Synthesis and insecticidal evaluation of aryl pyrazole 5-fluorouracil compounds

Yue Chen, Xiao-Dong Fu, Hai-Ping Mu, Xiao-Fei Qin and Rong Wan*

Department of Applied Chemistry, College of Science, Nanjing University of Technology, Nanjing 210009, P.R. China

Twenty eight aryl pyrazole derivatives containing 5-fluorouracil were designed and synthesised *via* the key intermediate 1-aryl-3-methyl-1*H*-pyrazole-5-carboxylic acid. The structures of target compounds were confirmed by ^{1}H NMR, FT-IR, EA and their insecticidal activities were evaluated. The bioassays revealed that aryl pyrazole derivatives containing 5-fluorouracil exhibited excellent insecticidal activities against *Culex pipiens* and *Musca domestica* at a concentration of 0.1%. Some compounds still showed good insecticidal activities even at a concentration of 0.05%.

Keywords: aryl pyrazole, 5-fluorouracil, insecticidal activity

Aryl pyrazole derivatives occupy an important position in medicinal and pesticide chemistry because of their diverse bioactivities. They are widely used as insecticides,[1–7] fungicides[8,9] and acaricides.[10–12] For example, as shown in Fig. 1, geranyl pyrazole-5-formate (Compound **A**), designed and synthesised by Sun *et al.*[2] was proved to possess an excellent insecticidal activity against aphids. The aryl pyrazole derivative (Compound **B**), displayed a strong action against *Plutella xylostella*, *Heliothis virescens* and certain other species of sucking insects.[4] Chlorantraniliprole analogue (Compound **C**), was reported to show an excellent performance on controlling a spectrum of agronomic invertebrate pests.[5] With growing applications on their synthesis and bioactivity, chemists and biologists have directed considerable attention to the research and application of aryl pyrazole derivatives in recent years.

On the other hand, 5-fluorouracil plays an important role in biologically active compounds. As a fluoropyrimidine, the mechanism of cytotoxicity of 5-fluorouracil has been ascribed to the misincorporation of fluoronucleotides into RNA and DNA and to the inhibition of the nucleotide synthetic enzyme thymidylate synthase. 5-Fluorouracil can be converted intracellularly to several active metabolites: fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP) and fluorouridine triphosphate (FUTP), and these active metabolites restrain the action of thymidylate synthase and disrupt RNA and DNA synthesis and repair.[13] Due to these satisfying advantages, 5-fluorouracil and its derivatives have been widely used as antitumour agents in the treatment of colon cancer,[14,15] gastric cancer[16,17] and oesophageal cancer.[18] However, there were little studies on the modification of heterocyclic derivatives with 5-fluorouracil. In our previous work, we found that incorporation of 5-fluorouracil with bioactive 1,3,4-thiadiazole compounds resulted in higher insecticidal activity.[19] We conceived that 5-fluorouracil group can be used as an important skeleton to explore bioactive molecules. Based on these results, we modified aryl pyrazole compounds with 5-fluorouracil and did get many novel heterocyclic compounds with superior bioactivities.[20]

Here, following our earlier report[20], we describe the design and synthesis of 28 aryl pyrazole derivatives containing 5-fluorouracil (Fig. 2). The insecticidal activities of the target compounds against *Culex pipiens* and *Musca domestica* were tested and are discussed here. In order to discover structure–activity relationships (SAR), different substituents were introduced to the aromatic ring and SAR are also discussed here in detail.

Results and discussion

The synthetic route designed for the synthesis of target compounds is shown in Scheme 1. Acetone **(1)** was advanced *via* intermediate **(2)** to afford the series **3-(1-28)** which, in turn, were advanced *via* the series **4-(1-28)** to give the series of aryl pyrazole-5-carboxylic acids **5-(1-28)** in 45–75% yields.[2,21]

Introduction of 2-chloroacetic acid into 5-fluorouracil **(6)** by nucleophilic substitution provided 2-(5-fluorouracil-1-yl) acetic acid **(7)** in 80% yield, which was further allowed to react with 2-aminoethanol to give compound **(8)** in the presence of peptide coupling reagents in 85% yield. The formation of intermediate **(8)** can be viewed as a simple amidation reaction. Initially, we attempted to employ 2-(5-fluorouracil-1-yl) acetic acid **7** to react directly with 2-aminoethanol to afford **(8)**. However, attempts by direct amidation were unsuccessful. Then, introduction of peptide coupling reagents made the transformation possible.

