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Diastereoselective intramolecular *hetero* Diels–Alder approach towards polycyclic heterocycles

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Abstract—Several different heterocyclic aldehydes, derived from pyrazole, pyrimidine, pyridine, indole and thiazole, were converted to polyheterocyclic compounds containing four to seven rings. The key steps in the sequence were a Knoevenagel condensation of the aldehyde and a heterocyclic carbonyl compound, such as pyrazolone and isoxazolone, followed by an intramolecular *hetero* Diels–Alder reaction. Most final products were isolated with high yield and diastereoselecivity. The isoxazolo fused cycloadducts formed interesting spiro-adducts upon heating. The *cis* nature of the bridging hydrogens of the heterocycles was evidenced by X-ray diffraction analysis.† © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

In a series of publications by Tietze et al.,[1] the use of the intramolecular *hetero* Diels–Alder reaction was described to construct fused heterocycles, which in many cases are formed with high diastereoselectivity. Furthermore, the *hetero* Diels–Alder reaction has been established by Tietze[2] and others[3] as a powerful tool in natural product synthesis. We recently communicated[4] an application of this reaction, starting from 5-chloropyrazole-4-aldehydes and leading to tetracyclic pyrazoles. We will now prove the generality of this reaction sequence by varying the heterocyclic building blocks, which will result in a number of unprecedented new polyheterocycles.

2. Results

Heterocyclic β-chloro aldehydes are interesting synthons, which can be transformed in a number of ways to fused heterocycles by using the reactivity of the chlorine for nucleophilic substitution in combination with the multitude of transformations possible starting from the aldehyde function.[5] Thus, an unsaturated side chain can be smoothly introduced by substitution of 5-chloro-4-formyl-1-phenylpyrazoles **1a**,**b** with prenyl thiolate. The latter have been prepared by chloroformylation of the appropriate pyrazolone.[7] The resulting aldehydes **2a**,**b** and their analogs have been previously used by us as a starting point for intramolecular 1,3-dipolar cycloadditions, affording several new polyheterocyclic systems.[6]

Following the Tietze protocol of domino Knoevenagel condensation/intramolecular *hetero* Diels–Alder cycloaddition, we condensed pyrazoles **2a** and **2b** with pyrazolones **5a**–**d**. The intermediate Knoevenagel adducts **3a**–**f** could be observed by TLC control and the appearance of an orange–yellow color. They were not isolated but cyclized upon reflux in acetonitrile to the *cis*-fused tetracyclic bispyrazoles **4a**–**e** with high yield (80–90%) and diastereoselectivity (>99%) (Scheme 1). The yield for **4f** was significantly lower (32%) which is probably due to steric hindrance between the two phenyl groups at the 3-positions of the pyrazole rings. The *cis* nature of the bridging hydrogens of the tetracycles **4a**–**f** was strongly supported by their coupling constant of 4 Hz in the ^{1}H NMR spectrum. This agrees well with the results found for similar benzo fused systems described by Tietze and coworkers.[1]

To get confirmation of the *cis*-fused structure of these polyheterocyclic compounds, X-ray analysis was carried out. The molecular structure of **4a** is depicted in Fig. 1 and is largely determined by the conformation of the central ring system. Both pyrazole rings are planar and make an angle of 67.9(3)° to each other, while the six-membered rings adopt a half-chair conformation. In order to reduce the steric hindrance with the central ring system, both phenyl rings are rotated by about 35° out of the plane of the pyrazole

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† Crystallographic data (excluding structure factors) ending pages for the structures in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 169436, CCDC 169437 and CCDC 169438. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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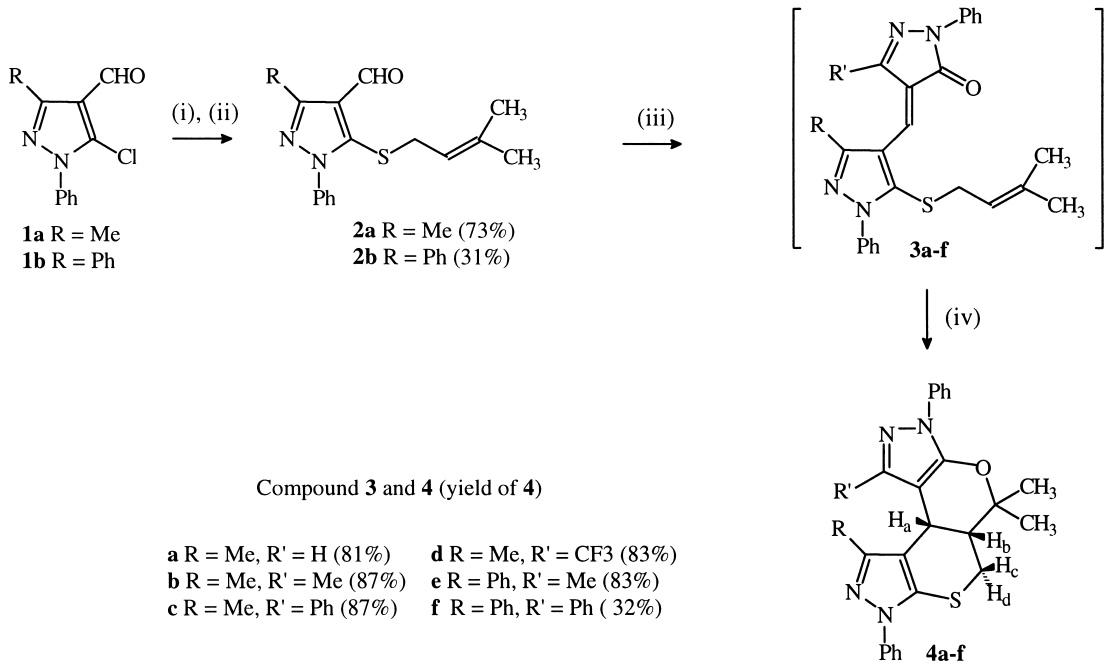


Scheme 1. (i) 4-Bromo-2-methyl-2-butene, thiourea, EtOH, reflux, (ii) NaOH, EtOH, reflux, (iii) pyrazolone **5a**–**d**, EDDA, CH_3CN, 30′ rt, (iv) hours reflux as indicated in Section 3.

rings. Due to the steric hindrance between the CF_3 and methyl groups in compound **4d**, the angle between both pyrazole rings is increased to 83.7(4)° (Fig. 2). The unit cell of **4d** (Fig. 2) contains three large voids (534 $Å^3$ each) which are surrounded by the phenyl substituents, and are possible solvent areas. Indeed, the maxima in the final difference density suggest the occurrence of disordered solvent molecules in this region. In **4a** (Fig. 1), the asymmetric unit contains a molecule of water which forms an infinite chain of water through the whole crystal.

In the same way, *N*,*N*′-dimethylbarbituric acid **5e** was condensed with **2a** to give tetracyclic pyrimidine **6** in excellent yield (92%) (Scheme 2). The reaction of **2a** with oxazolone **5f** took a slightly different course. The expected adduct **7** was indeed formed and could be isolated, but on prolonged reflux in acetonitrile (5 days) or toluene (3 days) **7** was completely transformed in a mixture of isomers **8a**,**b** (Scheme 2). The two products **8a** and **8b** (ratio 9:11) could be separated without problems by column chromatography, giving a combined yield of 93%. The examination of the NMR spectra showed that a ring contraction of the isoxazole **7** to the (2*H*)azirines **8a**,**b** had occurred. The ^1H NMR spectra of **7**, **8a**,**b** again were in accordance with a *cis* fusion of the pyran and thiopyran rings. The ^{13}C NMR spectra of **8a** and **8b** displayed typical signals for the azirine sp^3 carbon at 37.1 and 40.5 ppm, and the azirine sp^2 carbon at 171.1 and 172.0 ppm, respectively. The IR spectra of **8a** and **8b** show the ester C=O stretching at 1722 and 1716 cm^{-1}, respectively. 2D-HETCOR spectra were needed to assign the structure of **8a** or **8b** and we concluded the following. The methyl group of pyrazole **8a** resonates at rather high field, with δ 1.60 ppm, while the corresponding methyl peak for **8b** was found back at δ 2.02 ppm, which is a normal value

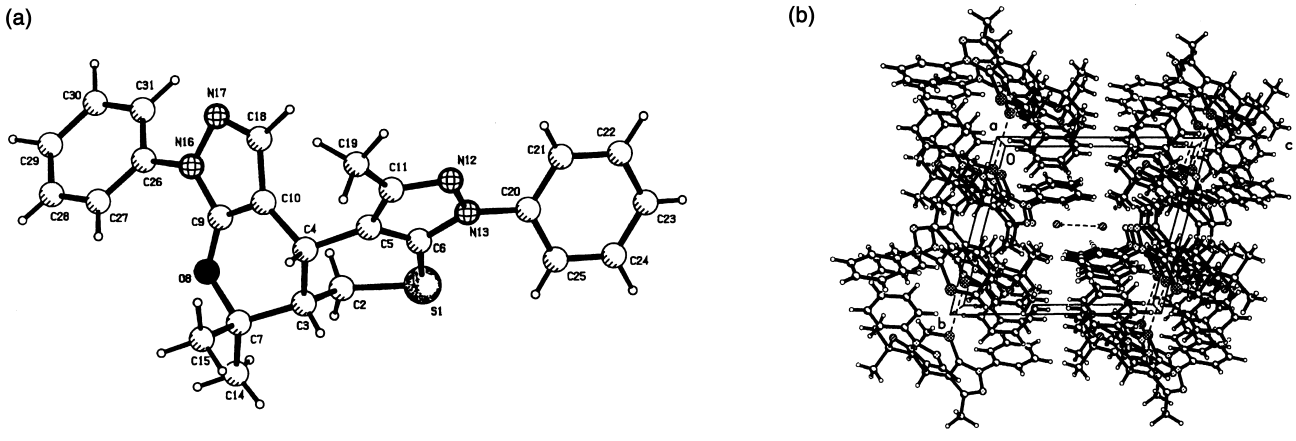


Figure 1. (a) Molecular structure of compound **4a**. (b) Crystal packing of compound **4a**.

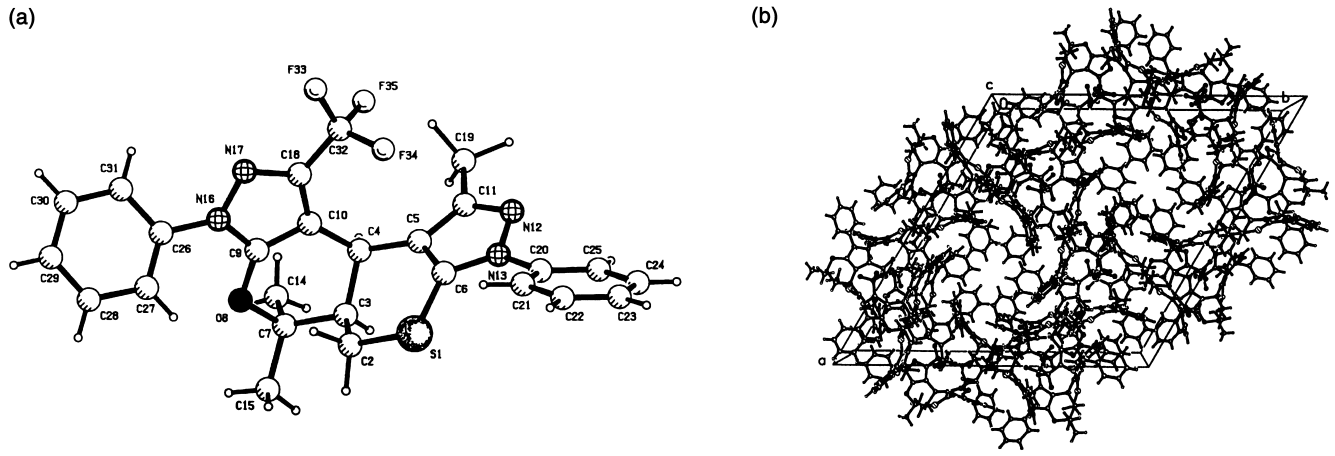


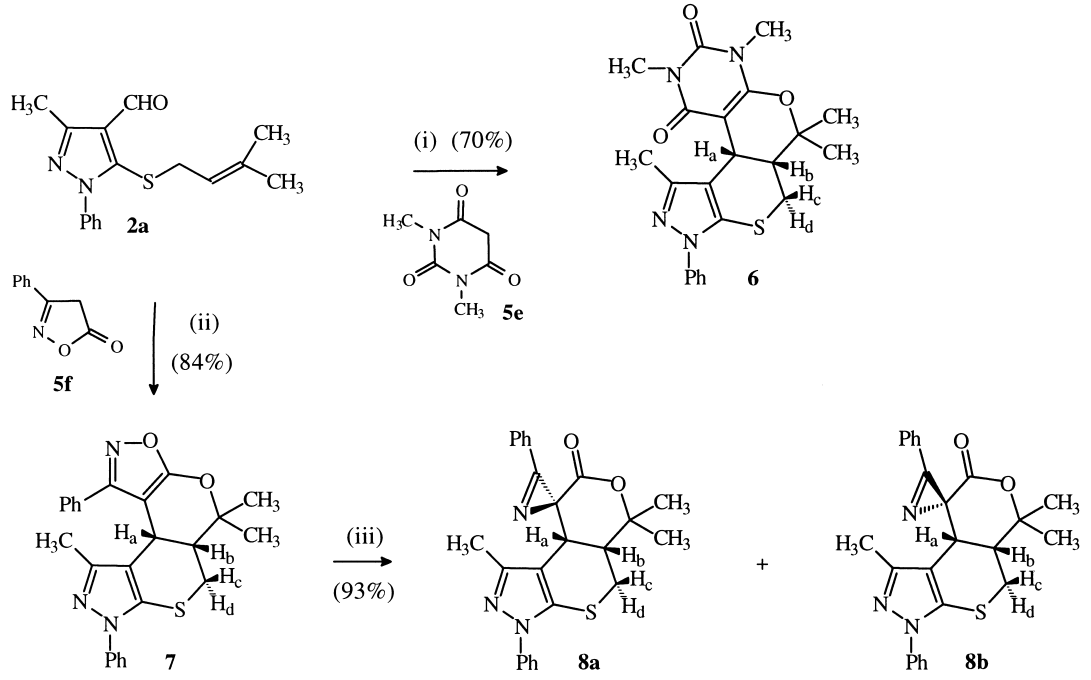
Figure 2. (a) Molecular structure of compound **4d**. (b) Crystal packing of compound **4d**.

for 3-methylpyrazoles. The methyl group in isomer **8a** clearly is much more influenced by the anisotropic effect of the neighbouring azirine 3-phenyl group.

