synthesis of substituted pyrazole carbaldehydes 3a,b (General method). A mixture of aldehyde **1** (20 mmol), substituted thiophenol **2a** or **2b** (22 mmol), and K_2CO_3 (70 mmol) in DMF (20 ml) was heated with continuous stirring for 5–6 h at 90–100°C, and the progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and concentrated under reduced pressure. The residue was poured into ice H_2O (100 ml), and the resulting precipitate was filtered off, washed with H_2O, dried, and recrystallized.

3-Methyl-1-phenyl-5-(phenylsulfanyl)-1*H*-pyrazole-4-carbaldehyde (3a). Yield 4.53 g (77%), yellow crystals, mp 68–70°C. IR spectrum, ν, cm^{-1}: 3140, 3055, 2900, 2740, 1690, 1600, 1585, 1440, 1377, 1170, 790. ^{1}H NMR spectrum, δ, ppm: 2.35 (3H, s, CH_3); 7.15–7.22 (3H, m,

H Ar); 7.24–7.27 (3H, m, H Ar); 7.32–7.36 (2H, m, H Ar); 7.77–7.80 (2H, m, H Ar); 10.11 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 13.2 (CH_3); 121.8; 124.7; 125.2; 129.2 (2C); 131.5; 131.7; 139.4; 142.1; 145.2; 189.2 (C=O). Found, %: C 69.35; H 4.90; N 9.50; S 10.73. $C_{17}H_{14}N_2OS$. Calculated, %: C 69.38; H 4.76; N 9.52; S 10.88.

5-(Benzylsulfanyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3b). Yield 5.42 g (88%), pale-yellow crystals, mp 49–52°C (mp 52–54°C[41b]). IR spectrum, ν, cm^{-1}: 3136, 3030, 2930, 2740, 1685, 1600, 1580, 1445, 1360, 1180, 755. ^{1}H NMR spectrum, δ, ppm: 2.35 (3H, s, CH_3); 4.43 (2H, s, CH_2); 7.15–7.22 (1H, m, H Ar); 7.24–7.26 (1H, m, H Ar); 7.28–7.35 (4H, m, H Ar); 7.40–7.43 (2H, m, H Ar); 7.73–7.75 (2H, m, H Ar); 10.10 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 12.5 (CH_3); 28.0 (CH_2); 118.5; 124.7; 129.2; 129.9; 131.5; 134.1; 137.5; 140.5; 150.2; 185.7 (C=O). Found, %: C 70.33; H 5.15; N 8.91; S 10.25. $C_{18}H_{16}N_2OS$. Calculated, %: C 70.12; H 5.19; N 9.09; S 10.38.

Synthesis of pyrazole amines 5a,b (General method). Ice-cold solution of $KMnO_4$ (3.2 g, 20 mmol) in H_2O (7 ml) was added dropwise to a solution of aldehyde **3a**,**b** (5.4 g, 18 mmol) in Me_2CO (30 ml) over 20 min with efficient stirring. After complete addition, the mixture was allowed to stir for 1 h at room temperature and then it was heated on a steam bath at 70–80°C for 3 h. A solution of 10% KOH (30 ml) was slowly added to this mixture with stirring until the solution turned alkaline, afterward, the reaction mixture was filtered. Acidification of the resulting filtrate to pH 3.0 using 30% HCl solution (50 ml) resulted in a solid, which was filtered off, washed with H_2O, and dried yielding the crude acids **4a**,**b**.

NaN_3 (0.8 g, 12 mmol) was added portionwise over 40 min to a stirred solution of acid **4a**,**b** (10 mmol) in 30% H_2SO_4 (15 ml) at 0–5°C. After complete addition, the mixture was allowed to stir at ambient temperature for 1 h and then it was heated with constant stirring at 60–70°C for 4 h. Again, the mixture was cooled to 0°C and then it poured onto crushed ice (200 g), followed by the addition of 50% NaOH solution (30 ml). The mixture was extracted with EtOAc (3×50 ml), and the combined organic layer was washed with brine, dried over $MgSO_4$, concentrated under reduced pressure, and purified with column chromatography (basic alumina, CH_2Cl_2–hexane, 3:7) to give the crude amines **5a**,**b**.

3-Methyl-1-phenyl-5-(phenylsulfanyl)-1*H*-pyrazole-4-carboxylic acid (4a). Yield 4.69 g (84%), white crystals, mp 154–156°C. IR spectrum, ν, cm^{-1}: 3410, 3050, 2966, 1690, 1600 1580, 1440, 1360, 1280, 1070, 775. ^{1}H NMR spectrum, δ, ppm: 2.39 (3H, s, CH_3); 7.13–7.22 (3H, m, H Ar); 7.23–7.27 (3H, m, H Ar); 7.38–7.42 (2H, m, H Ar); 7.78–7.80 (2H, m, H Ar); 9.94 (1H, s, COOH). ^{13}C NMR spectrum, δ, ppm: 13.2 (CH_3); 121.8; 124.7; 125.2; 129.1; 129.2; 131.5; 131.7; 139.4; 142.1; 145.2; 168.8 (C=O). Found, % C 65.87; H 4.66; N 8.84; S 10.46. $C_{17}H_{14}N_2O_2S$. Calculated, %: C 65.80; H 4.51; N 9.03; S 10.32.

5-(Benzylsulfanyl)-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid (4b). Yield 5.02 g (86%), white crystals, mp 185°C (decomp.). IR spectrum, ν, cm^{-1}: 3440, 3070, 2946, 1688, 1605 1580, 1440, 1390, 1280, 1145, 784. ^{1}H NMR spectrum, δ, ppm: 2.39 (3H, s, CH_3); 4.35 (2H, s, CH_2); 7.15–7.32 (6H, m, H Ar); 7.43–7.47 (2H, m, H Ar); 7.78–7.80 (2H, m, H Ar); 10.42 (1H, s, COOH). ^{13}C NMR spectrum, δ, ppm: 13.1 (CH_3); 35.7 (CH_2); 121.8; 124.7; 128.7; 128.9; 129.1; 129.2; 137.1; 139.3; 142.0 (C-3); 145.2 (C-5); 168.8 (C=O). Found, %: C 66.50; H 5.13; N 8.80; S 9.84. $C_{18}H_{16}N_2O_2S$. Calculated, %: C 66.66; H 4.93; N 8.64; S 9.87.

3-Methyl-1-phenyl-5-(phenylsulfanyl)-1*H*-pyrazol-4-amine (5a). Yield 2.02 g (77%), white plates, mp 110–112°C. IR spectrum, ν, cm^{-1}: 3395, 3350, 2955, 1600, 1580, 1440, 1380, 1268, 779. ^{1}H NMR spectrum, δ, ppm: 2.14 (3H, s, CH_3); 7.13–7.16 (4H, m, H Ar); 7.22–7.26 (2H, m, H Ar); 7.41–7.45 (2H, m, H Ar); 7.63–7.65 (2H, m, H Ar), 10.21 (2H, s, NH_2). ^{13}C NMR spectrum, δ, ppm: 11.4 (CH_3); 121.8; 124.7; 125.2; 129.2; 131.5; 131.7; 137.5; 139.4; 152.0 (C-3); 155.7 (C-5). Found, %: C 68.22; H 5.50; N 15.02; S 11.21. $C_{16}H_{15}N_3S$. Calculated, %: C 68.32; H 5.33; N 14.94; S 11.38.