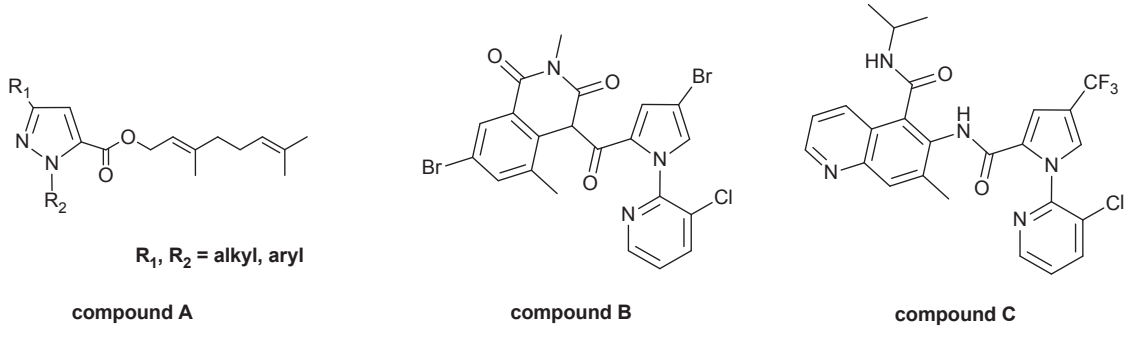


Fig. 1 Structures of some aryl pyrazole derivatives.

* Correspondent. E-mail: rwan@njut.edu.cn

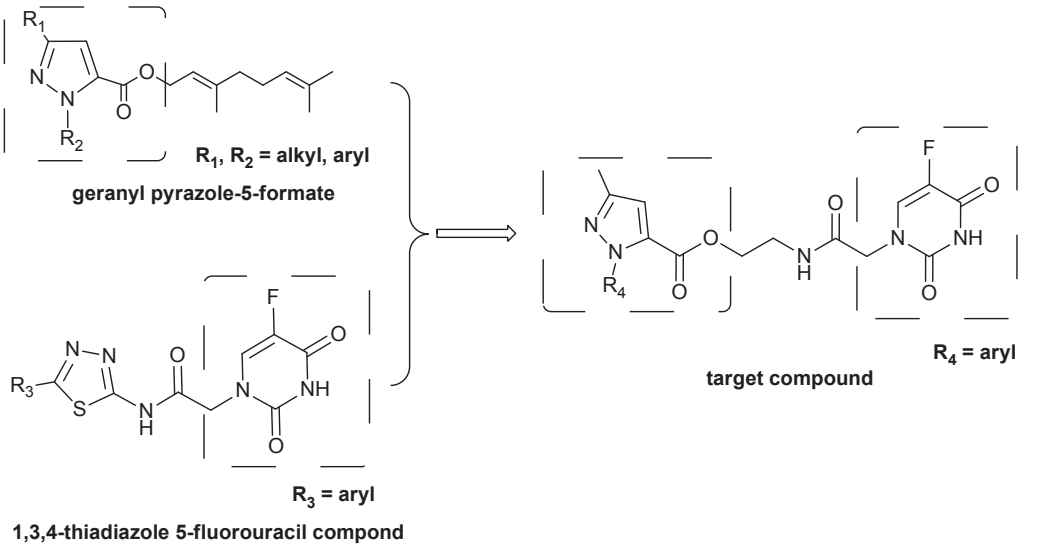
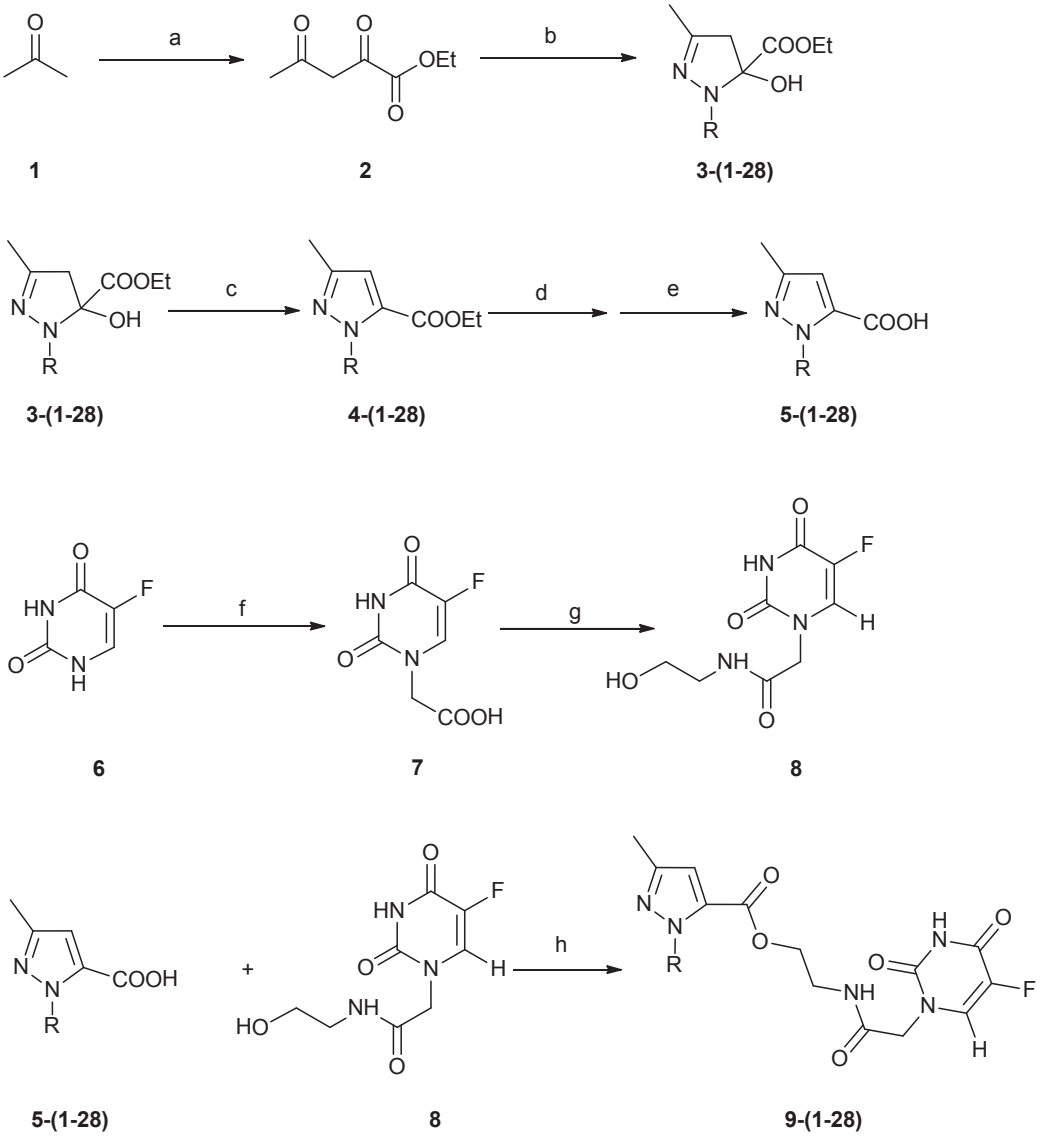