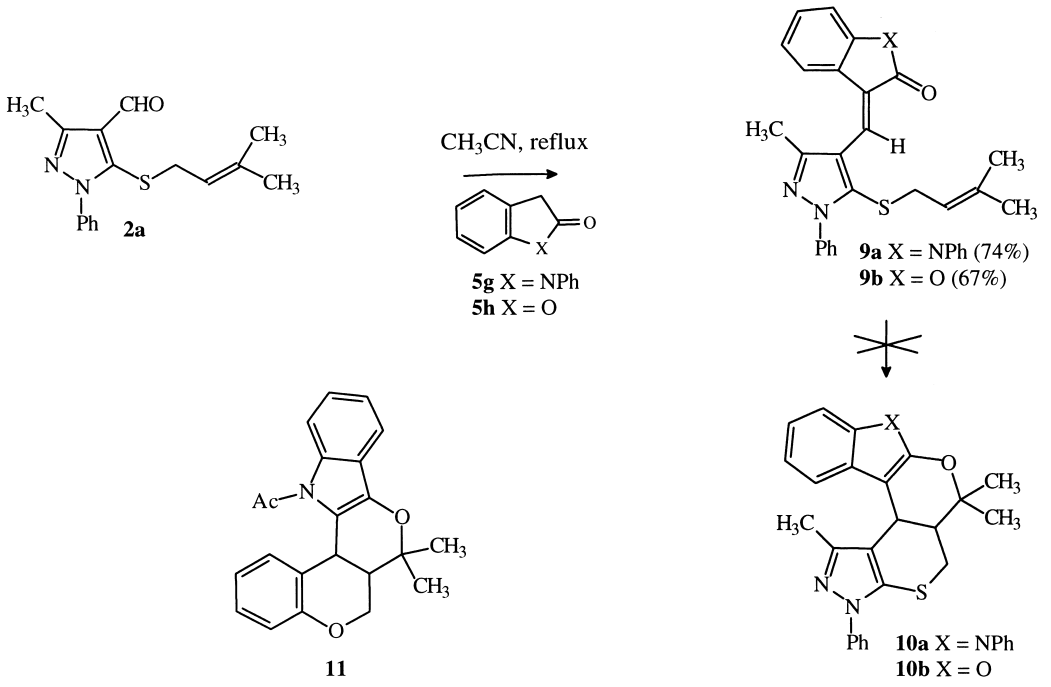
It is interesting to remark that similar reactions of the isoxazolone **5f** with the benzene analogues were reported by Tietze et al.[8] to yield the unrearranged products. Thermal or photochemical ring contractions of isoxazoles to (2*H*)azirines are well known in the literature, with the reaction proceeding in most cases to the thermodynamically stable oxazoles.[9] However, we found no trace of an oxazolo fused isomer of **7**, **8a**,**b**. In fact, the ring contraction of **7** occurs at relatively low temperatures and may be a way to alleviate ring strain or steric hindrance.

Pyrazole **2a** was condensed with 2-indolone **5g**[10] or 2-coumaranone **5h** to afford the Knoevenagel adducts **9a** and **9b**, which could not be brought to transform in the corresponding cycloadducts **10a** and **10b**, even on heating at 190°C. The products **9a**,**b** had the *E*-configuration as could be inferred from their ^{1}H NMR spectra. The $^{3}J_{CH}$ coupling constant between the carbonyl carbon and the alkylidene hydrogen had a typical value of 7 Hz. It can be argued that the indole or benzofuran rings that would be formed in **10a**,**b** have not sufficient aromatic stabilization to offset the amide or ester stabilization present in the Knoevenagel adducts **9a**,**b**, respectively. Recently, the cycloadduct **11** was formed at 190°C from a 3-indolone derivative, where the amide resonance is absent[11] (Scheme 3).

So far we have always started from a 5-chloro-4-formylpyrazole **2**. A number of other heterocycles with similar functionalities are found in the literature. The commercial



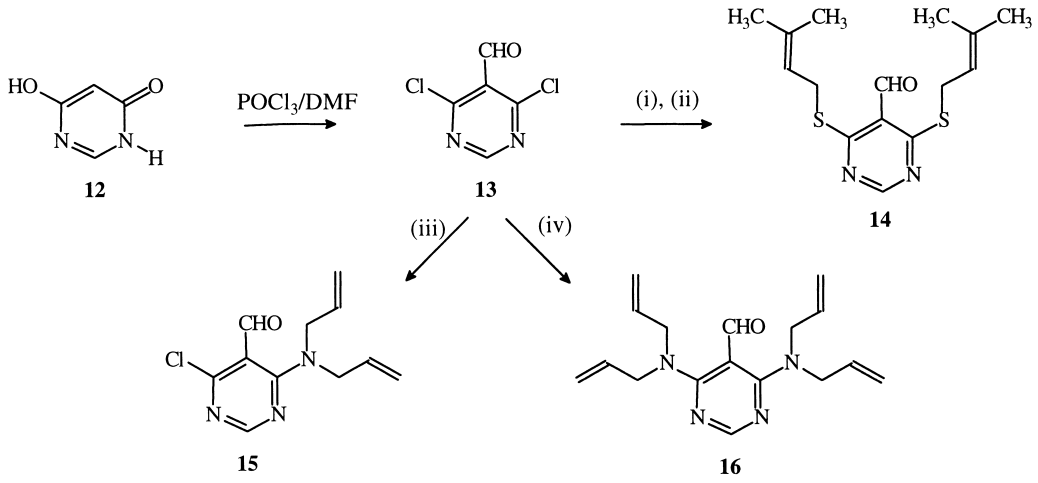
Scheme 2. (i) Barbituric acid **5e**, CH_3CN, reflux, (ii) pyrazolone **5f**, CH_3CN, reflux, (iii) CH_3CN or toluene, reflux.



Scheme 3.

4,6-dihydroxypyrimidine **12** was smoothly transformed with an excess Vilsmeier reagent to afford the highly reactive 4,6-dichloropyrimidine-5-aldehyde **13** according to a published procedure.[12] Mono- and disubstitution of the two chlorine functions by nucleophiles are possible. Thus, the use of prenylthiolate gave only the disubstituted pyrimidine **14**. With diallylamine either the monosubstituted **15** or the disubstituted **16** could be obtained in good yield. Earlier we found that pyrazoles **2a** do not react with amines[6] (Scheme 4).

We were now able to use the aldehydes **14**–**16** in analogous *hetero* Diels–Alder reactions by condensation reactions with pyrazolone **5b** and oxazolone **5f**. The reaction outcome was completely analogous, with the formation of the tetracyclic pyrazoles **17** (from **14** and **5b**) and **19** (from **15** and **5b**), and the (2*H*)azirine isomers **18a**,**b** (from **14** and **5f**), and **20a**,**b** (from **15** and **5f**). In the latter two cases the isoxazolo fused intermediates were not detected, but rearranged directy to the azirines **18** and **20**, even in acetonitrile solution. This showed that the structure of the fused isoxazole has an influence on the rate of the ring contraction. The NMR data of **17**–**20** were similar to those found for the pyrazole analogs, and again the same high selectivity for *cis* fusion was found (Fig. 3). A reaction of the disubstituted pyrimidine **16** with pyrazolone **5b** in acetonitrile solution did not give the expected ring closed product. Instead, only starting material was isolated even on refluxing in toluene for five days. Probably due to steric hindrance of the allyl groups, the pyrazolone cannot react with the aldehyde to



Scheme 4. (i) 4-Bromo-2-methyl-2-butene, thiourea, EtOH, reflux, (ii) NaOH, EtOH, reflux, (iii) 1 equiv. diallylamine, Et_3N, THF, reflux, (iv) 2 equiv. diallylamine, Et_3N, THF, reflux.

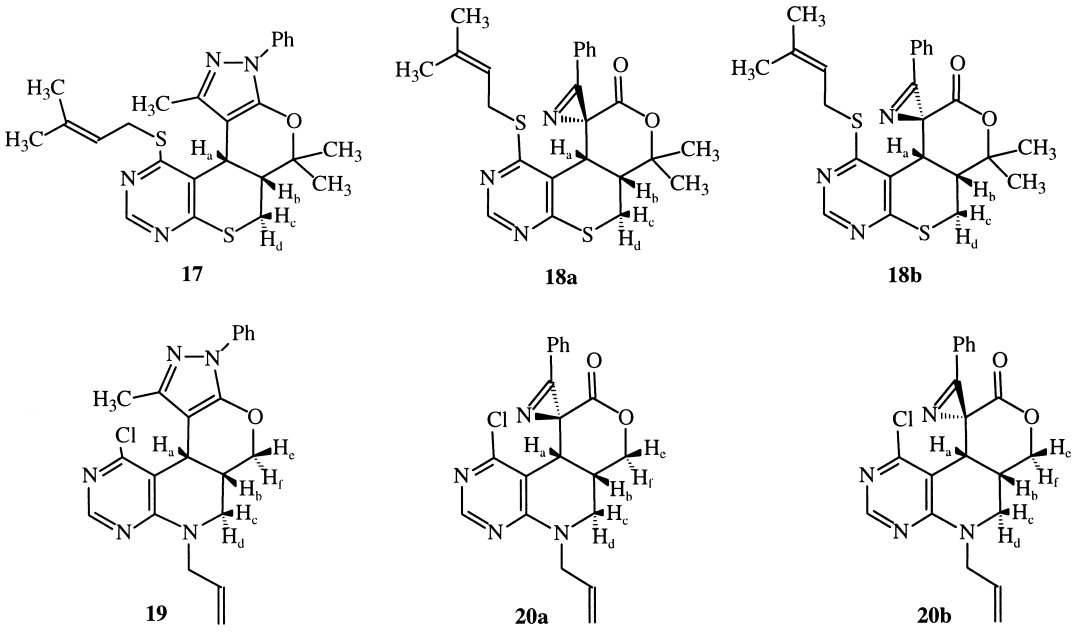


Figure 3.

form the Knoevenagel adduct. Fig. 4 shows the molecular structure of **18b** (only the prenyl thiolate group with the highest occupancy is shown, see Section 3). The pyrimidine ring is planar, while the oxane and thiane rings adopt an envelope conformation. The pyrimidine and thiane rings are lying almost in the same plane (the angle between the best planes through both rings is 13.1(2)°). The thiane and oxane rings make an angle of 69.9(2)°. The azirine nitrogen atom is situated at the same side of the fused rings as the bridging hydrogens at atoms C4 and C5. The angle between the

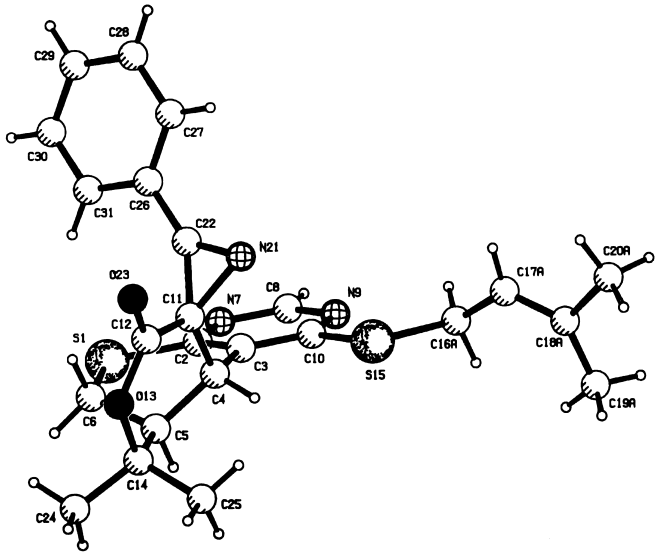


Figure 4. Molecular structure of compound **18b**.