5-(Benzylsulfanyl)-3-methyl-1-phenyl-1*H*-pyrazol-4-amine (5b). Yield 2.18 g (74%), white plates, mp 142–145°C. IR spectrum, ν, cm^{-1}: 3453, 3160, 2939, 1690, 1610, 1580, 1445, 1385, 1170, 769. ^{1}H NMR spectrum, δ, ppm: 2.16 (3H, s, CH_3); 4.31 (2H, s, CH_2); 7.13–7.15 (1H, m, H Ar); 7.17–7.19 (1H, m, H Ar); 7.22–7.32 (4H, m, H Ar); 7.40–7.44 (2H, m, H Ar); 7.62–7.64 (2H, m, H Ar); 9.90 (2H, s, NH_2). ^{13}C NMR spectrum, δ, ppm: 11.4 (CH_3); 35.7 (CH_2); 121.8; 124.7; 128.7; 128.9; 129.1; 137.1; 137.4; 139.3; 152.0 (C-3); 155.6 (C-5). Found, %: C 69.12; H 5.64; N 14.10; S 10.95. $C_{17}H_{17}N_3S$. Calculated, %: C 69.15; H 5.76; N 14.23; S 10.84.

Synthesis of esters 7a–d (General method). Haloester **6a**,**b** (ethyl bromoacetate or ethyl bromopropionate) (7 mmol) was added slowly to a hot (60–70°C) and stirred mixture of amine **5a**,**b** (5 mmol) and K_2CO_3 (15 mmol) in DMF (15 ml) over 10 min. The mixture was heated at 90–100°C for 4–6 h. When TLC analysis (EtOAc–hexane, 3:7) showed the reaction to be complete, the mixture was cooled to room temperature and poured into ice-cold H_2O (300 m). The resulting light solid was collected and washed thoroughly with H_2O and dried to afford the crude product. This product was further purified by flash column chromatography (basic alumina, EtOAc–hexane, 3:7).

Ethyl 2-[3-methyl-1-phenyl-5-(phenylsulfanyl)-1*H*-pyrazol-4-ylamino]acetate (7a). Yield 1.56 g (85%), white needles, mp 147–150°C (Me_2CO). IR spectrum, ν, cm^{-1}: 3415, 3028, 2970, 1735, 1600, 1580, 1445, 1376, 1290, 785. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.13 (3H, s, CH_3); 3.91 (2H, s, CH_2CO); 4.14 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 7.14–7.18 (4H, m, H Ar); 7.22–7.26 (2H, m, H Ar); 7.41–7.45 (2H, m, H Ar); 7.63–7.65 (2H, m, H Ar); 9.88 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 11.4 ($CH_2\underline{C}H_3$); 14.1 (CH_3); 44.1 (CH_2); 61.6 ($\underline{C}H_2CH_3$); 121.8; 124.7; 125.2; 129.2; 131.5; 131.7; 137.5; 139.4; 152.0 (C-3); 155.7 (C-5); 171.1 (C=O). Found, %: C 65.41; H 5.90; N 11.24; S 8.66. $C_{20}H_{21}N_3O_2S$. Calculated, %: C 65.39; H 5.72; N 11.44; S 8.71.

Ethyl 3-[3-methyl-1-phenyl-5-(phenylsulfanyl)-1*H*-pyrazol-4-ylamino]propanoate (7b). Yield 1.56 g (82%),

white needles, mp 124–126°C (EtOH). IR spectrum, ν, cm^{-1}: 3380, 3060, 2933, 1740, 1605, 1580, 1445, 1340, 1290, 778. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.13 (3H, s, CH_3); 2.52 (2H, t, *J* = 6.7, CH_2CO); 3.21 (2H, t, *J* = 6.7, CH_2NH); 4.12 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 7.11–7.16 (4H, m, H Ar); 7.22–7.26 (2H, m, H Ar); 7.40–7.45 (2H, m, H Ar); 7.63–7.65 (2H, m, H Ar); 10.02 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 11.4 ($CH_2\underline{C}H_3$); 14.1 (CH_3); 34.1 (CH_2NH); 43.1 ($\underline{C}H_2CO$); 60.7 ($\underline{C}H_2CH_3$); 121.8; 124.7; 125.2; 129.2; 131.5; 131.7; 137.5; 139.4; 152.0 (C-3); 155.7 (C-5); 172.0 (C=O). Found, %: C 65.98; H 5.85; N 11.13; S 8.50. $C_{21}H_{23}N_3O_2S$. Calculated, %: C 66.14; H 6.03; N 11.02; S 8.39.

Ethyl 2-[5-(benzylsulfanyl)-3-methyl-1-phenyl-1*H*-pyrazol-4-ylamino]acetate (7c). Yield 1.48 g (78%), white crystals, mp 162–165°C (Me_2CO). IR spectrum, ν, cm^{-1}: 3411, 3045, 2960, 1738, 1600, 1585, 1440, 1393, 1280, 789. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.15 (3H, s, CH_3); 3.85 (2H, s, CH_2); 4.14 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 4.29 (2H, s, CH_2CO); 7.18–7.28 (6H, m, H Ar); 7.34–7.38 (2H, m, H Ar); 7.62–7.64 (2H, m, H Ar); 10.20 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 11.4 ($CH_2\underline{C}H_3$); 14.1 (CH_3); 35.7 (CH_2); 44.1 ($\underline{C}H_2CO$); 61.6 ($\underline{C}H_2CH_3$); 121.8; 124.7; 128.8; 129.0; 129.1; 129.2; 137.1; 137.5; 139.4; 152.0 (C-3); 155.7 (C-5); 171.1 (C=O). Found, %: C 66.10; H 6.15; N 11.09; S 8.17. $C_{21}H_{23}N_3O_2S$. Calculated, %: C 66.14; H 6.03; N 11.02; S 8.39.

Ethyl 3-[5-(benzylsulfanyl)-3-methyl-1-phenyl-1*H*-pyrazol-4-ylamino]propanoate (7d). Yield 1.60 g (81%), white crystals, mp 119–122°C (Me_2CO). IR spectrum, ν, cm^{-1}: 3390, 3030, 2953, 1740, 1605, 1580, 1440, 1388, 1160, 775. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, t, *J* = 7.1, $CH_2C\underline{H}3$); 2.15 (3H, s, CH_3); 2.52 (2H, t, *J* = 6.7, CH_2CO); 3.20 (2H, t, *J* = 6.7, CH_2NH); 4.12 (2H, q, *J* = 7.1, $C\underline{H}2CH_3$); 4.27 (2H, s, CH_2); 7.15–7.28 (6H, m, H Ar); 7.34–7.38 (2H, m, H Ar); 7.62–7.64 (2H, m, H Ar); 9.81 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 11.4 ($CH_2\underline{C}H_3$); 14.1 (CH_3); 34.1 ($\underline{C}H_2CO$); 35.7 (CH_2); 43.1 (CH_2NH); 60.7 ($\underline{C}H_2CH_3$); 121.8; 124.7 (C-4); 128.8; 128.9; 129.0; 129.2; 137.1; 137.5; 139.4; 152.0 (C-3); 155.7 (C-5); 172.0 (C=O). Found, %: C 67.01; H 6.10; N 10.53; S 8.26. $C_{22}H_{25}N_3O_2S$. Calculated, %: C 66.83; H 6.32; N 10.63; S 8.10.