Fig. 2 Design strategy of the target compounds.



Scheme 1 (a) ref. 2; (b) R-NHNH$_2$, EtOH, 0–5 °C; (c) 36.5% hydrochloric acid, THF, reflux, 4 h; (d) 50% NaOH solution, reflux 4 h; (e) 36.5% hydrochloric acid; (f) ref. 19; (g) $NH_2CH_2CH_2OH$, PDCP, DMF; (h) CDI, DMAP, DMF, 20–25 °C.

Key intermediates **5-(1-28)** were, respectively, reacted with compound **8** in the presence of peptide coupling reagents to afford target compounds **9-(1-28)**. It is noteworthy that the reaction cannot proceed smoothly by direct esterification. With the introduction of a peptide coupling agent, such as PDCP, CDI, HOBT and so on, pyrazole-5-carboxylic acids **5-(1-28)** can react smoothly with compound **8** to afford title compounds **9-(1-28)** in satisfactory yields.

The insecticidal activities against C*ulex pipiens* and *Musca domestica* are presented in Table 1, target compounds displayed excellent insecticidal activities against *Culex pipiens*. For example, the knock down rates (24 h) of compounds **9-1**, **9-2**, **9-4**, **9-7**, **9-17**, **9-18**, **9-19**, **9-20**, **9-21**, **9-22**, **9-23**, **9-25** and **9-28** were all 100%, equal to commercial insecticide prallethrin (100%) and superior to dextral tetramethrin (75.6%); compound **9-3**'s knock down rate is 82.5%, similar to commercial prallethrin. Among these compounds, **9-21** and **9-28** were more potent than the control prallethrin (with KT50 values of 1′42″, 2′36″ and 2′42″ respectively), while compounds **9-17**, **9-18**, **9-19**, **9-20**, **9-25**, **9-1**, **9-2**, **9-3** and **9-4** showed slightly less potency compared with prallethrin. In addition, the other compounds possessed potential insecticidal activities.

Also indicated in Table 1, title compounds, such as **9-1**, **9-3**, **9-4**, **9-6**, **9-7**, **9-18**, **9-19**, **9-21**, **9-22**, **9-23**, **9-25** and **9-28** possessed excellent activity against *Musca domestica* with 100% knock down rates, the same as prallethrin (100%). Other compounds, such as compounds **9-17** and **9-5** showed 92.2 and 80% activities respectively, which were similar to prallethrin. Interestingly, compounds **9-21** and **9-28** demonstrated much more potency than prallethrin with KT50 values of 1′54″. In addition, **9-17**, **9-18**, **9-19**, **9-20** and **9-2** exhibited higher activities than dextral tetramethrin, but less lower than prallethrin (KT50 values were 2′25″, 4′05″, 3′30″, 3′39″, 4′11″ and 2′06″, respectively).