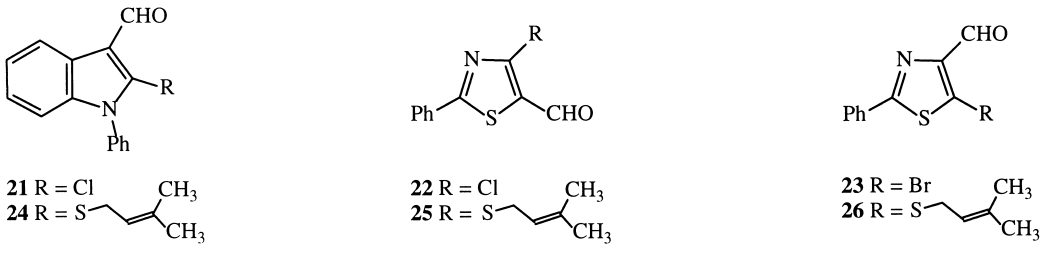
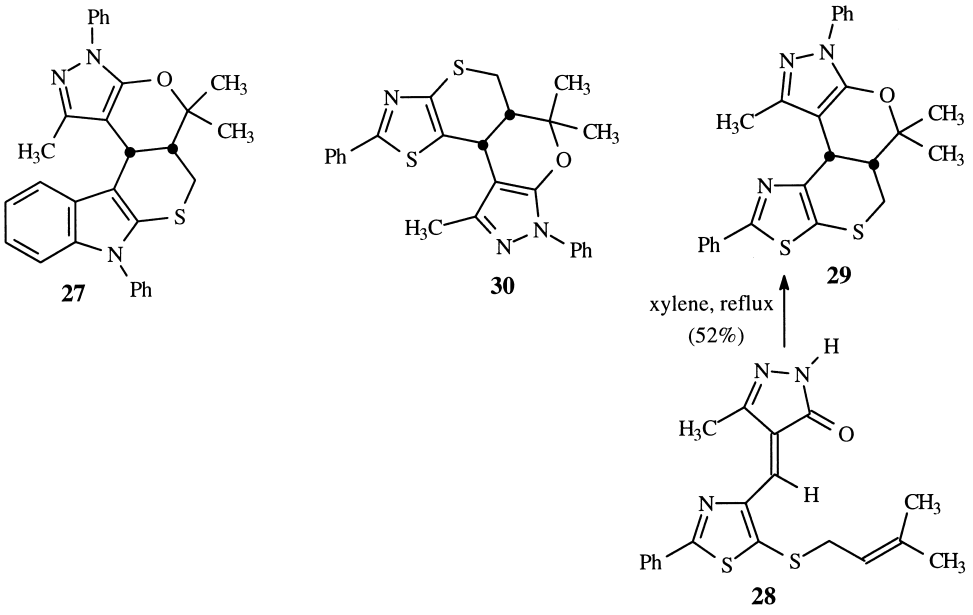


Figure 5.

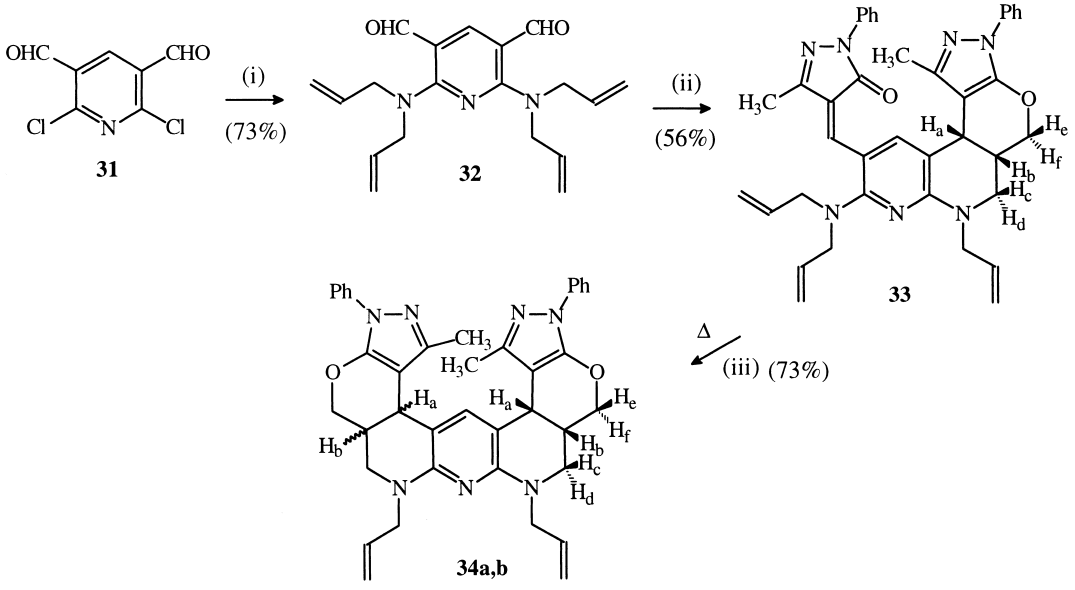


Scheme 5.

prenyl thiolate substituent and the pyrimidine ring is 73.7(3)°.

To extend the scope of this domino procedure for polyheterocyclic compounds, this method was applied to β-halo aldehydes **21**,[10] **22**[13] and **23**.[14] Substitution with prenyl thiolate again gave the sulfides **24**–**26** (Fig. 5), which were transformed with **5b**, respectively to the tetracyclic indole **27** and the tetracyclic thiazole regioisomers **29** and **30**. In the case of the thiazole derivative **26** the Knoevenagel adduct **28** was slow to cyclize in refluxing acetonitrile and could be isolated. However **28** cyclized in refluxing toluene to afford tetracyclic **29**. Therefore, the isomeric compound **30** was immediately prepared from **25** in refluxing toluene (Scheme 5).

Finally, the known 2,6-dichloropyridine-3,5-dialdehyde **31**, which has two β chloro aldehyde moieties, was prepared from glutarimide following a literature procedure.[15] Substitution with diallylamine yielded the di-aldehyde **32**, which was treated with pyrazolone **5b** under the usual conditions. An oil was formed from acetonitrile solution which corresponded to a compound **33** which was only ringclosed (as a *cis* compound) to one side. The other side was the Knoevenageladduct with a *Z*-configuration ($^3J_{CH}$=10 Hz). Further heating of **33** in toluene afforded a mixture of the remarkable heptacyclic cycloadducts **34a**,**b**, which could be separated by chromatography. The ^{1}H NMR showed for both compounds the typical values for the bridged protons and the coupling constants of approximately 4 Hz for coupling of proton H_a and H_b (Scheme 6).



Scheme 6. (i) 2 equiv. diallylamine, Et_3N, THF, reflux, (ii) pyrazolone **5b**, CH_3CN, reflux, (iii) toluene, reflux.

3. Experimental

3.1. General

Mps were determined using a Reichert Thermovar apparatus. IR spectra were recorded on a Perkin–Elmer 1720 FT spectrometer, and NMR spectra on either a Bruker AMX-400 or a Bruker WM-250 instrument. The NMR spectra were measured with deuteriochloroform solutions unless otherwise specified. The *J* values are recorded in Hz. Low resolution mass spectra were measured with a Hewlett Packard 5989 A instrument, at 70 eV for EI spectra, and with methane as reagent gas for CI spectra. The high resolution mass spectra were recorded with a Kratos MS 50 TC machine. Cell constants and reflections were measured with a Siemens P4–PC four-circle diffractometer (graphite monochromator, λ(Mo Kα)=0.71073 Å). Lattice parameters were obtained from least-squares of 25 reflections (for **4d**: $16<2\theta<21°$; for **18b**: $23<2\theta<25°$) and **32** reflections (for **4a**: $19<2\theta<25°$). The structures were solved by direct methods and refined by full-matrix least-squares on F^2. Hydrogen atoms were refined in the riding mode allowing the X–H distances to refine. Non-hydrogen atoms were refined anisotropic; hydrogen atoms with *U* 1.2 times U_{eq} of the parent atom. The program package SHELXTL-PC[16] was used for all calculations and PLATON[17] for drawings.

3.2. Synthesis

All the carbonyl compounds were produced by literature methods (**5a** (Ref. 16), **5c**,**d** (Ref. 6) and **5g** (Ref. 10)) or were commercially available (**5b**, **5e**, **5f** and **5h**).

3.3. General procedure for the synthesis of the aldehydes 2a, 2b, 14, 24, 25 and 26

A solution of 4-bromo-2-methyl-2-butene (1 mmol) and thiourea (1 mmol) in ethanol (10 ml) was refluxed for 1 h. After addition of sodiumhydroxide (2 mmol) in ethanol (5 ml) reflux was continued for an additional hour and then the appropriate carbaldehyde (0.7 mmol) was added. The mixture was refluxed for half an hour, water (10 ml) was added and the mixture extracted with dichloromethane (3×50 ml). The combined extracts were dried over magnesium sulfate, the solvent evaporated and the residue was purified by chromatography on silica gel with dichloromethane (unless otherwise specified) as the eluent. Further purification was done by crystallization.

3.3.1. Compound 2a. Colorless needles from ethanol (73%), mp: 71–72°C; IR (KBr, cm^{-1}, 1600 FT) 1675 (s, CO); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 10.02 (s, 1H, CHO), 7.58 (d, 2H, *ortho* phenyl), 7.51 and 7.45 (2×t, 2H and 1H, *meta* and *para* phenyl), 5.03 (t×m, 1H, CH═), 3.18 (d, 2H, S–CH_2), 2.56 (s, 3H, CH_3 pyrazole) and 1.60 and 1.24 (2×s, 2×3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 13.6 (CH_3, pyrazole), 17.2 and 25.6 (2×CH_3), 34.7 (S–CH_2), 117.8 (CH═), 124.4 (C-4), 125.8, 128.7, 128.9 (C-2, C-3, C-4, phenyl), 138.4 (C-1, phenyl), 138.6 ($C(CH_3)_2$), 140.8 (C-5), 151.3 (C-3) and 186.7 (CHO); MS (*m*/*z*, %) 286 ($M^{+\cdot}$, 5), 253 ($M^{+\cdot}-SH$, 14), 218 ($M^{+\cdot}-C_5H_8$, 33), 77 ($C_6H_5^+$, 27) and 69 ($C_5H_9^+$, 100).

3.3.2. Compound 2b. Light yellow powder from ethanol (31%), mp: 78–79°C; IR (KBr, cm^{-1}, 1600 FT) 1592 (w, phenyl), 1681 (s, CO), 2973 (w, alkyl) and 3072 (w, phenyl); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.85–7.88 (d, 2H, *ortho N*-phenyl), 7.61–7.63 (d, 2H, *ortho*), 7.43–7.55 (m, 6H, *meta* and *para* phenyl and *N*-phenyl), 5.07 (t×m, 1H, vinyl H), 3.37 (d, 2H, CH_2), 1.62 (s, 3H, CH_3) and 1.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 17.3 and 25.6 (2×s, 2 CH_3), 34.8 (S–CH_2), 118.1 (CH═), 122.8 (C-4), 126.2, 128.3, 128.9, 129.0, 129.0 and 129.2 (*ortho*, *meta* and *para*, phenyl and *N*-phenyl), 131.4 (C-1, phenyl), 138.6 ($C(CH_3)_2$), 138.6 (C-1, *N*-phenyl), 141.8 (C-5), 154.0 (C-2) and 186.0 (CHO); MS (*m*/*z*, %) 348 ($M^{+\cdot}$, 54), 315 ($M^{+\cdot}-SH$, 75), 280 ($M^{+\cdot}-C_5H_8$, 100), 251 ($M^{+\cdot}-C_5H_8$–CHO, 26), 154 (34), 77 ($C_6H_5^+$, 52), 69 ($C_4H_9^+$, 94) and 41 ($C_3H_5^+$, 72).

3.3.3. Compound 14. Two equivalents of 4-bromo-2-methyl-2-bytene, thiourea and sodiumhydroxide were used. Chromatography with dichloormethane–*n*-hexane 4/1, light yellow needles from *n*-hexane (45%), mp: 32.5–33.5°C; IR (KBr, cm^{-1}, 1600 FT) 1485 (s), 1515 (s, phenyl), 1680 (s, CO), 2911–2968 (w, alkyl) and 3029 (w, arom); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 10.43 (s, 1H, CHO), 8.63 (s,1H, H-2 pyrimidine), 5.34 (tr, 2H, CH═, ^3J=7.8 Hz), 3.88 (d, 4H, CH_2, ^3J=7.8 Hz) and 1.74 (2×s, 2×6H, 4CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 17.6 (q×d, CH_3, ^1J=126 Hz, ^3J=4 Hz), 25.4 (CH_3, ^1J=126 Hz), 28.2 (CH_2, ^1J=144 Hz), 137.4 (m, $C(CH_3)_2$, ^2J=6 Hz), 117.6 (tr×m, CH═, ^1J= 158 Hz, ^2J=6 Hz), 121.5 (d, C-5, ^2J=25 Hz), 156.4 (d, C-2, ^1J=200 Hz), 172.4 (d, C-4 and C-6, ^3J=11 Hz) and 186.4 (d, CHO, ^1J=179 Hz); MS (*m*/*z*, %) 308 ($M^{+\cdot}$, 47), 239 ($M^{+\cdot}-C_5H_9$), 207 (38), 271 (M 239$-C_5H_8$, 57), 144 (22), 69 ($C_5H_9^+$, 99), 53 (17), 41 (100) and 39 (23).

3.3.4. Compound 24. Light red needles from ethanol (30%), mp: 89.9–90.5°C; IR (KBr, cm^{-1}, 1600 FT) 1594 (w, phenyl), 1658 (s, alkyl), 2961 (w, alkyl) and 3052 (w, phenyl); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 10.29 (s, 1H, CHO), 8.42 (d, 1H, H-4 indole), 7.60–7.55 (m, 3H, *meta* and *para N*-phenyl), 7.43 (d, 2H, *ortho N*-phenyl), 7.30 (m, 1H, H-5 indole), 7.26 (m, 1H, H-6 indole), 7.12 d, 1H, H-7 indole) 5.05 (t×m, 1H, CH═), 3.14 (d, 2H, S–CH_2) and 1.61 and 1.21 (2×s, 2×3H, 2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 17.2 and 25.5 (2CH_3), 35.3 (S–CH_2), 110.8 (C-7, indole), 118.0 (CH═), 121.8 (C-3, indole), 121.7, 123.4, 124.8 (C-4, C-5, C-6, indole), 124.8 (C-3a), 128.5 (C-4, phenyl), 129.0 (C-2, phenyl), 129.4 (C-3, phenyl), 136.2 (C-1, phenyl), 138.5 ($C(CH_3)_2$), 139.0 (C-7a), 142.5 (C-2 indole) and 187.6 (CHO); MS (*m*/*z*, %) 321 ($M^{+\cdot}$, 43), 288 ($M^{+}-SH$, 50), 254 ($M^{+\cdot}-C_5H_7$), 253 ($M^{+\cdot}-C_5H_8$, 100), 252 ($M^{+\cdot}-C_5H_9$, 82), 224 ($M^{+\cdot}-C_5H_9S$, 34), 233 ($M^{+\cdot}-C_5H_9-CHO$, 41), 69 ($C_4H_9^+$, 53) and 41 ($C_3H_5^+$, 51).