Synthesis of acrylic acids 9a–d (General method). Compounds were obtained in two reaction steps starting from aldehyde **1**. Step 1. Et_3N (20 mmol) was added to a stirred suspension of aldehyde **1a**,**b** (3.5 g, 15 mmol), acid anhydride (acetic or propionic anhydride) (18 mmol), and the sodium salt of the corresponding acid (18 mmol). The mixture was heated at 120–130°C for 4–5 h, cooled to room temperature, and then poured with stirring onto crushed ice (300 g). The hydrolyzed mother liquor was basified with 30% Na_2CO_3 solution (40 ml) and extracted with EtOAc (3×30 ml). The resulting aqueous solution was heated with decolorizing carbon (2 g) for 10 min and then filtered. The clear filtrate was poured while it still hot into the ice-cold 30% HCl solution (100 ml). The precipitate of compound **8a**–**d** was collected, washed with H_2O, and dried.

Step 2. Na/Hg (25 g, 2.5%) was added portionwise to a hot (40–50°C) stirred solution of acid **8a**–**d** (10 mmol) in 1 N NaOH solution (20 ml) over 5 min. The reaction mixture was stirred for 2 h at the same temperature, cooled, and mercury was separated. The solution was filtered, and the resulting clear filtrate was acidified with 30% HCl solution (20 ml). After standing overnight in the refrigerator, the resulting precipitate was collected, washed with H_2O, and then dried to afford the crude product **9**.

(*E*)-3-[3-Methyl-1-phenyl-5-(phenylsulfanyl)-1*H*-pyrazol-4-yl]acrylic acid (8a). Yield 3.73 g (74%), yellow crystals, mp 155–158°C (Me_2CO). IR spectrum, ν, cm^{-1}: 3110, 3080, 2590, 1684, 1570, 1440, 1400, 1345, 1182, 782. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.29 (3H, s, CH_3); 6.50 (1H, d, *J* = 16.0, =CHCO); 7.11–7.30 (6H, m, H Ar); 7.45–7.49 (2H, m, H Ar); 7.76–7.80 (2H, m, H Ar); 7.78 (1H, d, *J* = 16.0, =CH); 10.09 (1H, s, COOH). ^{13}C NMR spectrum, δ, ppm: 13.1 (CH_3); 119.9 (=$\underline{C}$HCO); 121.8; 124.7; 125.1; 129.1; 129.2; 131.4; 131.6; 132.1; 139.3 (=CH); 142.0 (C-3); 145.2 (C-5); 167.6 (C=O). Found, %: C 67.82; H 4.82; N 8.45; S 9.38. $C_{19}H_{16}N_2O_2S$. Calculated, %: C 67.85; H 4.76; N 8.33; S 9.52.

(*E*)-2-Methyl-3-[3-methyl-1-phenyl-5-(phenylsulfanyl)-1*H*-pyrazol-4-yl]acrylic acid (8b). Yield 4.09 g (78%), pale-yellow crystals, mp 139–142°C (Me_2CO). IR spectrum, ν, cm^{-1}: 3115, 3053, 2610, 1682, 1600, 1480, 1400, 1340, 1273, 715. ^{1}H NMR spectrum, δ, ppm: 2.07 (3H, s, CH_3); 2.27 (3H, s, =CCH_3); 7.11–7.29 (5H, m, H, Ar); 7.33–7.47 (3H, m, H Ar); 7.76–7.78 (2H, m, H Ar); 7.80 (1H, s, =CH); 10.11 (1H, s, COOH). ^{13}C NMR spectrum, δ, ppm: 13.1 (CH_3); 15.8 (=$C\underline{C}H_3$); 121.8; 124.7; 125.1; 128.1 (=$\underline{C}CH_3$); 129.1; 129.2; 131.4; 131.6; 133.0; 139.3 (=CH); 142.0 (C-3); 145.2 (C-5); 172.8 (C=O). Found, %: C 68.47; H 5.30; N 8.14; S 9.15. $C_{20}H_{18}N_2O_2S$. Calculated, %: C 68.57; H 5.14; N 8.00; S 9.14.

(*E*)-3-[5-(Benzylsulfanyl)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl]acrylic acid (8c). Yield 4.25 g (81%), cream-colored crystals, mp 121–124°C (PhH). IR spectrum, ν, cm^{-1}: 3150, 3033, 2585, 1688, 1570, 1440, 1370, 1282, 771. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.26 (3H, s, CH_3); 4.40 (2H, s, CH_2); 6.48 (1H, d, *J* = 16.0, =CHCO); 7.16–7.20 (2H, m, H Ar); 7.27–7.28 (2H, m, H Ar); 7.37–7.39 (2H, m, H Ar); 7.44–7.47 (2H, m, H Ar); 7.76–7.79 (2H, m, H Ar) 7.78 (1H, d, *J* = 16.0, =CH); 10.16 (1H, s, COOH). ^{13}C NMR spectrum, δ, ppm: 13.1 (CH_3); 35.7 (CH_2); 119.9 (=$\underline{C}$HCO); 121.8; 124.7; 128.7; 128.9; 129.1; 129.2; 132.1; 137.1; 139.3 (=CH); 142.0 (C-3); 145.2 (C-5); 167.6 (C=O). Found, %: C 68.44; H 5.23; N 8.17; S 9.05. $C_{20}H_{18}N_2O_2S$. Calculated, %: C 68.57; H 5.14; N 8.00; S 9.14.

(*E*)-3-[5-(Benzylsulfanyl)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl]-2-methylacrylic acid (8d). Yield 4.15 g (76%), white plates, mp 165–168°C (PhH). IR spectrum, ν, cm^{-1}: 3205, 3030, 2965, 2670, 1685, 1585, 1470, 1440, 1394, 1270, 779. ^{1}H NMR spectrum, δ, ppm: 2.10 (3H, s, CH_3); 2.22 (3H, s, CH_3); 4.41 (2H, s, CH_2); 7.18–7.20 (2H, m, H Ar); 7.27–7.28 (2H, m, H Ar); 7.34–7.38 (2H, m, H Ar); 7.75–7.78 (2H, m, H Ar); 7.78 (1H, s, =CH); 10.22 (1H, s, COOH). ^{13}C NMR spectrum, δ, ppm: 13.1 (CH_3); 15.8 (=$C\underline{C}H_3$); 35.7 (CH_2); 121.8; 124.7 (C-4); 128.1 (=$\underline{C}CH_3$); 128.7; 128.9; 129.1; 129.2; 133.0; 137.1; 139.3 (=CH);

142.0 (C-3); 145.2 (C-5); 172.8 (C=O). Found, %: C 69.31; H 5.52; N 7.55; S 8.83. $C_{21}H_{20}N_2O_2S$. Calculated, %: C 69.23; H 5.49; N 7.69; S 8.79.

2-Methyl-4-[3-methyl-1-phenyl-5-(phenylsulfanyl)-pyrazol-4-yl]butanoic acid (9a). Yield 3.01 g (89%), pale-yellow solid, mp 142–145°C (Me_2CO). IR spectrum, ν, cm^{-1}: 3030, 2928, 2675, 1720, 1600, 1590, 1500, 1440, 1282, 1170, 768. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, s, CH_3); 2.57 (2H, t, *J* = 7.4, CH_2); 3.03 (2H, t, *J* = 7.4, CH_2CO); 7.14–7.24 (4H, m, H Ar); 7.26–7.32 (4H, m, H Ar); 7.71 (2H, m, H Ar); 10.52 (1H, s, COOH). ^{13}C NMR spectrum, δ, ppm: 13.2 (CH_3); 30.1 ($\underline{C}H_2CO$); 34.3 (CH_2); 121.8; 124.7; 125.2; 129.1; 129.2; 131.5; 131.7; 139.4; 142.1 (C-3); 145.2 (C-5); 177.7 (C=O). Found, %: C 67.48; H 5.35; N 8.15; S 9.55. $C_{19}H_{18}N_2O_2S$. Calculated, %: C 67.45; H 5.32; N 8.28; S 9.46.

2-Methyl-3-[3-methyl-1-phenyl-5-(phenylsulfanyl)-pyrazol-4-yl]propanoic acid (9b). Yield 3.16 g (90%), pale-yellow solid, mp 111–114°C (Me_2CO). IR spectrum, ν, cm^{-1}: 3050, 2930, 2664, 1715, 1600, 1590, 1440, 1400, 1266, 1170, 794. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, d, *J* = 6.8, $CHC\underline{H}_3$); 2.30 (3H, s, CH_3); 2.73 (1H, tq, *J* = 7.5, *J* = 6.8, CHCO); 2.90 (2H, d, *J* = 7.5, CH_2); 7.13–7.20 (4H, m, H Ar); 7.22–7.32 (4H, m, H Ar); 7.70–7.72 (2H, m, H Ar); 10.48 (1H, s, COOH). ^{13}C NMR spectrum, δ, ppm: 13.2 (CH_3); 16.8 ($C\underline{C}H_3$); 32.1 ($\underline{C}HCO$); 39.1 (CH_2); 121.8; 124.7 (C-4); 125.2; 129.1; 129.2; 131.5; 131.7; 139.4; 142.1 (C-3); 145.2 (C-5); 181.2 (C=O). Found, %: C 67.97; H 5.59; N 8.09; S 9.16. $C_{20}H_{20}N_2O_2S$. Calculated, %: C 68.18; H 5.68; N 7.95; S 9.09.

4-[(5-Benzylsulfanyl)-3-methyl-1-phenylpyrazol-4-yl]-2-methylbutanoic acid (9c). Yield 3.06 g (87%), pale-yellow plates, mp 137–140°C (PhH). IR spectrum, ν, cm^{-1}: 3065, 2933, 2670, 1730, 1600, 1590, 1440, 1400, 1255, 1170, 780. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.27 (3H, s, CH_3); 2.54 (2H, t, *J* = 7.4, CH_2); 2.95 (2H, t, *J* = 7.4, CH_2); 4.28 (2H, s, CH_2); 7.12–7.20 (3H, m, H Ar); 7.27–7.28 (3H, m, H Ar); 7.37–7.41 (2H, m, H Ar); 7.70–7.72 (2H, m, H Ar); 10.24 (1H, s, COOH). ^{13}C NMR spectrum, δ, ppm: 13.2 (CH_3); 30.1 (CH_2); 34.3 (CH_2); 35.7 (CH_2); 121.8; 124.7; 128.8; 128.9; 129.0; 129.2; 137.1; 139.4; 142.1 (C-3); 145.2 (C-5); 177.7 (C=O). Found, %: C 68.30; H 5.53; N 8.13; S 9.02. $C_{20}H_{20}N_2O_2S$. Calculated, %: C 68.18; H 5.68; N 7.95; S 9.09.

3-[(5-Benzylsulfanyl)-3-methyl-1-phenylpyrazol-4-yl]-2-methylpropanoic acid (9d). Yield 3.22 g (88%), white crystals, mp 139–142°C (Me_2CO). IR spectrum, ν, cm^{-1}: 3045, 2970, 2630, 1718, 1585, 1440, 1325, 1265, 1075, 760. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, d, *J* = 6.8, $CHC\underline{H}_3$); 2.28 (3H, s, CH_3); 2.73 (1H, tq, *J* = 7.0, *J* = 6.8, CHCO); 2.86 (2H, d, *J* = 7.0, CH_2); 4.28 (2H, s, CH_2); 7.13–7.20 (3H, m, H Ar); 7.26–7.28 (3H, m, H Ar); 7.37–7.41 (2H, m, H Ar); 7.69–7.72 (2H, m, H Ar); 10.09 (1H, s, COOH). ^{13}C NMR spectrum, δ, ppm: 13.2 (CH_3); 16.8 ($C\underline{C}H_3$); 32.1 ($\underline{C}H_2CO$); 35.7 (CH_2); 39.1 (CH_2); 121.8; 124.7; 128.8; 128.9; 129.1; 129.2; 137.1; 139.4; 142.1 (C-3); 145.2 (C-5); 181.2 (C=O). Found, %: C 68.80; H 6.17; N 7.62; S 8.55. $C_{21}H_{21}N_2O_2S$. Calculated, %: C 68.85; H 6.01; N 7.65; S 8.74.

Ring closure of heterocyclic esters 7a–d and acids 9a–d (General procedure). Method I. A solution of ester **7a**–**d** or acid **9a**–**d** (2 mmol) in CH_2Cl_2 (10 ml) was added dropwise to $AlCl_3$ (10 mmol) in $MeNO_2$ (100 mmol) over 10 min at ambient temperature. The mixture was stirred for the time given in Table 1. Afterward, the mixture was quenched with ice-cold 10% HCl solution (20 ml) and extracted with Et_2O (3×20 ml). The combined organic layer was washed twice with H_2O and 10% Na_2CO_3 (20 ml). After drying the organic layer over $MgSO_4$ and filtration, the solution was evaporated under reduced pressure to give the crude products **10**, **11 a**–**d**.

Method II. TfOH (12 mmol) was added dropwise to a cooled (0°C) solution of ester **7a**–**d** or acid **9a**–**d** (3 mmol) in DCE (20 ml), and the mixture was stirred with reflux for the time given in Table 1. Thereafter, the mixture was quenched by aqueous 50% $NaHCO_3$ solution (50 ml) at 0°C and the product was extracted with EtOAc (3×30 ml). The organic extracts were washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give the crude products **10**, **11 a**–**d**.

Method III. A mixture of ester **7a**–**d** or acid **9a**–**d** (3 mmol) and PPA (15 g) was heated on an oil bath at 160–180°C for the time given in Table 1. Completion of the reaction was monitored by TLC (EtOAc–hexane, 2:8). Then the mixture was cooled to room temperature and made alkaline by addition of 50% $NaHCO_3$ solution (40 ml) and then extracted with Et_2O (3×30 ml). The combined organics were washed with saturated brine solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the desired products **10**, **11 a**–**d**.

In all procedures, the crude residue was purified by flash chromatography (basic alumina, EtOAc–hexane, 1:4) to afford the pure tricyclic products **10**, **11 a**–**d**.