3.3.5. Compound 25. Previous to the addition of the appropriate thiazolecarbaldehyde, the mixture was cooled to room temperature. After the addition of the carbaldehyde, the mixture was refluxed for 1 h. A dark red oil was formed after chromatography with dichloromethane (79%); IR (CCl_4, cm^{-1}, 1600 FT) 1549 (s, phenyl), 1664 (m, CO), 2856 (w, alkyl), 2923 (alkyl) and 3036 (arom H); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 10.03 (s, 1H, CHO), 8.02–7.99 (d×m,

2H, *ortho* phenyl), 7.52–7.44 (m, 3H, *meta* and *para* phenyl), 5.39 (t, 1H, CH═, ^3J=7.9 Hz, ^4J=1.4 Hz), 4.00 (d, 2H, CH_2, ^3J=8 Hz), 1.73 (s, 3H, CH_3) and 1.69 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 17.8 (CH_3), 25.7 (CH_3), 31.4 (CH_2), 118.9 (*C*H═), 127.1 (C-2, phenyl), 129.1 (C-3, phenyl), 130.7 (C-5), 131.9 (C-4, phenyl), 132.4 (C-1, phenyl), 137.6 ($C(CH_3)_2$), 160.8 (C-4), 173.5 (C-2) and 181.4 (CHO); MS (*m*/*z*, %) 289 ($M^{+\cdot}$, 49), 256 (100), 221 ($M^{+\cdot}-C_5H_8$, 41), 193 ($M^{+\cdot}-C_5H_8-CO$, 64), 69 ($C_5H_9^+$, 64) and 41 ($C_3H_5^+$, 40); HRMS (*m*/*z*) calcd for $C_{15}H_{15}NOS_2$ 289.0595, found 289.0597.

3.3.6. Compound 26. Previous to the addition of the appropriate thiazolecarbaldehyde, the mixture was cooled to room temperature. After the addition of the carbaldehyde, the mixture was refluxed for 1 h. Chromatography with dichloromethane–diethyl ether 20/1 gives a yellow oil (72%); IR (KBr, cm^{-1}, 1600 FT) 1551 (s, phenyl), 1680(s, CO), 2835 (w), 2916 (w), 2977 (w, alkyl) and 3068 (w, arom H); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 10.13 (s, 1H, CHO), 7.92–7.89 (m, 2H, *ortho* phenyl), 7.46–7.44 (m, 3H, *meta* and *para* phenyl), 5.36 (t×m, 1H, CH═, ^3J=7.8 Hz, ^4J= 0.7 Hz), 3.68 (d, 2H, CH_2, ^3J=7.8 Hz), 1.76 (d, 3H, CH_3, ^4J=0.7 Hz) and 1.68 (d, 3H, CH_3, ^4J=0.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 17.9 (CH_3), 25.7 (CH_3), 35.6 (CH_2), 117.2 (*C*H═), 126.4 (C-2, phenyl), 129.1 (C-3, phenyl), 130.6 (C-4, phenyl), 132.7 (C-1, phenyl), 139.8 ($C(CH_3)_2$), 147.3 (C-4), 149.5 (C-5), 165.3 (C-2) and 184.6 (CO); MS (*m*/*z*, %) 289 ($M^{+\cdot}$, 27), 256 (44), 221 ($M^{+\cdot}-C_5H_8$, 100), 193 ($M^{+\cdot}-C_5H_8-CO$, 69), 69 ($C_5H_9^+$, 91) and 41 ($C_3H_5^+$, 43).

3.4. General procedure for the synthesis of the diallylic compounds 15, 16 and 32

A solution of the appropriate aldehyde (1 mmol), diallylamine (1 mmol) and triethylamine (1 mmol) in tetrahydrofuran (25 ml) was refluxed. After cooling the mixture to room temperature, the precipitate was filtered and the filtrate evaporated. Purification was carried out by chromatography on silica gel with dichloromethane–diethyl ether as the eluent.

3.4.1. Compound 15. The mixture was refluxed for 3 h. Chromatography with dichloromethane–diethyl ether 20/1 (67%), mp: 47.5°C; IR (KBr, cm^{-1}, 1600 FT) 1681 (s CO), 2932 (w, alkyl) and 3062 (w, arom H); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 10.28 (s, 1H, CHO), 8.37 (s, 1H, pyrimidine H), 5.75 (d×d×tr, 2H, CH═), 5.26 (d×d, 2H, CH═CH_2 *cis*, $^2J_{gem}$=1.3 Hz, $^3J_{cis}$=10.3 Hz), 5.19 (d×d, 2H, CH═CH_2 *trans*, $^3J_{trans}$=16.9 Hz) and 4.15 (d×d, 4H, $^2J_{gem}$=1.3 Hz, ^3J=4.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 53.0 (N–*C*H_2), 110.7 (C-5), 119.3 (═*C*H_2), 131.7 (*C*H═), 157.5 (C-2), 160.4 (C-6), 163.8 (C-4) and 187.2 (CO); MS (*m*/*z*, %) 238 ($M^{+\cdot}$+H, 2).

3.4.2. Compound 16. Two equivalents of diallylamine and triethylamine were used. The mixture was refluxed for 24 h. Chromatography with dichloromethane–diethyl ether 10/1 gives a yellow oil (44%); IR (CCl_4, cm^{-1}, 1600 FT) 1680 (s CO), 2945 (w, alkyl) and 3055 (w, arom H); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 9.44 (s, 1H, CHO), 8.08 (s, 1H, pyrimidine H), 5.89 (d×d×tr, 4H, CH═), 5.25 (d×d, 4H, CH═CH_2 *cis*, $^2J_{gem}$=1.3 Hz, $^3J_{cis}$=10.4 Hz), 5.21 (d×d, 4H, CH═CH_2 *trans*, $^3J_{trans}$=16.8 Hz) and 4.22 (d×d, 4H, ^3J=5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 52.8 (N–*C*H_2), 97.1 (C-5), 118.2 (═*C*H_2), 133.4 (*C*H═), 158.4 (C-2), 165.5 (C-4) and 181.9 (CO); MS (*m*/*z*, %) 297. ($M^{+\cdot}$−H, 6).

3.4.3. Compound 32. Two equivalents of diallylamine and triethylamine were used. The mixture was refluxed for 6 h. Chromatography with dichloromethane–diethyl ether 5/1 gives a yellow oil (73%); IR (CCl_4, cm^{-1}, 1600 FT) 1525 (s, phenyl), 1548 (s, phenyl), 1657 (s, CHO), 2931 (w, aliph H) and 3081 (w, pyridine H); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 9.67 (s, 2H, 2 CHO), 8.32 (s, 1H, pyridine H), 5.92–5.86 (m, 4H, *C*H═), 5.24–5.17 (2d×d, 8H, CH═*C*H_2) and 4.16–4.14 (d, 8H, N–*C*H_2); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 52.8 (d, N–CH_2, ^1J=138 Hz), 110.6 (d, C-3 pyridine, ^2J=25 Hz), 118.0 (t, CH═*C*H_2, ^1J=154 Hz), 133.3 (d, *C*H═CH_2, ^1J= 156 Hz), 152.5 (d×t, C-4 pyridine, ^1J=157 Hz, ^3J=3 Hz) and 186.2 (d, CHO, ^1J=173 Hz); MS (*m*/*z*, %) 325 ($M^{+\cdot}$, 13); HRMS (*m*/*z*) calcd for $C_{19}H_{23}N_3O_2$ 325.1790, found 325.1785.

3.5. General procedure for the synthesis of the polycyclic compounds

A solution of aldehyde (2.1 mmol), carbonyl compound (2.0 mmol) and ethylenediammonium diacetate in acetonitrile (100 ml) was left for 30 min at room temperature. The yellow–orange color reveals the presence of the Knoevenagel condensation product. This mixture was then refluxed for several hours (indicated for each compound). Evaporation of the solvent leaves a residue, which was chromatographed on silica gel with a mixture of dichloromethane–diethyl ether (unless otherwise specified) as the eluent to give the ring closed compound. Further purification was done by crystallization.

3.5.1. Compound 4a. Reflux of compound **2a** with pyrazolone **5a** for 36 h. Chromatography with dichloromethane–diethyl ether 5/1. White small needles from chloroform–diethyl ether (81%), mp: 237°C; IR (KBr, cm^{-1}, 1720 FT) 1502 (s, phenyl), 1592 (s, phenyl), 1701 (s, CO), 2985 (w, alkyl) and 3043 (w, phenyl); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.77–7.58 (2 d, 4H, *ortho* phenyl), 7.45–7.39 (m, 4H, *meta* phenyl), 7.37 (s, 1H, H-3 pyrazole, 7.29–7.24 (2t, 2H, *para* phenyl), 4.19 (br d, 1H, H_a $^3J_{ae}$=3.9 Hz), 3.00 (d×d×d, 1H, H_c, $^3J_{ae}$=2.4 Hz), 2.88 (d×d, 1H, H_d, $^3J_{aa}$=12.6 Hz, $^2J_{gem}$= 12.5 Hz), 2.51 (s, 3H, CH_3 pyrazole), 2.09 (d×d×d, 1H, H_b) and 1.79 and 1.58 (2s, 2×3H, $2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 12.8 (CH_3 pyrazole), 24.1 (S–CH_2), 25.9 (C_b), 26.1 and 26.7 ($2CH_3$), 40.7 (C_a), 82.2 (O–*C*$(CH_3)_2$), 99.4 (C_a–*C*–CH), 115.3 (C_a–*C*–CCH_3), 120.5 and 122.6 (2C-2, phenyl), 125.9 and 127.0 (2C-4, phenyl), 129.0 and 129.2 (2C-3, phenyl), 130.4 (N–*C*–S), 138.5 (C–H pyrazole), 138.8 and 139.7 (2C-1, phenyl), 147.1 (N–*C*–O) and 148.3 (*C*–CH_3 pyrazole); MS (*m*/*z*, %) 428 ($M^{+\cdot}$, 13), 360 ($M^{+\cdot}-C_5H_8$, 11), 327 ($M^{+\cdot}-C_5H_9S$, 100), 225 ($M^{+\cdot}$ 1-phenyl-5(4*H*)-pyrazolon-propane, 24), 128 (C_6H_5–N≡C–C≡CH^+, 11), 77 ($C_6H_5^+$, 48), 69 ($C_5H_9^+$, 30) and 41 ($CH_3CN^{+\cdot}$, 41); HRMS (*m*/*z*) calcd for $C_{25}H_{24}N_4OS$ 428.1671, found 428.1673; X-ray structural analysis: $C_{25}H_{24}N_4OS$, MW=428.55, a white transparent crystal of

0.4×0.3×0.2 mm^3 size, space group *P*-1, *Z*=2, triclinic, *a*=9.952(1), *b*=10.245(1), *c*=11.852(2) Å, α=104.55(1), β=94.89(1), γ=92.40(1)°, *V*=1162.9(4) $Å^3$, d_{calc}= 1.224 g cm^{-3}, *F*(000)=452, *T*=289 K, ω-scan, $\Delta\omega$=0.60°, 2.0<ω<60.0° min^{-1}, 3435 collected reflections ((sin θ/λ)max=0.53), 2830 unique reflections (R_{int}=2.5%). Final *R*-values: R_1=0.0850 for 2414 reflections with $I>2\sigma(I)$ and R_1=0.0942, wR_2= 0.2955 for all reflections. The asymmetric unit contains a water molecule forming an infinite water chain through the crystal.

3.5.2. Compound 4b. Reflux of compound **2a** with pyrazolone **5b** for 36 h. Product **4b** precipitated from the mixture. Yellow–white powder from diethyl ether (87%), mp: 219°C; IR (KBr, cm^{-1}, 1600 FT) 1514 (s, phenyl), 1594 (s, phenyl), 2958 (m, alkyl) and 3058 (w, phenyl); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.74–7.63 (2 d, 4H, *ortho* phenyl), 7.46–7.38 (m, 4H, *meta* phenyl), 7.30–7.21 (2t, 2H, *para* phenyl), 4.21 (br d, 1H, H_a, $^3J_{ae}$=4.0 Hz), 3.07 (d×d, 1H, H_d, $^3J_{aa}$=12.5 Hz, $^2J_{gem}$=12.4 Hz), 2.98 (d×d×d, 1H, H_c, $^3J_{ae}$=2.3 Hz), 2.46 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 1.95 (d×t, 1H, H_b), 1.63 and 1.56 (2 s, 2×3H, $2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 12.6 and 13.7 ($2CH_3$ pyrazole), 23.2 (S–CH_2), 26.4 (C_b), 26.4 and 26.6 ($2CH_3$), 40.1 (C_a), 81.6 (O–*C*(CH_3)$_2$), 96.6 (C_a–*C*–CCH_3 furanring), 113.0 (C_a–*C*–CCH_3), 120.4 and 122.4 (2C-2, phenyl), 125.4 and 126.9 (2C-4, phenyl), 128.9 and 129.2 (2C-3, phenyl), 130.7 (N–*C*–S), 138.7 and 139.8 (2C-1, phenyl), 147.0 and 147.6 (2*C*–CH_3 pyrazole), 148.9 (N–*C*–O); MS (*m*/*z*, %) 442 ($M^{+\cdot}$, 8), 341 ($M^{+\cdot}-C_5H_9S$, 100), 225 ($M^{+\cdot}$−3-methyl-1-phenyl-5(4*H*)-pyrazolon-propane, 35), 128 (C_6H_5–N≡C–C≡CH^+, 18) and 77 ($C_6H_5^+$, 52); HRMS (*m*/*z*) calcd for $C_{26}H_{26}N_4OS$ 442.1827, found 442.1830.