6-Methyl-4-phenyl-2-thia-4,5,8-triazatricyclo[9.4.0.0^{3,7}]-pentadeca-1(11),3(7),5,12,14-pentaen-10-one (10a). Yield 0.52 g (81%, method I), 0.75 g (78%, method II), 0.70 g (73%, method III), pale-yellow crystals, mp 184°C (decomp., Me_2CO). IR spectrum, ν, cm^{-1}: 3412, 3077, 2930, 1700, 1600, 1590, 1440, 1370, 1289, 779. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.14 (3H, s, CH_3); 4.65 (2H, s, 5-CH_2); 7.12–7.16 (1H, m, H Ar); 7.41–7.47 (3H, m, H Ar); 7.63–7.67 (4H, m, H Ar); 7.89–7.92 (1H, m, H Ar); 9.93 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 11.4 (CH_3); 49.6 (C-5); 121.8; 124.7; 126.9; 127.5; 129.2; 129.4; 129.8; 131.5; 137.5; 138.3; 139.4; 152.0; 155.7; 191.7 (C=O). Found, %: C 67.41; H 4.80; N 12.86; S 9.78. $C_{18}H_{15}N_3OS$. Calculated, %: C 67.28; H 4.67; N 13.08; S 9.96.

6-Methyl-4-phenyl-2-thia-4,5,8-triazatricyclo[10.4.0.0^{3,7}]-hexadeca-1(12),3(7),5,13,15-pentaen-11-one (10b). Yield 0.56 g (84%, method I), 0.78 g (80%, method II), 0.74 g (75%, method III), yellow crystals, mp 141–144°C (Me_2CO). IR spectrum, ν, cm^{-1}: 3420, 3030, 2956, 1696, 1600, 1590, 1480, 1440, 1350, 1280, 788. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.13 (3H, s, CH_3); 2.81 (2H, ddd, *J* = 14.0, *J* = 8.8, *J* = 5.8, 6-CH_2); 3.50 (2H, ddd, *J* = 9.2, *J* = 8.8, *J* = 1.4, 5-CH_2); 7.12–7.16 (1H, m, H Ar); 7.41–7.45 (2H, m, H Ar); 7.46–7.51 (1H, m, H Ar); 7.54–7.59 (1H, m, H Ar); 7.62–7.65 (2H, m, H Ar); 7.70–7.72 (1H,

m, H Ar); 7.85–7.87 (1H, m, H Ar); 10.22 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 11.4 (CH_3); 38.9 (C-5); 43.1 (C-6); 121.8; 124.7; 126.9; 127.5; 129.2; 129.4; 129.8; 131.5; 137.5; 138.3; 139.4; 152.0; 155.7; 199.2 (C=O). Found, %: C 68.20; H 5.19; N 12.50; S 9.33. $C_{19}H_{17}N_3OS$. Calculated, %: C 68.05; H 5.07; N 12.53; S 9.55.

7-Methyl-5-phenyl-3-thia-5,6,9-triazatricyclo[10.4.0.0^{4,8}]-hexadeca-1(12),4(8),6,13,15-pentaen-11-one (10c). Yield 0.51 g (78%, method I), 0.72 g (72%, method II), 0.69 g (70%, method III), yellow solid, mp 154–157°C (Me_2CO). IR spectrum, ν, cm^{-1}: 3390, 3040, 2973, 1713, 1600, 1590, 1470, 1384, 1260, 785. ^{1}H NMR spectrum, δ, ppm: 2.15 (3H, s, CH_3); 4.55 (2H, s, 11-CH_2); 4.67 (2H, s, 5-CH_2); 7.17–7.26 (2H, m, H Ar); 7.34–7.39 (3H, m, H Ar); 7.49–7.51 (1H, m, H Ar); 7.62–7.64 (2H, m, H Ar); 7.90–7.93 (1H, m, H Ar); 10.14 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 11.4 (CH_3); 35.7 (C-11); 49.6 (C-5); 121.8; 124.7; 125.9; 128.4; 129.2; 130.5; 132.4; 133.0; 133.2; 137.5; 139.4; 152.0; 155.7; 195.0 (C=O). Found, %: C 68.09; H 5.22; N 12.58; S 9.35. $C_{19}H_{17}N_3OS$. Calculated, %: C 68.05; H 5.07; N 12.53; S 9.55.

7-Methyl-5-phenyl-3-thia-5,6,9-triazatricyclo[11.4.0.0^{4,8}]-heptadeca-1(13),4(8),6,14,16-pentaen-12-one (10d). Yield 0.54 g (79%, method I), 0.82 g (81%, method II), 0.77 g (75%, method III), white crystals, mp 170–173°C (EtOH). IR spectrum, ν, cm^{-1}: 3410, 3050, 2920, 1714, 1600, 1585, 1470, 1385, 1280, 779. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.15 (3H, s, CH_3); 2.76 (2H, ddd, *J* = 15.4, *J* = 10.1, *J* = 3.3, 6-CH_2); 3.34 (2H, ddd, *J* = 11.5, *J* = 10.1, *J* = 2.0, 5-CH_2); 4.09 (2H, s, 12-CH_2); 7.19–7.26 (2H, m, H Ar); 7.34–7.38 (3H, m, H Ar); 7.46–7.51 (1H, m, H Ar); 7.62–7.64 (2H, m, H Ar); 7.75–7.78 (1H, m, H Ar); 9.81 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 11.4 (CH_3); 35.7 (C-12); 38.9 (C-5); 43.1 (C-6); 121.8; 124.7; 125.9; 128.4; 129.2; 130.5; 132.4; 133.0; 133.2; 137.5; 139.4; 152.0; 155.7; 199.2 (C=O). Found, %: C 68.59; H 5.28; N 12.17; S 9.02. $C_{20}H_{19}N_3OS$. Calculated, %: C 68.76; H 5.44; N 12.03; S 9.16.

6-Methyl-4-phenyl-2-thia-4,5-diazatricyclo[9.4.0.0^{3,7}]-pentadeca-1(11),3(7),5,12,14-pentaen-10-one (11a). Yield 0.52 g (83%, method I), 0.71 g (74%, method II), 0.71 g (75%, method III), yellow crystals, mp 190°C (decomp., PhH). IR spectrum, ν, cm^{-1}: 3015, 2940, 1688, 1600, 1485, 1440, 1389, 1245, 770. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, s, CH_3); 2.90 (2H, ddd, *J* = 16.8, *J* = 6.3, *J* = 2.1, 4-CH_2); 3.19 (2H, ddd, *J* = 10.2, *J* = 6.3, *J* = 2.1, 5-CH_2); 7.17–7.19 (1H, m, H Ar); 7.28–7.32 (2H, m, H Ar); 7.37–7.39 (1H, m, H Ar); 7.56–7.58 (1H, m, H Ar); 7.66–7.73 (3H, m, H Ar); 7.89–7.91 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 13.2 (CH_3); 30.1 (C-4); 38.8 (C-5); 121.8; 124.7; 126.9; 127.5; 129.2; 129.3; 129.4; 129.8; 131.5; 138.3; 139.4; 142.1; 145.2; 199.2 (C=O). Found, %: C 71.29; H 5.17; N 8.65; S 10.08. $C_{19}H_{16}N_2OS$. Calculated, %: C 71.25; H 5.00; N 8.75; S 10.00.