3.5.3. Compound 4c. Reflux of compound **2a** with pyrazolone **5c** for 36 h. Chromatography with dichloromethane–diethyl ether 8/1. White powder from chloroform–diethyl ether (87%), mp: 221.5°C; IR (KBr, cm^{-1}, 1600 FT) 1503 (s, phenyl), 1515 (s, phenyl), 1599 (m, phenyl), 2979 (w, alkyl) and 3063 (w, phenyl); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.90–7.70 (2d, 4H, *ortho* phenyl), 7.55–7.10 (m, 11H, phenyl), 4.19 (d, 1H, H_a, $^3J_{ae}$=3.9 Hz), 3.24 (d×d, 1H, H_d, $^3J_{aa}$=12.5 Hz, $^2J_{gem}$=12.6 Hz), 3.08 (d×d, 1H, H_c, $^3J_{ae}$= 2.3 Hz), 2.02 (d×t, 1H, H_b), 1.68 and 1.60 (2s, 2×3H, $2CH_3$) and 1.40 (s, 3H, CH_3 pyrazole); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 10.8 (CH_3 pyrazole), 24.1 (S–CH_2), 26.3 and 26.9 ($2CH_3$), 27.0 (C_b), 40.8 (C_a), 81.9 (O–*C*(CH_3)$_2$), 96.8 (C_a–*C*–C phenyl), 114.8 (C_a–*C*–CCH_3), 120.9, 122.5, 125.8, 126.8, 127.8, 128.1, 128.9, 129.2, and 129.7 (C-2, C-3 and C-4, phenyl), 130.2 (N–*C*–S), 138.5 (C–H pyrazole), 134.1, 138.7 and 139.9 (C-1, phenyl), 147.7 (*C*–CH_3 pyrazole) and 150.2 and 150.3 (*C*-phenyl pyrazole and N–*C*–O); MS (*m*/*z*, %) 504 ($M^{+\cdot}$, 8), 403 ($M^{+\cdot}-C_5H_9S$, 68), 225 ($M^{+\cdot}$−1,3-diphenyl-5(4*H*)-pyrazolon-propane, 42), 128 (C_6H_5–N≡C–C≡CH^+, 30), 77 ($C_6H_5^+$, 91), 69 ($C_5H_9^+$, 66) and 41 ($CH_3CN^{+\cdot}$, 100); HRMS (*m*/*z*) calcd for $C_{31}H_{28}N_4OS$ 504.1984, found 504.1978.

3.5.4. Compound 4d. Reflux of compound **2a** with pyrazolone **5d** for 36 h. Chromatography with dichloromethane–diethyl ether 10/1. White powder from chloroform–diethyl ether (83%), mp: 141.5°C; IR (KBr, cm^{-1}, 1600 FT) 1504 (s, phenyl), 1595 (s, phenyl), 2981 (w, alkyl) and 3066 (w, phenyl); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.77–7.59 (2 d, 4H, *ortho* phenyl), 7.48–7.40 (m, 4H, *meta* phenyl), 7.35–7.25 (2×t, 2H, *para* phenyl), 4.32 (br d, 1H, H_a, $^3J_{ae}$=4.0 Hz), 3.04 (d×d×d, 1H, H_c, $^3J_{ae}$=2.4 Hz), 2.98 (d×d, 1H, H_d, $^3J_{aa}$=12.7 Hz, $^2J_{gem}$=12.8 Hz), 2.40 (s, 3H, CH_3 pyrazole), 2.05 (d×t, 1H, H_b) and 1.61 and 1.59 (2×s, 2×3H, $2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 15.3 (CH_3 pyrazole), 23.7 (S–CH_2), 26.3 (C_b), 26.7 (2 CH_3), 40.7 (C_a), 82.8 (O–*C*(CH_3)$_2$), 96.7 (C_a–*C*–CCF_3), 113.6 (C_a–*C*–CCH_3), 121.0 (CF_3), 121.6 and 122.5 (2C-2, phenyl), 126.9 and 127.2 (2C-4, phenyl), 129.1 and 129.2 (2C-3, phenyl), 130.6 (N–*C*–S), 137.8 and 139.7 (2C-1, phenyl), 138.5 (*C*–CF_3), 148.7 (N–*C*–O) and 149.1 (*C*–CH_3 pyrazole); MS (*m*/*z*, %) 496 ($M^{+\cdot}$, 13), 395 ($M^{+\cdot}-C_5H_9S$, 66), 359 ($M^{+\cdot}-CF_3-C_5H_8$, 20), 225 ($M^{+\cdot}$−1-phenyl-trifluoromethyl-5(4*H*)-pyrazolon-propane, 28), 128 (C_6H_5–N≡C–C≡CH^+, 14), 77 ($C_6H_5^+$, 88), 69 ($C_5H_9^+$, 100) and 41 (CH_3CN^+, 77); X-ray structural analysis: $C_{26}H_{23}F_3N_4OS$, MW=496.54, a white transparent crystal of 0.4×0.4×0.4 mm^3 size, space group *R*-3, *Z*=18, hexagonal, *a*= 30.749(4), *c*=14.487(3) Å, *V*=11862(3) $Å^3$, d_{calc}= 1.251 g cm^{-3}, *F*(000)=4644, *T*=289 K, ω-scan, $\Delta\omega$= 0.60°, 3.0<ω<60.0° min^{-1}, 3990 collected reflections ((sin θ/λ)max=0.53), 3189 unique reflections (R_{int}= 3.3%). Final *R*-values: R_1=0.0852 for 2322 reflections with $I>2\sigma(I)$ and R_1=0.1113, wR_2=0.2834 for all reflections.

3.5.5. Compound 4e. Reflux of compound **2b** with pyrazolone **5b** for 30 h. Chromatography with dichloromethane–diethyl ether 10/1. White powder from ethanol (83%), mp: 250.1°C; IR (CCl_4, cm^{-1}, 1600 FT) 2961 (w, alkyl) and 3065 (w, phenyl); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.97–7.95 (d×t, 2H, *meta* phenyl), 7.76–7.71 (2 d×t, 4H, *meta* phenyl), 7.50–7.34 (m, 8H, *ortho* and *para* phenyl), 7.23–7.20 (t×t, 1H, *para* phenyl), 4.74 (d, 1H, H_a, $^3J_{ae}$=3.6 Hz), 3.08 (d×d, 1H, H_d, $^3J_{aa}$=12.7 Hz, $^2J_{gem}$=11.8 Hz), 3.03 (d×d, H, H_c, $^3J_{ae}$=2.8 Hz), 2.04 (d×t, 1H, H_b), 1.88 (s, 3H, CH_3), 1.65 and 1.61 (2s, 2×3H, $2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 13.9 (CH_3 pyrazole), 23.0 (S–CH_2), 26.6 and 26.8 ($2CH_3$), 27.5 (C_b), 40.2 (C_a), 81.8 (O–*C*(CH_3)$_2$), 96.4 (C_a–*C*–CCH_3), 112.1 (C_a–*C*–C phenyl), 120.4, 121.1, 123.0, 125.5, 127.2, 127.4, 128.0, 128.8 and 128.9 (phenyl), 129.2 (C-1, phenyl), 131.6 (N–*C*–S), 138.6 and 139.7 (2C-1, phenyl), 147.5 and 147.8 (C–CH_3 and C-phenyl), 150.6 (N–*C*–O); MS (*m*/*z*, %) 504 ($M^{+\cdot}$, 36), 403 ($M^{+\cdot}-C_5H_9S$, 100), 287 ($M^{+\cdot}$−1,3-diphenyl-5(4*H*)-pyrazolon-propane, 24), 128 (C_6H_5–N≡C–C≡CH^+, 12), 77 ($C_6H_5^+$, 25), 69 ($C_5H_9^+$, 16), 49 ((12) and 41 (CH_3CN^+, 21); HRMS (*m*/*z*) calcd for $C_{31}H_{28}N_4OS$ 504.1984, found 504.1989.

3.5.6. Compound 4f. Reflux of compound **2b** with pyrazolone **5c** for 72 h. Chromatography with dichloromethane–diethyl ether 20/1. White powder from ethanol (32%), mp: 127.8°C; IR (KBr, cm^{-1} 1600 FT) 1500 (m, phenyl), 1596 (m, phenyl), 2981 (w, alkyl) and 3058 (w, phenyl); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.87–7.85 and 7.74–7.72 (d×d, 4H, *ortho N*-phenyl), 7.51–7.35 (m, 7H, phenyl), 7.23 (t×t, 1H, *para* phenyl), 7.17–7.15 (m, 3H, phenyl), 6.98–6.95 (m, 5H, phenyl), 4.64 (d, 1H, H_a, $^3J_{ae}$=3.3 Hz), 3.29 (d×d, 1H, H_d, $^3J_{aa}$=12.1 Hz, $^2J_{gem}$=12.1 Hz), 3.11 (d×d, 1H, H_c, $^3J_{ae}$=

3.2 Hz), 2.05 (d×t, 1H, H_b), 1.65 and 1.60 (2s, 2×3H, $2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 23.3 (S–CH_2), 26.4 and 27.1 ($2CH_3$), 27.5 (C_b), 40.3 (C_a), 81.8 (O–$C(CH_3)_2$), 96.1 (C_a–*C*–C phenyl), 113.9 (C_a–*C*–C phenyl), 120.6, 122.7, 125.7, 126.8, 127.1, 127.2, 127.5, 127.7, 128.7, 129.1 and 129.2 (phenyl), 133.6 (N–*C*–S), 130.8 and 132.2 (2C-1, phenyl), 138.5 and 139.7 (C-1, *N*-phenyl), 147.9 (N–*C*–O), 150.9 and 151.4 (2*C*-phenyl pyrazole); MS (*m/z*, %) 566 ($M^{+\cdot}$, 29), 465 ($M^{+\cdot}-C_5H_9S$, 100), 287 ($M^{+\cdot}$−1,3-diphenyl-5(4*H*)-pyrazolon-propane, 28), 128 (C_6H_5–N≡C–C≡CH^+, 24), 91 ($C_6H_5N^+$, 90), 77 ($C_6H_5^+$, 51), 69 ($C_5H_9^+$, 30), 51 ($C_4H_3^+$, 23), 49 (C_4H^+, 40) and 41 (CH_3CN^+, 47); HRMS (*m/z*) calcd for $C_{36}H_{30}N_4OS$ 566.2140, found 566.2148.

3.5.7. Compound 6. Reflux of compound **2a** with barbituric acid **5e** for 36 h. Chromatography with dichloromethane–diethyl ether 10/1. Yellow powder from chloroform–diethyl ether (70%), mp: 190°C; IR (KBr, cm^{-1}, 1600 FT) 1610 (m, phenyl), 1648 (m, CO), 1704 (m, CO) and 2982 (w, alkyl); ^1H NMR (400 MHz, $CDCl_3$, δ) 7.59 (d, 2H, *ortho* phenyl), 7.40 (t, 2H, *meta* phenyl), 7.25 (t, 1H, *para* phenyl), 4.44 (d, 1H, H_a, $^3J_{ae}$=4.0 Hz), 3.36 (s, 3H, N–CH_3), 3.31 (s, 3H, N–CH_3), 3.04 (d×d×d, 1H, H_c, $^3J_{ae}$=2.4 Hz), 2.92 (d×d, 1H, H_d, $^3J_{aa}$=12.5 Hz, $^2J_{gem}$=12.6 Hz), 2.43 (s, 3H, CH_3 pyrazole), 2.12 (d×t, 1H, H_b) and 1.54 (s, 6H, $2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 13.2 (CH_3 pyrazole), 24.6 (S–CH_2), 25.4 (C_b), 27.0 and 27.3 ($2CH_3$), 28.0 and 28.8 (2N–CH_3), 40.7 (C_a), 82.2 (O–$C(CH_3)_2$), 87.4 (C_a–*C*–CO), 113.9 (C_a–*C*–CCH_3), 122.4 (C-2, phenyl), 126.5 (C-4, phenyl), 129.0 (C-3, phenyl), 130.1 (N–*C*–S), 139.7 (C-1, phenyl), 150.9 and 151.0 (H_3CN–*C*–O and *C*–CH_3 pyrazole), 154.3 (*C*O) and 162.1 (N–*C*O–N); MS (*m/z*, %) 424 ($M^{+\cdot}$, 12), 323 ($M^{+\cdot}-C_5H_9S$, 47), 269 ($M^{+\cdot}-C_6H_7N_2O_3$, 14), 266 ($M^{+\cdot}-C_6H_8N_2O_3$, 16), 235 ($M^{+\cdot}-C_6H_7N_2O_3$–SH, 16), 128 (C_6H_5–N≡C–C≡CH^+, 18), 77 ($C_6H_5^+$, 35), 69 ($C_5H_9^+$, 73), 51 ($C_4H_3^+$, 13), 41 (CH_3CN^+, 100) and 39 ($C_3H_3^+$, 14); HRMS (*m/z*) calcd for $C_{22}H_{25}N_4O_3S$ 424.1569, found 424.1573.