6,9-Dimethyl-4-phenyl-2-thia-4,5-diazatricyclo[9.4.0.0^{3,7}]-pentadeca-1(11),3(7),5,12,14-pentaen-10-one (11b). Yield 0.53 g (79%, method I), 0.76 g (82%, method II), 0.75 g (80%, method III), yellow needles, mp 152–155°C (EtOAc). IR spectrum, ν, cm^{-1}: 3042, 2938, 1695, 1600, 1485, 1440, 1385, 1289, 788. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.14 (3H, d, *J* = 6.6, 5-CH_3); 2.31 (3H, s, CH_3); 3.06–3.08 (2H, m, 4-CH_2); 3.24–3.29 (1H, m, 5-CH); 7.15–7.20 (1H, m, H Ar); 7.28–7.32 (2H, m, H Ar); 7.37–7.40 (1H, m, H Ar); 7.56–7.58 (1H, m, H Ar); 7.66–7.75 (3H, m, H Ar); 7.89–7.91 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 13.2 (CH_3); 15.7 (CH_3); 32.1 (C-4); 44.2 (C-5); 121.8; 124.7; 126.9; 127.5; 129.2; 129.3; 129.4; 129.8; 131.5; 138.3; 139.4; 142.1; 145.2; 199.9 (C=O). Found, %: C 71.92; H 5.40; N 8.32; S 9.37. $C_{20}H_{18}N_2OS$. Calculated, %: C 71.85; H 5.38; N 8.38; S 9.58.

7-Methyl-5-phenyl-3-thia-5,6-diazatricyclo[10.4.0.0^{4,8}]-hexadeca-1(12),4(8),6,13,15-pentaen-11-one (11c). Yield 0.51 g (81%, method I), 0.80 g (77%, method II), 0.75 g (75%, method III), yellow needles, mp 161–163°C (EtOAc). IR spectrum, ν, cm^{-1}: 3025, 2940, 1690, 1600, 1580, 1445, 1370, 1240, 772. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.27 (3H, s, CH_3); 2.99–3.05 (4H, m, 4,5-CH_2); 4.64 (2H, s, 11-CH_2); 7.15–7.22 (2H, m, H Ar); 7.36–7.41 (3H, m, H Ar); 7.46–7.50 (1H, m, H Ar); 7.69–7.71 (2H, m, H Ar); 7.80–7.82 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 13.2 (CH_3); 30.1 (C-4); 35.7 (C-5); 38.8 (C-11); 121.8; 124.7; 125.9; 128.4; 129.2; 130.5; 132.4; 133.0; 133.2; 139.4; 142.1; 145.2; 206.8 (C=O). Found, %: C 71.99; H 5.51; N 8.24; S 9.45. $C_{20}H_{18}N_2OS$. Calculated, %: C 71.85; H 5.38; N 8.38; S 9.58.

7,10-Dimethyl-5-phenyl-3-thia-5,6-diazatricyclo-[10.4.0.0^{4,8}]hexadeca-1(12),4(8),6,13,15-pentaen-11-one (11d). Yield 0.62 g (85%, method I), 0.82 g (80%, method II), 0.76 g (73%, method III), white crystals, mp 150–153°C (Me_2CO). IR spectrum, ν, cm^{-1}: 3038, 2968, 1700, 1600, 1575, 1440, 1383, 1270, 1162, 779. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.17 (3H, d, *J* = 6.6, 5-CH_3); 2.28 (3H, s, CH_3); 3.01 (2H, d, *J* = 6.0, CH_2); 3.50–3.70 (1H, m, 5-CH); 4.23 (1H, d, *J* = 16.6, 11-CH_2); 4.44 (1H, d, *J* = 16.6, 11-CH_2); 7.13–7.17 (1H, m, H Ar); 7.28–7.30 (1H, m, H Ar); 7.34–7.41 (3H, m, H Ar); 7.46–7.50 (1H, m, H Ar); 7.69–7.71 (2H, m, H Ar); 7.74–7.76 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 13.2 (CH_3); 15.7 (CH_3); 32.1 (C-4); 35.7 (C-5); 44.2 (C-11); 121.8; 124.7; 125.9; 128.4; 129.2; 130.5; 132.4; 133.0; 133.2; 139.4; 142.1; 145.2; 199.9 (C=O). Found, %: C 72.40; H 5.91; N 7.93; S 9.32. $C_{21}H_{20}N_2OS$. Calculated, %: C 72.41; H 5.74; N 8.04; S 9.19.

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of all synthesized compounds is available at the journal website at http://link.springer.com/journal/10593.

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References

1. (a) Koul, A.; Arnoult, E.; Lounis, N.; Guillemont, J.; Andries, K. *Nature* **2011**, *469*, 483. (b) Antonow, D.; Thurston, D. E. *Chem Rev.* **2011**, *111*, 2815. (c) *Dictionary of Alkaloids*; Buckingham, J.; Baggaley, K. H.; Roberts, A. D.; Szabó, L. F., Eds.; CRC Press, 2010, 2nd ed. (d) *Modern Alkaloids: Structure*, *Isolation*, *Synthesis*, *and Biology*; Fattorusso, E.;

Taglialatela-Scafati, O. Eds.; Wiley-VCH: Weinheim, 2008. (e) Passler, U. In *The Alkaloids*; Knolker, H.-J., Ed.; Academic: New York, 2011, Vol. 70, p. 79. (f) Garg, N.; Chandra, T.; Jain, A. B.; Kumar, A. *Eur. J. Med. Chem*. **2010**, *45*, 1529. (g) Hall, J. E.; Matlock, J. V.; Ward, J. W.; Gray, K. V.; Clayden, J. *Angew. Chem*., *Int. Ed.* **2016**, *55*, 11153.

2. (b) Wagman, A. S.; Wentland, M. P. In *Comprehensive Medicinal Chemistry II*; Taylor, J. B.; Triggle, D. J., Eds.; Elsevier Ltd.: Oxford, 2007, Vol. 7, p. 567. (c) Kresze, G. In *Sulfur*, *Its Significance for Chemistry*, *for the Geo-*, *Bio- and Cosmosphere and Technology*; Müller, A.; Krebs, B., Eds.; Elsevier: Amsterdam, 1984, Vol. 5, p. 93. (d) Hagiwara, M.; Adachi-Akahane, S.; Nagao, T. *Eur. J. Pharmacol.* **2003**, *466*, 63. (e) Arias, H. R.; Targowska-Duda, K. M.; Feuerbach, D.; Sullivan, C. J.; Maciejewski, R.; Jozwiak, K. *Neurochem. Int*. **2010**, *56*, 642. (f) Shen, M.; Driver, T. G. *Org. Lett.* **2008**, *10*, 3367. (g) Thevis, M.; Opfermann, G.; Schänzer, W. *J. Anal. Toxicol*. **2003**, *27*, 53. (h) Tricco, A. C.; Soobiah, C.; Berliner, S.; Ho, J. M.; Ng, C. H.; Ashoor, H. M.; Chen, M. H.; Hemmelgarn, B.; Straus, S. E. *CMAJ* **2013**, *185*, 1393. (i) Smith, R; Schwartz, A. *N. Engl. J. Med.* **1984**, *310*, 1327. (j) Tatsumi, M.; Groshan, K.; Blakely, R. D.; Richelson, E. *Eur. J. Pharmacol*. **1997**, *340*, 249.
3. (a) Ryabchuk, P.; Matheny, J. P.; Rubina, M.; Rubin, M. *Org. Lett.* **2016**, *18*, 6272. (b) Arya, K.; Dandia, A. *Bioorg. Med. Chem. Lett.* **2008**, *28*, 114. (c) O'Neil, I. A.; Murray, C. L.; Hunter, R. C.; Kalindjian, S. B.; Jenkins, T. C. *Synlett* **1997**, 75. (d) Kang, G.; Yamagami, M.; Vellalath, S.; Romo, D. *Angew. Chem.*, *Int. Ed.* **2018**, *57*, 6527. (e) Majumdar, K. C. *RSC Adv.* **2011**, *1*, 1152. (f) Donald, J. R.; Unsworth, W. P. *Chem.–Eur. J.* **2017**, *23*, 8780. (g) Li, R.; Farmer, P. S.; Wang, J.; Boyd, R. J.; Cameron, T. S.; Quilliam, M. A.; Walter, J. A.; Howlett, S. E. *Drug Des. Discovery* **1995**, *12*, 337. (h) Bariwal, J. B.; Upadhyay, K. D.; Manvar, A. T.; Trivedi, J. C.; Singh, J. S.; Jain, K. S.; Shah, A. K. *Eur. J. Med. Chem*. **2008**, *43*, 2279. (i) Gyömöre, Á.; Csámpai, A.; Holzbauer, T.; Czugler, M. *Tetrahedron* **2011**, *67*, 2979. (j) Arnold, L. A.; Luo, W.; Guy, R. K. *Org Lett.* **2004**, *6*, 3005. (k) Incerti, M.; Acquotti, D.; Sandor, P.; Vicini, P. *Tetrahedron* **2009**, *65*, 7487.
4. Michaut, A.; Rodriguez, J. *Angew. Chem.*, *Int. Ed.* **2006**, *45*, 5740.
5. Limanto, J.; Snapper, M. L. *J. Am. Chem. Soc*. **2000**, *122*, 8071.
6. Ayala, S. L. G.; Stashenko, E.; Palma, A.; Bahsas, A.; Amaro-Luis, J. M. *Synlett* **2006**, 2275.
7. Ha, H.-J.; Choi, C.-J.; Ahn, Y.-G.; Yun, H.; Dong, Y.; Lee, W. K. *J. Org. Chem*. **2000**, *65*, 8384.
8. Anand, A.; Singh, P.; Mehra, V.; Amandeep; Kumar, V.; Mahajan, M. P. *Tetrahedron Lett.* **2012**, *53*, 2417.
9. Upadhayaya, R. S.; Lahore, S. V.; Sayyed, A. Y.; Dixit, S. S.; Shinde, P. D.; Chattopadhyaya, J. *Org. Biomol. Chem.* **2010**, *8*, 2180.
10. Ylijoki, K. E. O.; Stryker, J. M. *Chem. Rev.* **2012**, *113*, 2244.
11. (a) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (b) Müller, T. J. *Synthesis* **2012**, 159.
12. Goswami, P.; Borah, A. J.; Phukan, P. *J. Org. Chem.* **2014**, *80*, 438.
13. Curran, D. P.; Porter, N. A.; Giese, B.; Eliel, E. L. *Stereochemistry of Radical Reactions: Concepts*, *Guidelines*, *and Synthetic Applications*; VCH: New York, 1996.
14. Basavaiah, D.; Reddy, G. C. *ARKIVOC* **2016**, (ii), 172.
15. Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.
16. Ihara, M. *Chem. Pharm. Bull.* **2006**, *54*, 765.
17. (a) Ried, W.; Marx, W. *Chem. Ber.* **1957**, *90*, 2683. (b) Khatik, G. L.; Kumar, R.; Chakraborti, A. K. *Synthesis* **2007**, 541. (c) Shcherbakova, I. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Pergamon Press: New York, 2008, Vol. 14, p. 255. (d) Calvo, L. A.; Gonzalez-Ortega, A.; Marcos, R.; Perez, R. M.; Sanudo, M. C. *Tetrahedron* **2008**, *64*, 3691. (e) Levai; Jeko, J. *ARKIVOC* **2008**, (xvii), 234.
18. (a) Paquette, L. A.; Barton, W. R. S.; Gallucci, J. C. *Org. Lett*. **2004**, *6*, 1313. (b) Karsch, S.; Freitag, D.; Schwab, P.; Metz, P. *Synthesis* **2004**, 1696. (c) Chihab-Eddine, A.; Daich, A.; Jilale, A.; Decroix, B. *J. Heterocycl. Chem.* **2000**, *37*, 1543. (d) Freitag, D.; Schwab, P.; Metz, P. *Tetrahedron Lett*. **2004**, *45*, 3589.
19. (a) Alvarez, M.; Joule, J. A. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: New York, 2001, Vol. 57, p. 235. (b) Alper, K. R.; Lotsof, H. S.; Kaplan, C. D. *J. Ethnopharmacol*. **2008**, *115*, 9. (c) Baumann, M. H.; Rothman, R. B.; Pablo, J. P.; Mash, D. C. *J. Pharmacol. Exp. Ther*. **2001**, *297*, 531. (d) Noguchi, Y.; Hirose, T.; Furuya, Y.; Ishiyama, A.; Otoguro, K.; Omura, S.; Sunazuka, T. *Tetrahedron Lett*. **2012**, *53*, 1802.
20. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.
21. (a) Parenty, A.; Moreau, X.; Campagne, J. M. *Chem. Rev.* **2006**, *106*, 911. (b) Kobayashi, Y.; Asano, M.; Yoshida, S.; Takeuchi, A. *Org. Lett.* **2005**, *7*, 1533. (c) Buszek, K. R.; Jeong, Y.; Sato, N.; Still, P. C.; Muiño, P. L.; Ghosh, I. *Synth. Commun.* **2001**, *31*, 1781. (d) Nagata, T.; Nakagawa. M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484. (e) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535. (f) Petri, A. F.; Bayer, A.; Maier, M. E. *Angew. Chem.*, *Int. Ed.* **2004**, *43*, 5821. (g) Trost, B. M.; Chisholm, J. D. *Org. Lett.* **2002**, *4*, 3743. (h) Marcantoni, E.; Massaccesi, M.; Petrini, M.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2000**, *65*, 4553.
22. Bates, D. K.; Li, X.; Jog, P. V. *J. Org. Chem*. **2004**, *69*, 2750.
23. Lu, S. M.; Alper, H. *J. Am. Chem. Soc*. **2005**, *127*, 14776.
24. Pei, Y.; Lilly, M. J.; Owen, D. J.; D'Souza, L. J.; Tang, X. Q.; Yu, J.; Nazarbaghi, R.; Hunter, A.; Anderson, C. M.; Glasco, S.; Ede, N. J.; James, I. W.; Maitra, U.; Chandrasekaran, S.; Moos, W. H.; Ghosh, S. S. *J. Org. Chem*. **2003**, *68*, 92.
25. Mukherjee, C.; Biehl, E. *Heterocycles* **2004**, *63*, 2309.
26. Doxsee, K. M. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996, Vol. 9, p. 527.
27. Griesbeck, A. G.; Oelgemöller, M.; Lex, J.; Haeuseler, A.; Schmittel, M. *Eur. J. Org. Chem.* **2001**, 1831.
28. Bates, D. K.; Li, K. *J. Org. Chem*. **2002**, *67*, 8662.
29. Moormann, A. E.; Metz, S.; Toth, M. V.; Moore, W. M.; Jerome, G.; Kormeier, C.; Manning, P.; Hansen, D. W.; Pitzele, B. S.; Webber, R. K. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 2651.
30. Maraccini, S.; Miguel, D.; Torroba, T.; Garcìa-Valverde, M., *J. Org. Chem.* **2003**, *68*, 3315.
31. Campiani, G.; Nacci, V.; Fiorini, I.; De Filippis, M. P.; Garofano, A.; Ciani, S. M.; Greco, G.; Novellino, E.; Manzoni, C.; Pennini, T. *Eur. J. Med. Chem*. **1997**, *32*, 241.
32. Kuti, M.; Rábai, J.; Kapovits, I.; Jalsovszky, I.; Argay, G.; Kálmán, A.; Párkányi, L. *J. Mol. Struct*. **1996**, *382*, 1
33. Federsel, H. J.; Glassare, G.; Högström, K.; Wiestal, J.; Zinko, B.; Odman, C. *J. Org. Chem*. **1995**, *60*, 2597.
34. Sashida, H.; Tsuchiya, T. *Heterocycles* **1984**, *22*, 1303.
35. Manhas, M. S.; Amin, S. G.; Bose, A. K. *Heterocycles* **1976**, *5*, 669.
36. (a) Barclay, L. R. C. In *Friedel–Crafts and Related Reactions*; Olah, G. A., Ed.; Wiley Interscience: New York, 1964, Vol. II,