3.5.8. Compound 7. Reflux of compound **2a** with isoxazolone **5f** for 36 h. The white precipitate was purified by crystallization from acetonitrile (84%), mp: 221°C; IR (KBr, cm^{-1}, 1600 FT) 1504 (m, phenyl), 1600 (m, phenyl), 2981 (w, alkyl) and 3058 (w, phenyl); ^1H NMR (400 MHz, $CDCl_3$, δ) 7.62 (d×8.7 Hz, 2H, *ortho* phenyl (isoxazole), ^3J=), 7.47 (t, 2H, *meta* phenyl (pyrazole)), 7.33 (t×t, 1H, *para* phenyl (pyrazole)), 7.32 (t×t, 1H, *para* phenyl (isoxazole)), 7.25 (t, 2H, *meta* phenyl (isoxazole), 7.04 (d, 2H, *ortho* phenyl (pyrazole), ^3J=7.1 Hz), 4.08 (d, 1H, H_a, $^3J_{ae}$= 4 Hz), 3.10 (d, 2H, H_d and H_c, ^3J=7.6 Hz), 2.05 (t×d, 1H, H_b), 1.67 and 1.57 (2s, 2×3H, $2CH_3$) and 1.35 (s, 3H, CH_3 pyrazole); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 10.7 (CH_3 pyrazole), 23.5 (S–CH_2), 25.9 and 26.0 ($2CH_3$), 26.8 (C_b), 40.5 (C_a), 84.2 (O–$C(CH_3)_2$), 87.9 (C_a–*C*–C phenyl), 113.0 (C_a–*C*–C–CH_3), 122.5 (2C-2, phenyl), 127.0 and 129.4 (2C-4, phenyl), 128.1 and 129.2 (2C-3, phenyl), 129.5 (C-1, phenyl isoxazole), 130.3 (N–*C*–S), 139.7 (C-1, phenyl pyrazole), 150.0 (*C*–CH_3 pyrazole), 164.5 (*C*-phenyl) and 167.3 (O–*C*–O); MS (*m/z*, %) 429 ($M^{+\cdot}$, 38), 414 ($M^{+\cdot}-CH_3$, 11), 361 ($M^{+\cdot}-C_5H_8$, 33), 316 (38), 128 (C_6H_5–N≡C–C≡CH^+, 13), 105 ($C_6H_5N_2^+$, 100), 77 ($C_6H_5^+$, 78), 69 ($C_5H_9^+$, 55), 51 ($C_4H_3^+$, 26), 41 (CH_3CN^+, 68) and 39 ($C_3H_3^+$, 14); HRMS (*m/z*) calcd for $C_{25}H_{23}N_3O_2S$ 429.1511, found 429.1506.

3.5.9. Compound 8a,b. The polycyclic compound **7** (300 mg, 0.7 mmol) was refluxed for 5 days in acetonitrile or 3 days in toluene. The two formed compounds were separated by chromatography on silica gel with dichloromethane as the eluent.

8a: crystallisation from chloroform–diethylether (43%), mp: 265°C; IR (KBr, cm^{-1}, 1600 FT) 1502 (s, phenyl), 1598 (m, phenyl), 1722 (s, CO), 2933 (w, alkyl), 2980 (m, alkyl) and 3052 (w, phenyl); ^1H NMR (400 MHz, $CDCl_3$, δ) 7.87, 7.65 and 7.58 (m, 5H, *ortho*, *para* and *meta* phenyl on azirine), 7.56, 7.42 and 7.29 (m, 5H, *ortho*, *meta* and *para* phenyl on pyrazole), 4.1 (d×d, 1H, H_a, $^3J_{ae}$=3.8 Hz, $^4J_{ee}$= 1.4 Hz), 3.66 (t, 1H, H_d, $^3J_{aa}$=12.9 Hz, $^2J_{gem}$=12.2 Hz), 3.26 (d×d, 1H, H_c, $^3J_{ae}$=2.5 Hz), 2.41 (d×d×d, 1H, H_b), 1.88 and 1.68 (2s, 2×3H, $2CH_3$) and 1.60 (s, 3H, CH_3 pyrazole); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 12.1 (CH_3 pyrazole), 23.6 (S–CH_2), 27.4 and 29.1 ($2CH_3$), 30.9 (C_a), 37.1 (C_a–*C*–CO), 42.4 (C_b), 81.6 (O–$C(CH_3)_2$), 109.6 (C_a–*C*–C–CH_3), 121.9, 129.6, 130.3 and 134.1 (C-1, C-3, C-2 and C-4 phenyl on azirine), 122.6, 127.0, 129.1 and 139.5 (C-2, C-4, C-3 and C-1 phenyl), 131.8 (N–*C*–S), 148.4 (*C*–CH_3 pyrazole) 155.1 (N=*C*) and 171.0 (CO); MS (*m/z*, %) 429 ($M^{+\cdot}$, 11), 361 ($M^{+\cdot}-C_5H_8$, 26), 258 ($M^{+\cdot}-C_5H_8-C_6H_5CN$, 21), 228 (17), 105 ($C_6H_5N_2^+$, 100), 77 ($C_6H_5^+$, 39), 69 ($C_5H_9^+$, 37), 51 ($C_4H_3^+$, 11) and 41 ($CH_3CN^+$, 29); HRMS (*m/z*) calcd for $C_{25}H_{23}N_3O_2S$ 429.1511, found 429.1518.

8b: crystallisation from chloroform–diethylether (50%), mp: 219.5°C; IR (KBr, cm^{-1} 1600 FT) 1501 (m, phenyl), 1596 (w, phenyl), 1715 (s, CO), 2937 (w, alkyl), 2978 (w, alkyl) and 3049 (w, phenyl); ^1H NMR (400 MHz, $CDCl_3$, δ) 7.56, 7.48 and 7.38 (5H, *ortho*, *para* and *meta* phenyl on azirine), 7.38, 7.28 and 7.23 (*meta*, *para* and *ortho* phenyl on pyrazole), 3.93 (d×d, 1H, H_a, $^3J_{ae}$=4.3 Hz, $^4J_{ee}$=1.1 Hz), 3.47 (t, 1H, H_d, $^3J_{aa}$=12.0 Hz, $^2J_{gem}$=13.3 Hz), 3.36 (d×d, 1H, H_c, $^3J_{ae}$=3.0 Hz), 2.43 (d×d×d, 1H, H_b), 2.02 (s, 3H, CH_3 pyrazole), 1.92 and 1.68 (2s, 2×3H, 2 CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 12.2 (CH_3 pyrazole), 24.1 (S–CH_2), 27.3 and 29.0 ($2CH_3$), 30.9 (C_a), 40.5 (C_a–*C*–CO), 42.0 (C_b), 81.6 (O–$C(CH_3)_2$), 111.4 (C_a–*C*–C–CH_3), 121.6, 129.1, 129.3 and 133.5 (C-1, C-3, C-2 and C-4 phenyl on azirine), 122.9, 127.4, 129.1 and 139.2 (C-2, C-4, C-3 and C-1 phenyl), 129.8 (N–*C*–S), 148.7 (*C*–CH_3 pyrazole) 159.2 (N=*C*) and 170.9 (CO); MS (*m/z*, %) 429 ($M^{+\cdot}$, 7), 401 ($M^{+\cdot}-C_2H_4^+$, 13), 361 ($M^{+\cdot}-C_5H_8$, 47), 258 ($M^{+\cdot}-C_5H_8-C_6H_5CN$, 37), 257 ($M^{+\cdot}-C_5H_9-C_6H_5CN$, 13), 228 (32), 227 (21), 128 (C_6H_5–N≡C–C≡CH^+, 14), 105 ($C_6H_5N_2^+$, 100), 77 ($C_6H_5^+$, 57), 69 ($C_5H_9^+$, 53), 51 ($C_4H_3^+$, 17) and 41 (CH_3CN^+, 38); HRMS (*m/z*) calcd for $C_{25}H_{23}N_3O_2S$ 429.1511, found 429.1512.

3.5.10. Compound 9a. Reaction of compound **2a** with indolone **5g**, reflux for 30 h. Chromatography with dichloromethane afforded the Knoevenagel adduct **9a** as a yellow oil (74%); IR (CCl_4, cm^{-1} 1600 FT) 1549 (s, phenyl), 1718 (m, CO), 2929 (w, alkyl) and 3063 (w, phenyl); ^1H NMR (400 MHz, $CDCl_3$, δ) 7.83 (s, 1H, imine), 7.70–7.61 and 7.58–7.35 (2 m, 10 H, phenyl on pyrazole and phenyl on

indole), 7.27 (d, 1H, H-7 indole), 7.17 (t, 1H, H-6 indole), 6.99 (t, 1H, H-5 indole), 6.58 (d, 1H, H-4 indole), 4.96 (t, 1H, C*H*═), 3.13 (d, 2H, S–CH_2, ^3J=7.9 Hz), 2.32 (s, 3H, CH_3 pyrazole) and 1.52 and 1.31 (2s, 2×3H, $2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 13.7 (CH_3 pyrazole), 17.3 and 25.5 ($2CH_3$), 34.3 (CH_2), 109.3 (C-7 indole), 118.4 (CH_2–C═), 121.7 (C-4 pyrazole), 122.3, 123.4 and 125.3 (C-4, C-5 and C-6 indole), 126.5 (C-3a indole), 127.8, 128.0, 128.6, 128.7, 129.3, 129.4, 129.7 and 134.6 (phenyl), 128.1 (C-3 indole), 129.5 (C imine), 137.5 (*C*(CH_3)), 139.2 (C-5 pyrazole), 143.7 (C-7a indole) 148.5 (C-3 pyrazole) and 167.3 (C-2 indole); MS (*m*/*z*, %) 477 ($M^{+\cdot}$, 25), 376 ($M^{+\cdot}-C_5H_8S$, 100), 408 ($M^{+\cdot}-C_5H_9^+$, 23), 393 ($M^{+\cdot}-C_5H_9^+-CH_3$, 18), 204 (22), 77 ($C_6H_5^+$, 22), 69 ($C_5H_9^+$, 31) and 41 (CH_3CN^+, 31).

3.5.11. Compound 9b. Reaction of compound **2a** with coumaranone **5h**, reflux for 24 h. Chromatography with dichloromethane afforded the Knoevenagel adduct **9b** as a yellow oil (67%); IR (CCl_4, cm^{-1} 1600 FT) 1548 (s, phenyl), 1793 (s, CO), 2930 (w, alkyl), 2976 (w, alkyl) and 3064 (w, phenyl); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.79 (s, 1H, imine), 7.69–7.67 (d, 2H, *ortho* phenyl), 7.52–7.48 (t, 2H, *meta* phenyl), 7.43–7.41 (t, 1H, *para* phenyl), 7.35–7.20 and 7.15–7.05 (2 m, 4H, coumaranone), 4.92 (t×t, 1H, C*H*═), 3.09 (d, 2H, S–CH_2, ^3J=7.9 Hz), 2.28 (s, 3H, CH_3 pyrazole), 1.49 and 1.27 (2s, 2×3H, $2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 13.6 (CH_3 pyrazole), 17.0 and 25.2 ($2CH_3$), 34.2 (CH_2), 110.6 (C-7 coumaranone), 118.1 (CH_2–C═), 121.7 (C-4 pyrazole), 122.1, 123.2 and 124.5 (C-4, C-5 and C-6 coumaranone), 123.4 (C-3a coumaranone), 128.0, 128.9 and 129.4 (C-2, C-3 and C-4, phenyl), 130.2 (C-3 coumaranone), 130.9 (C imine), 134.9 (C-1, phenyl), 137.4 (*C*(CH_3)), 138.9 (C-5 pyrazole), 148.3 (C-3 pyrazole), 154.0 (C-7a indole) and 168.1 (C-2 indole); MS (*m*/*z*, %) 402 ($M^{+\cdot}$, 60), 336 ($M^{+\cdot}-C_5H_6$, 27), 335 ($M^{+\cdot}-C_5H_7$, 44), 334 ($M^{+\cdot}-C_5H_8$, 100), 307 ($M^{+\cdot}-C_5H_7$–CO, 27), 306 $M^{+\cdot}-C_5H_8$–CO, 79), 302 ($M^{+\cdot}-C_5H_7S$, 28), 301 ($M^{+\cdot}-C_5H_9S$, 82), 145 ($M^{+\cdot}-C_9H_5O^+$, 23), 77 ($C_6H_5^+$, 39), 69 ($C_5H_9^+$, 66), 51 ($C_4H_3^+$, 16) and 41 (CH_3CN^+, 55).

3.5.12. Compound 17. Reaction of compound **14** with pyrazolone **5b**, reflux for 60 h. Chromatography with dichloromethane. Yellow crystals from chloroform–diethylether (98%), mp: 167.3°C; IR (KBr, cm^{-1}, 1600 FT) 1512 (s), 1574 (m), 1596 (m), 2908 (br, aliph CH), 3063 (w, arom CH); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.57 (s, 1H, H-2 pyrimidine), 7.72 (d, 2H, *ortho* H, ^3J=7.5 Hz), 7.38 (tr, 2H, *meta* H, ^3J=7.5 Hz), 7.18 (tr, 1H, *para* H, ^3J=7.5 Hz), 5.38 (tr, CH═, ^3J=7.9 Hz, ^4J=1.4 Hz), 4.49 (d, 1H, H_a, $^3J_{ae}$=4 Hz), 3.94 (m, 2H, CH_2), 3.05 (d×d, 1H, H_d, $^2J_{gem}$= 12.7 Hz, $^3J_{aa}$=11.6 Hz), 2.98 (d×d×d, 1H, H_c, $^3J_{ae}$=4 Hz, $^4J_{aa}$=1 Hz), 2.01 (d×d×d, 1H, H_b), 1.93 (s, 3H, CH_3 pyrazole), 1.60–1.59 (2×s, 2×3H, CH_3 pyranring), 1.76–1.74 (2×s, 2×3H, CH_3 alkene); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 13.3 (CH_3 pyrazole), 17.9 and 25.6 ($2CH_3$ alkene), 23.5 (S–CH_2), 28.5 (S–CH_2 alkene), 26.0 and 26.7 ($2CH_3$ furan), 30.1 (C_a), 37.2 (C_b), 81.8 (*C*(CH_3) furan), 93.6 (C_a–*C*═CCH_3), 118.1 (CH_2–C═alkene), 120.4 (C-2, phenyl), 122.1 (C-5 pyrimidine), 125.5 (C-4, phenyl), 128.8 (C-3, phenyl), 137.3 (═*C*–$(CH3)_2$), 138.6 (C-1, phenyl), 146.5 (*C*–CH_3 pyrazole), 148.1 (N–*C*–O), 155.0 (C-2 pyrimidine), 163.8 (C-6 pyrimidine) and 169.4 (C-4 pyrimidine); MS (*m*/*z*, %) 464 ($M^{+\cdot}$, 19) and 395 ($M^{+\cdot}-C_5H_9$, 100); HRMS (*m*/*z*) calcd for $C_{25}H_{28}N_4OS_2$ 464.1705, found 464.1705.

3.5.13. Compound 18a,b. Reaction of compound **14** with isoxazolone **5f**, reflux for 60 h. Chromatography with dichloromethane–*n*-hexane afforded two azirine compounds **19a**,**b**.

18a: crystallization from methanol (52%), mp: 178.3°C; IR (KBr, cm^{-1}, 1600 FT) 1504 (m, phenyl), 1525 (s, phenyl), 1720 (s, ═O), 1766 (W), 2922 (w, aliph H), 2984 (w, aliph H), 3070 (w, arom H); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.22 (s, 1H, H pyr), 7.66 (d, 2H, *ortho* phenyl), 7.5 (tr, 1H, *para* phenyl), 7.42 (tr, 2H, *meta* phenyl), 5.29 (tr,1H, CH═), 4.28 (d×d, 1H, H_a, $^3J_{ae}$=3.8 Hz, $^4J_{aa}$=1.7 Hz), 3.82/3.74 (d×m, 2H, S–CH_2 alkene), 3.63 (d×d, 1H, H_d, $^3J_{gem}$=12.9 Hz, $^3J_{aa}$=12.9 Hz), 3.37 (d×tr, 1H, H_c, $^3J_{ae}$=4 Hz), 2.39 (d×tr,1H, Hb), 1.9/1.62 (2×s, 2×3H, 2 CH_3), 1.73 (s, 2×3H, $2CH_3$ alkene); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 17.9 and 25.7 (CH_3 alkene), 24.0 (S–CH_2), 26.8 and 29.0 (CH_3 furan), 29.4 (S–CH_2 alkene), 35.1 (C_a), 39.2 (C_b), 38.7 (C_a–*C*–CO), 81.7 (*C*(CH_3) furan), 118.2 (*C*H═), 120.1 (C-5 pyridine), 121.1, 129.2, 129.5 and 133.7 (phenyl), 137.4 (═*C*–$(CH3)_2$), 154.9 (C-2 pyridine), 156.5 (*C*-phenyl), 163.3 (C-6 pyridine), 169.8 (C-4 pyridine) and 170.0 (CO); MS (*m*/*z*, %) 452 ($M^{+\cdot}$+1, 100); HRMS (*m*/*z*) calcd for $C_{24}H_{25}N_3O_2S_2$ 451.1388, found 451.1402.

18b: crystallization from methanol (18%), mp: 180.1°C; IR (KBr, cm^{-1}, 1600 FT) 1529 (s, phenyl), 1715 (s, ═O), 1762 (w), 2924 (w,aliph H), 2974 (w, aliph H), 3036 (w, arom H); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.42 (s, 1H, 1H pyr), 7.82 (d, 2H, *ortho* phenyl), 7.57 (tr, 1H, *para* phenyl), 7.49 (tr, 2H, *meta* phenyl), 4.70 (tr, 1H, CH═), 4.39 (d×d, 1H, H_a, $^3J_{ae}$=3.3 Hz, $^4J_{aa}$=1.8 Hz), 3.50/3.40 (d×m, 2H, S–CH_2 alkene), 3.83 (d×d, 1H, H_d, $^2J_{gem}$=12.8 Hz, $^3J_{aa}$=12.8 Hz), 3.28 (d×tr, 1H, H_c, $^3J_{ae}$=3.5 Hz), 2.39 (d×tr, 1H, H_b), 1.85/1.62 (2×s, 2×3H, $2CH_3$), 1.59/1.47 (2×s, 2×3H, $2CH_3$ alkene); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 17.6 and 25.6 (CH_3 alkene), 23.9 (S–CH_2), 26.9 and 29.1 (CH_3 furan), 28.2 (S–CH_2 alkene), 33.6 (C_a), 35.9 (C_a–*C*–CO), 39.0 (C_b), 82.1 (*C*(CH_3) furan), 117.0 (*C*H═), 118.9 (C-5 pyridine), 122.3, 128.8, 130.7 and 133.3 (phenyl), 137.4 (═*C*–$(CH3)_2$), 155.2 (C-2 pyridine), 156.8 (*C*-phenyl), 165.1 (C-6 pyridine), 168.0 (C-4 pyridine) and 170.4 (CO); MS (*m*/*z*, %) 452 ($M^{+\cdot}$+1, 100); HRMS (*m*/*z*) calcd for $C_{24}H_{25}N_3O_2S_2$ 451.1388, found 451.1392; X-ray structural analysis: $C_{24}H_{25}N_3O_2S_2$, MW=451.39, a white transparent crystal of 0.2×0.2×0.2 mm^3 size, space group *P*-1, *Z*=2, triclinic, *a*=9.876(2), *b*=11.303(2), *c*=11.640(2) Å, α=72.55(1), β=81.79(1), γ=79.03(1)°, *V*=1211.81(4) $Å^3$, d_{calc}= 1.237 g cm^{-3}, *F*(000)=476, *T*=289 K, ω-scan, $\Delta\omega$=0.60°, $2.0<\omega<60.0°$ min^{-1}, 3705 collected reflections ((sin θ/λ)max=0.53), 2951 unique reflections (R_{int}=3.4%). Final *R*-values: R_1=0.0484 for 2090 reflections with $I>2\sigma(I)$ and R_1=0.0796, wR_2=0.1288 for all reflections. The asymmetric unit contains a disordered methanol molecule. For the prenyl thiolate substituent two conformations have been refined with population parameters 0.71 and 0.29.

3.5.14. Compound 19. Reaction of compound **15** with

pyrazolone **5b**, reflux for 48 h. Chromatography with dichloromethane–diethylether 10/1. Yellow powder from chloroform–diethylether (39%), mp: 156.2°C; IR (KBr, cm^{-1}, 1600 FT) 3055 (w, pyrimidine H), 2924 and 2860 (m, aliph H), 1729 (w), 1575 (s, phenyl), 1516 (s, phenyl); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.28 (s, 1H, pyri H), 7.70 (d, 2H, *ortho* H), 7.39 (tr, 2H, *meta* H), 7.22 (tr, 1H, *para* H), 5.77 (m, 1H, C*H*=CH_2), 5.16 (d, 1H, CH=CH_2), 5.05 (d, 1H, CH=CH_2), 4.55 (m, 4H, H_a, N–CH_2 (1H), O–CH_2), 3.92 (d×d, 1H, N–CH_2,), 3.50 (d×d, 1H, H_d, $^2J_{gem}$=12.6 Hz, $^3J_{aa}$=12.6 Hz), 3.33 (d×d, 1H, H_c, $^3J_{ae}$=5.4), 2.35 (d×d, 1H, H_b, $^3J_{ae}$=5.2), 2.05 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 13.5 (CH_3), 28.1 (C_a), 30.9 (C_b), 44.0 (N–CH_2), 50.6 (N–CH_2 alkene), 69.8 (O–CH_2), 95.2 (C_a–*C*–CCH_3), 117.3 (CH=*C*H_2), 120.1 (C-5 pyrimidine), 120.5 (C-2, phenyl), 125.8 (C-4, phenyl), 127.0 (C-1, phenyl), 128.9 (C-3, phenyl), 131.8 (*C*H=CH_2), 147.1 (C_aC–*C*–CH_3), 147.6 (N–*C*–O), 156.5 (C-2 pyrimidine) and 158.8 and 158.2 (C-4 and C-6 pyrimidine); MS (*m*/*z*, %) 393 ($M^{+\cdot}$, 37), 378 ($M^{+\cdot}-CH_3$, 12), 206 (61), 77 ($C_6H_5^+$, 64), 51 ($C_4H_3^+$, 19), 41 ($C_3H_6^+$, 100) and 39 ($C_3H_3^+$, 32); HRMS (*m*/*z*) calcd for $C_{21}H_{20}N_5O$ 393.1356, found 393.1359.

3.5.15. Compound 20a,b. Reaction of compound **15** with isoxazolone **5f**, reflux for 70 h. Chromatography with dichloromethane–diethylether 9/1 afforded two azirine compounds **20a**,**b**.

20a: crystallization from chloroform–diethylether (19%), mp: 225°C; IR (KBr, cm^{-1}, 1600 FT) 3067 (w, arom H), 2973 (w, aliph H), 2919 (w, aliph H), 1768 (s), 1579 (s, phenyl) and 1515 (m, phenyl); ^{1}H NMR (400 MHz, CDCl3, δ) 7.93 (s, 1H, pyridine H), 7.51 (tr, 1H, *para* H), 7.48 (d, 2H, *ortho* H), 7.40 (d, 2H, *meta* H), 5.83 (m, 1H, C*H*=CH_2), 5.30 (d×d, 2H, CH=CH_2), 4.94 (d×d, 1H, O–C*H*, $^2J_{gem}$=12.1 Hz, $^3J_{aa}$=2.6 Hz), 4.57 (d×d, 1H, O–C*H*, $^3J_{ae}$=1.7 Hz), 4.37–4.18 (AB-pattern, 2H, N–CH_2), 4.26 (d×d, 1H, H_a, $^3J_{ae}$=4.4 Hz), 3.98 (d×d, 1H, H_d, $^2J_{dc}$=12.9 Hz, $^3J_{aa}$=12.9 Hz), 3.62 (d×d, 1H, H_c, $^3J_{ae}$=5.5 Hz, $^4J_{aa}$=1.7 Hz), 2.62 (d×d, 1H, H_b); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 29.6 (C_a), 36.9 (C_b), 39.1 (C_a–*C*–CO), 44.7 (N–CH_2), 51.1 (N–CH_2 alkene), 68.9 (O–CH_2), 107.6 (C-5 pyridine), 118.9 (CH=*C*H_2), 121.0, 129.2, 129.3 and 133.9 (phenyl), 131.4 (*C*H=CH_2), 156.7 (C-2 pyridine), 157.8, 158.26 and 158.32 (*C*-phenyl, C-4 and C-6 pyridine) and 170.0 (CO); MS (*m*/*z*, %) 381 ($M^{+\cdot}$+1, 100); HRMS (*m*/*z*) calcd for $C_{20}H_{17}ClN_4O_2$ 380.1040, found 380.1036.

20b: crystallization from chloroform–diethylether (29%), mp: 176.2°C; IR (KBr, cm^{-1}, 1600 FT) 3026 (w, arom H), 2963 (w, aliph H), 2925 (w, aliph H), 1721 (s), 1581 (s, phenyl) and 1514 (w, phenyl); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.18 (s, 1H, pyri H), 7.85 (d, 2H, *ortho* phenyl), 7.58 (tr, 1H, *para* phenyl), 7.52 (tr, 2H, *meta* H), 5.85 (m, 1H, C*H*=CH_2), 5.25 (d×d, 2H, CH=CH_2 alkene), 4.89 (d×d, 1H, O–C*H*, $^2J_{gem}$=12.1 Hz, $^3J_{aa}$=3.1 Hz), 4.56 (d, 1H, O–C*H*, $^3J_{ae}$=1.5 Hz), 4.39–4.26 (AB-pattern, 2H, N–CH_2), 4.26 (d, 1H, H_a, $^3J_{ae}$=4 Hz), 4.10 (d×d, 1H, H_d, $^2J_{gem}$=12.8 Hz, $^3J_{aa}$=12.8 Hz), 3.50 (d×d, 1H, H_c, $^3J_{ae}$= 5 Hz, $^4J_{aa}$=1.9 Hz), 2.60 (d×d, 1H, H_b); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 29.7 (C_a), 35.9 (Cb), 36.0 (C_a–*C*–CO), 44.7 (N–CH_2), 50.9 (N–CH_2 alkene), 69.3 (O–CH_2), 106.5 (C-5 pyridine), 117.5 (CH=*C*H_2), 121.5, 129.1, 130.5 and 133.9 (phenyl), 131.7 (*C*H=CH_2), 156.4 (*C*-phenyl), 156.8 (C-2 pyridine), 157.3 and 159.3 (C-4 and C-6 pyridine) and 170.1 (CO); MS (*m*/*z*, %) 381 ($M^{+\cdot}$+1, 100); HRMS (*m*/*z*) calcd for $C_{20}H_{17}ClN_4O_2$ 380.1040, found 380.1039.