Chap. 22, p. 786. (b) Ross, J.; Xiao, J. L. *Green Chem*. **2002**, *4*, 129. (c) Simone, F. D.; Andres, J.; Torosantucci, R.; Waser, J. *Org. Lett.* **2009**, *11*, 1023. (d) Stang, E. M.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 14892. (e) Li, S.; Chiu, P. *Tetrahedron Lett.* **2008**, *49*, 1741. (f) Jorgensen, K. A. *Synthesis* **2003**, 1117. (g) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc*. **1995**, *117*, 10391. (h) Zhao, Y.-L.; Lou, Q.-X.; Wang, L.-S.; Hu, W.-H.; Zhao, J.-L. *Angew. Chem.*, *Int. Ed.* **2017**, *56*, 338. (i) Pilli, R. A.; Victor, M. M. *Tetrahedron Lett*. **1998**, *39*, 4421. (j) Fürstner, A. *Top. Catal.* **1997**, *4*, 285. (k) Anand, R. V.; Baktharaman, S.; Singh, V. K. *J. Org. Chem*. **2003**, *68*, 3356. (l) Wales, S. M.; Walker, M. M.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2558.

37. Galli, C.; Mandolini, L. Eur. *J. Org. Chem*. **2000**, 3117.
38. (a) Katritzky, A. R.; Xu, Y.-J.; He, H.-Y. *J. Chem. Soc.*, *Perkin Trans. 1* **2002**, 592. (b) Cul, A.; Daich, A.; Decroix, B.; Sanz, G.; Van Hijfte, L. *Heterocycles* **2004**, *64*, 33. (c) Mamouni, A.; Daich, A.; Decroix, B. *Synth. Commun*. **1997**, *27*, 2241. (d) Pigeon, P.; Decroix, B. *J. Heterocycl. Chem*. **1997**, *34*, 375. (e) Oniciu, D. C. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Pergamon Press: New York, 2008, Vol. 14, p. 1. (f) Chen, L.; Zhou, F.; Shi, T.-D.; Zhou, J. *J. Org. Chem.* **2012**, *77*, 4354. (g) Netchitailo, P.; Othman, M.; Decroix, B. *J. Heterocycl. Chem*. **1997**, *34*, 321.
39. (a) Abd El-Aal, H. A. K.; Khalaf, A. A. *Aust. J. Chem.* **2019**, *72*, 276. (b) Abd El-Aal, H. A. K. *ARKIVOC* **2018**, (iii), 45. (c) Abd El-Aal, H. A. K. *Aust. J. Chem*. **2017**, *70*, 1082. (d) Abd El-Aal, H. A. K.; Khalaf, A. A. *ARKIVOC* **2019**, (v), 265. (e) Abd El-Aal, H. A. K.; Khalaf, A. A. *ARKIVOC* **2013**, (iv), 306. (f) Abd El-Aal, H. A. K.; Khalaf, A. A. *Chem. Heterocycl. Compd.* **2019**, *55*, 632. [*Khim. Geterotsikl. Soedin.* **2019**, *55*, 632.] (g) Abd El-Aal, H. A. K.; Khalaf, A. A.; El-Khawaga, A. M. A. *J. Heterocycl. Chem.* **2014**, *51*, 262. (h) Abd El-Aal, H. A. K. *ARKIVOC* **2015**, (v), 230.
40. (a) Olah, G. A.; Krishnamurti, R.; Surya Prakash, G. K. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 3, p. 293. (b) Roberts, R. M.; Khalaf, A. A. *Friedel–Crafts Chemistry: A Century of Discovery*; Marcel Dekker: New York, 1984. (c) Olah, G. A. In *Friedel–Crafts Chemistry*; Olah, G. A., Ed.; Wiley: New York, 1973. (d) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199. (e) Terrasson, V.; Marcia de Figueiredo, R.; Campagne, J. M. *Eur. J. Org. Chem*. **2010**, *14*, 2635. (f) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev*. **2008**, *108*, 2903.
41. (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier: Oxford, 1996, Vol. 3, p. 1. (b) Brahmbhatt, G. C.; Sutariya, T. R.; Atara, H. D.; Parmar, N. J.; Gupta, V. K.; Lagunes, I.; Padrón, J. M.; Murumkar, P. R.; Yadav, M. R. *Mol. Diversity* **2020**, *24*, 355.
42. Dauben, W. G.; Tilles, H. *J. Am. Chem. Soc.* **1950**, *72*, 3185.
43. (a) Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214. (b) Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry. Part B: Reactions and Synthesis*; Kluwer Academic/Plenum Publishers: New York, 2001, 4th ed. (c) Olah, G. A.; Kobayashi, S. *J. Am. Chem. Soc.* **1971**, *93*, 6994. (d) Huffman, J. W.; Smith, V. J.; Padgett, L. W. *Tetrahedron* **2008**, *64*, 2104. (e) Tan, L. K.; Brownstein, S. *J. Org. Chem.* **1983**, *48*, 302. (f) Golebiewski, W.; Marek; Gucma, M. *Synthesis* **2007**, 3599.
44. Choi, S.; Brown, H. C. *J. Am. Chem. Soc*. **1963**, *85*, 2596.
45. March, J. *Advanced Organic Chemistry*; John Wiley and Sons: New York, 1999–2000, 4th ed.