3.5.16. Compound 27. Reaction of compound **24** with pyrazolone **5b**, reflux for 72 h. Chromatography with dichloromethane–diethylether 10/1. White–yellow powder from ethanol (88%), mp: 243.8°C; IR (KBr, cm^{-1}, 1600 FT) 1608 (s, phenyl), 2914 (w, alkyl), 2952 (w, alkyl) and 3058 (w, phenyl); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.76–7.72 and 7.66–7.24 (2 m, 10H, phenyl), 7.23–7.15 (m, 3H, H-4, H-5, H-6 indole), 7.10 (d, 1H, H-7 indole), 4.58 (br d, 1H, H_a, $^3J_{ae}$=3.7 Hz), 3.12 (d×d, 1H, H_c, $^3J_{ae}$=1.3 Hz), 3.06 (d×d, 1H, H_d, $^3J_{aa}$=12.7 Hz, $^2J_{gem}$=12.2 Hz), 2.08 (d×d×d, 1H, H_b), 1.95 (s, 3H, CH_3), 1.65 and 1.62 (2s, 2×3H, 2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 15.0 (CH_3 pyrazole), 23.5 (S–CH_2), 26.4 (C_b), 26.4 and 26.5 (2CH_3), 40.4 (C_a), 81.7 (O–*C*(CH_3)$_2$), 97.9 (C_a–*C*–CCH_3), 107.3 (C_a–*C*–indole), 109.5 (C-7 indole), 117.2, 120.0 and 121.0 (C-4, C-5 and C-6 indole), 125.3 (C-3a indole), 120.4, 127.2, 128.0, 128.9, 128.5 and 1296 (phenyl), 137.0 (C-1, phenyl indole), 137.7 (C-1, phenyl pyrazole), 138.2 and 138.3 (N–*C*–S and C-7a indole), 147.6 (*C*–CH_3 pyrazole), 147.7 (N–*C*–O); MS (*m*/*z*, %) 477 ($M^{+\cdot}$, 25), 376 ($M^{+\cdot}-C_5H_9S$, 100), 204 (13), 77 ($C_6H_5^+$, 26), 69 ($C_5H_9^+$, 19), 51 ($C_4H_3^+$, 10) and 41 (CH_3CN^+, 44); HRMS (*m*/*z*) calcd for $C_{30}H_{27}N_3OS$ 477.1875, found 477.1840.

3.5.17. Compound 28. Reaction of compound **26** with pyrazolone **5b**, reflux for 1 h. The precipitate is collected and is characterized as the Knoevenagel adduct **28**. This powder is of satisfactory quality for further use (89%), mp: 151.8°C; IR (KBr, cm^{-1}, 1600 FT) 1696 (s, CO), 2962 (w, aliph H); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.03–8.00 (d×d, 2H, *ortho* H), 7.97 (s, 1H, imine H), 7.94–7.91 (m, 2H, *ortho* H), 7.51–7.49 (m, 3H, *meta* and *para* H), 7.44–7.39 (d×d, 2H, *meta* H), 7.19–7.15 (tr, 1H, *para* H), 5.34 (tr×m, 1H, CH=), 3.59 (d, 2H, S–CH_2), 2.79 (s, 3H, CH_3 pyrazole), 1.69 (s, 3H, CH_3) and 1.52 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 17.8 (CH_3), 19.5 (CH_3), 25.8 (CH_3), 37.3 (S–CH_2), 118.6 (*C*–CO), 118.3, 124.6, 125.5, 126.6, 128.8, 129.3, 131.1, 131.9, 132.8, 138.5 (Phenyl), (*C*H imine), 139.4 (*C*(CH_3)$_2$), 144.2 (C-4 thiazole), 148.9 (*C*–CH_3 pyrazole), 151.7 (C-5 thiazole), 165.1 (C-2 thiazole) and 165.1 (CO); MS (*m*/*z*, %) 445 ($M^{+\cdot}$, 10), 377 ($M^{+\cdot}-C_5H_8$, 57), 344 ($M^{+\cdot}-C_5H_9S$, 100), 69 ($C_5H_9^+$, 19).

3.5.18. Compound 29. Heating of compound **28** in xylene afforded after 15 h the required ring-closed product **29**. Chromatography with dichloromethane–diethylether 10/1 (52%) mp: 194.5°C; IR (CCl_4, cm^{-1}, 1600 FT) 1549 (s, arom H), 2289 (w), 2927 (w, aliph H), 2984 (w, aliph H) and 3066 (w, arom H); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.91–7.88 (d×d, 2H, *ortho* H), 7.75–7.73 (d×d, 2H, *ortho* H), 7.46–7.36 (m, 5H, 2 *meta* and *para* H), 7.21–7.17 (t, 1H, *para* H), 4.54 (d, 1H, H_a, $^3J_{ae}$=4.48 Hz), 3.08 (m, 2H, H_c and H_d), 2.27 (s, 3H, CH_3 pyrazole), 2.25–2.21 (m, 1H, H_b), 1.65 (s, 3H, CH_3) and 1.53 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 15.3 (CH_3 pyrazole), 24.9 (CH_2–S),

25.9 (CH_3), 26.1 (CH_3), 32.0 (C_b), 41.7 (C_a), 81.7 ($C(CH_3)_2$), 96.2 (C_a–C–CCH_3), 124.1 (C_a–C–N), 120.4, 125.3, 125.9, 128.8, 129.0 and 129.7 (phenyl), 133.5 and 138.7 (2C-1, Phenyl), 146.8 and 147.6 (C–CH_3 and O–C–N–phenyl), 147.9 (S–C–S), 162.6 (C-2 thiazole); MS (*m/z*, %) 446 ($M^{+\cdot}$+1, 100); HRMS (*m/z*) calcd for $C_{25}H_{23}N_3O_2S_2$ 445.1283, found 445.1276.

3.5.19. Compound 30. Reaction of compound **25** with pyrazolone **5b**, reflux for 36 h. Chromatography with dichloromethane afforded an oily product **30** (65%); IR (KBr, cm^{-1}, 1600 FT) 1549 (s, arom H), 2289 (w), 2858 (w, aliph H) and 2925 (w, aliph H); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.94–7.91 (d, 2H, *ortho* phenyl), 7.749–7.72 (d, 2H, *ortho* phenyl), 7.44–7.37 (m, 5H, 2 *meta* and *para* phenyl), 7.23–7.19 (t, 1H, *para* phenyl), 4.41 (d, 1H, H_a, $^3J_{aa}$=4.7 Hz), 3.3.27 (d×d, 1H, H_c, $^2J_{gem}$=13.4 Hz, $^3J_{ae}$=3.0 Hz), 3.2–3.14 (d×d, 1H, H_d, $^3J_{aa}$=9.3 Hz), 2.36 (s, 3H, CH_3 pyrazole), 2.33–2.27 (m, 1H, H_b), 1.60 (s, 3H, CH_3) and 1.54 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 15.5 (CH_3 pyrazole), 25.0 (CH_2–S), 25.1 (CH_3), 26.6 (CH_3), 29.7 (C_b), 41.1 (C_a), 82.2 ($C(CH_3)_2$), 96.4 (C_a–C–CCH_3), 128.91 (N–C–S), 120.5, 125.6, 126.4, 128.9, and 130.2 (phenyl), 133.1 and 138.6 (C-1, phenyl), 143.7 (C_a–C–S), 146.4 and 148.1 (C–CH_3 and N–C–O) and 166.1 (C-2 thiazole); MS (*m/z*, %) 445 ($M^{+\cdot}$, 33) and 344 (100); HRMS (*m/z*) calcd for $C_{25}H_{23}N_3O_2S_2$ 445.1283, found 445.1286.

3.5.20. Compound 33. Reaction of compound **32** with pyrazolone **5b**, reflux for 12 h. Chromatography with dichloromethane–diethylether 8/1 afforded an oily red product (56%); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 9.25 (s, 1H, pyridine H), 8.02 (d×d, 2H, *ortho* phenyl), 7.70 (d×d, 2H, *ortho* H), 7.42 (s, 1H, imine H), 7.33–7.39 (m, 4H, *meta* phenyl), 7.18–7.08 (2 tr, 2H, *para* phenyl), 6.00–5.92 (m, 2H, 2 CH=CH_2 chain), 5.84–5.74 (m, 1H, CH=CH_2 six membered ring), 5.31–5.11 (m, 6H, CH_2=CH), 4.43–4.28 (m, 3H, O–CH_2, H_c of H_d), 4.17 (d, 1H, H_a, $^3J_{ae}$=4.6 Hz), 4.16–4.00 (m, 5H, H_c of H_d, N–(CH_2–CH=CH_2)$_2$), 3.55–3.46 (m, 2H, N–CH_2), 2.43 (m, 1H, H_b), 2.31 (s, 3H, CH_3) and 2.22 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 13.8 (CH_3), 14.3 (CH_3), 29.9 (C_b), 32.3 (C_a), 45.7 (N-CH_2 six membered ring), 51.1 (N–CH_2–CH=CH_2), 54.2 (2N–CH_2–CH=CH_2), 69.7 (O–CH_2), 97.6 (C–CCH_3), 105.7 and 109.3 (C-3 and C-5 pyridine), 117.2 (2N–CH_2–CH=CH_2), 117.5 (C–CH_3 imine and N–CH_2–CH=CH_2), 118.9 and 120.3 (C-2, phenyl), 123.9 and 125.4 (C-4, phenyl), 128.5 and 128.8 (C-3, phenyl), 132.9 (N–CH_2–CH=CH_2), 134.5 (2N–CH_2–CH=CH_2), 138.5 and 139.3 (C-1, phenyl), 142.9 (d×d, C-4 pyridine, ^1J=142 Hz), 143.3 (d×m, CH imine, ^1J=158 Hz), 148.0 (CH_2–O–C), 148.1 (q, C–CH_3), 151.1 (q×d, C–CH_3 imine), 154.4 and 162.9 (C-2 and C-6 pyridine) and 163.0 (CO, ^3J=10 Hz); MS (*m/z*, %) 637 ($M^{+\cdot}$, 100); HRMS (*m/z*) calcd for $C_{39}H_{39}N_7O_2$ 637.3165, found 637.3169.

3.5.21. Compound 34. Heating of compound **33** in toluene (15 ml) afforded after 15 h the required ring-closed products **34a**,**b**. Chromatography with dichloromethane–diethylether 7/1 (**34a** 30%, **34b** 43%)

34a: mp 234°C (chloroform–diethylether); IR (KBr, cm^{-1}, 1600 FT) 1549 (s, arom H) and 3070 (w, arom H); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.67–7.63 (d×m, 4H, *ortho* H), 7.37–7.33 (d×d, 4H, *meta* H), 7.19–7.15 (tr, 2H, *para* H), 7.04 (s, 1H, pyridine H), 5.83 (m, 2H, CH=), 5.12 (m, 4H, CH_2=CH), 4.34–4.31 (d×d, 2H, OCH_2, $^2J_{gem}$=10.8 Hz, $^3J_{ae}$=3.0 Hz), 4.29–4.22 (m, 4H, O–CH_2, $^3J_{aa}$=8.0 Hz and N–CH_2–CH=), 4.07–4.01 (d×d, 2H, N–CH_2–CH=), 3.97 (d, 2H, H_a, $^3J_{ae}$=4.8 Hz), 3.51 (d×d, 2H, H_c, $^2J_{gem}$=12.3 Hz, $^3J_{ae}$=4.4 Hz), 3.29 (d×d, 2H, H_d, $^3J_{aa}$=6.0 Hz), 2.44 (m, 2H, H_b) and 2.08 (s, 6H, 2 CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 13.8 (CH_3), 30.7 (C_b), 31.7 (C_a), 46.3 (N–CH_2), 50.9 (N–CH_2–CH=), 70.1 (O–CH_2), 99.5 (C_a–C–CCH_3), 104.2 (C-3 pyridine), 116.3 (CH=CH_2), 120.6 (C-2, phenyl), 125.5 (C-4, phenyl), 128.8 (C-3, phenyl), 134.8 (CH=CH_2), 138.6 (C-1, phenyl), 141.1 (C-4 pyridine), 146.8 (C–CH_3), 148.4 (CH_2–O–C) and 150.7 (C-2 pyridine); MS (*m/z*, %) 637 ($M^{+\cdot}$, 100), 622 ($M^{+\cdot}$–CH_3, 33), 450 (57); HRMS (*m/z*) calcd for $C_{39}H_{39}N_7O_2$ 637.3165, found 637.3165.

34b: mp 245°C (chloroform–diethylether); IR (KBr, cm^{-1}, 1600 FT) 1560 (s, arom), 1599 (s, arom), 3070 (w arom H); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.74–7.72 (d×m, 4H, *ortho* H), 7.40–7.36 (d×d, 4H, *meta* H), 7.21–7.16 (tr, 2H, *para* H), 6.98 (s, 1H, pyridine H), 5.82 (m, 2H, CH=), 5.12 (m, 4H, CH_2=CH), 4.35–4.31 (d×d, 2H, OCH_2, $^2J_{gem}$=10.6 Hz, $^3J_{ae}$=3.2 Hz), 4.29–4.22 (m, 4H, O–CH_2, $^3J_{aa}$=9.2 Hz), 4.23–4.08 (AB systeem, 4H, N–CH_2–CH=), 3.90 (d, 2H, H_a, $^3J_{ae}$=4.6 Hz), 3.57 (d×d, 2H, H_c, $^2J_{gem}$=12.4 Hz, $^3J_{ae}$=4.2 Hz), 3.29 (d×d, 2H, H_d, $^3J_{aa}$=4.5 Hz), 2.39 (m, 2H, H_b) and 2.26 (s, 6H, 2 CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 13.8 (CH_3), 30.7 (C_b), 31.3 (C_a), 46.7 (N–CH_2), 51.0 (N–CH_2–CH=), 69.8 (O–CH_2), 99.9 (C_a–C–CCH_3), 104.9 (C-3 pyridine), 116.3 (CH=CH_2), 120.4 (C-2, phenyl), 125.4 (C-4, phenyl), 128.9 (C-3, phenyl), 134.8 (CH=CH_2), 138.8 (C-1, phenyl), 140.5 (C-4 pyridine), 147.1 (C–CH_3), 148.8 (CH_2–O–C) and 150.4 (C-2 pyridine); MS (*m/z*, %) 637 ($M^{+\cdot}$, 100), 622 ($M^{+\cdot}$–CH_3, 32), 450 (45); HRMS (*m/z*) calcd for $C_{39}H_{39}N_7O_2$ 637.3165, found 637.3173.

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