The biological activities of the typical candidates **9-21** and **9-28** were further investigated by conducting the assay at a concentration of 0.05%. The knock down rates and KT50 values are listed in Table 2. The results indicate that the two compounds still exhibit promising insecticidal activities even at a lower concentration. The knock down rates of **9-21** and **9-28** were both 100% against *Culex pipiens* and 100%, and 85.6% against *Musca domestica*, respectively. The KT50 values of compound **9-21** were only 4′13″ and 3′40″ respectively, appearing far more superior to commercial insecticide dextral tetramethrin (KT50 values: 9′21″ and 7′34″ respectively).

On the basis of steric and electronic effects, we provide a rational account of structure–activity relationships. From the data presented in Table 1, we find that compounds substituted at the 4-position of benzene displayed higher insecticidal activities than those substituted at the 2- and 3-positions. For example, compounds **9-11**, **9-13** and **9-2** exhibited 17.8%, 25.6% and 100% insecticidal activities against *Culex pipiens*

Table 1 Insecticidal activities of target compound **9-(1-28)**

Compound	R	Insecticidal activities at conc. 0.1%			
		Culex pipiens		*Musca domestica*	
		KT50	Knock down rate (24 h)/%	KT50	Knock down rate (24 h)/%
9-1	4-Cl-Ph	4′42″	100.0	3′48″	100.0
9-2	4-F-Ph	4′55″	100.0	4′11″	65.6
9-3	3-Cl-Ph	5′36″	82.5	6′17″	100.0
9-4	2,4-F_2-Ph	5′48″	100.0	5′36″	100.0
9-5	2,6-F_2-Ph	/	0.0	15′45″	80.0
9-6	3,4-F_2-Ph	20′48″	40.0	4′30″	100.0
9-7	3,5-F_2-Ph	8′54″	100.0	6′54″	100.0
9-8	2-Br-Ph	/	7.8	/	25.6
9-9	3-Br-Ph	/	20.0	/	10.0
9-10	2,6-Cl_2-Ph	/	20.0	18′44″	55.2
9-11	2-F-Ph	/	17.8	/	33.3
9-12	2,4-Cl_2-Ph	/	0.0	/	37.8
9-13	3-F-Ph	/	25.6	/	5.6
9-14	2,3,4-F_3-Ph	18′44″	70.0	15′30″	15.6
9-15	4-Br-Ph	16′48″	62.2	18′04″	55.6
9-16	2-Cl-Ph	/	2.2	/	0.0
9-17	Ph	3′07″	100.0	2′25″	92.2
9-18	4-CH_3O-Ph	5′14″	100.0	4′05″	100.0
9-19	4-CH_3-Ph	4′51″	100.0	3′30″	100.0
9-20	4-NO_2-Ph	3′00″	100.0	3′39″	60.0
9-21	2,6-Cl_2-4-CF_3-Ph	1′42″	100.0	1′54″	100.0
9-22	3-CH_3-Ph	7′48″	100.0	8′56″	100.0
9-23	2-CH_3-Ph	8′41″	100.0	7′33″	100.0
9-24	3,5-$(CH_3)_2$-Ph	/	20.0	/	55.6
9-25	4-OCF_3-Ph	4′51″	100.0	8′33″	100.0
9-26	4-CF_3-Ph	/	35.6	/	35.6
9-27	3-CF_3-Ph	/	27.8	/	27.8
9-28	3-Chloro-pyridin-2-yl	2′36″	100.0	1′54″	100.0
Dextral tetramethrin		8′30″	75.6	4′14″	62.2
Prallethrin		2′42″	100.0	2′06″	100.0

KT50, Killing time of 50%.

Table 2 Insecticidal activities of title compounds **9-21** and **9-28**

Compounds	R	Insecticidal activities at conc. 0.05%			
		Culex pipiens		*Musca domestica*	
		KT50	knock down rate (24 h)/%	KT50	Knock down rate (24 h)/%
9-21	2,6-Cl_2-4-CF_3-Ph	4′13″	100.0	3′40″	100.0
9-28	3-Chloro-pyridin-2-yl	9′17″	100.0	5′14″	85.6
Dextral tetramethrin		9′21″	63.0	7′34″	57.5

KT50, Killing time of 50%.

at 0.1%, respectively. Compounds **9-16**, **9-3** and **9-1** displayed the same result (2.2%, 82.5% and 100% insecticidal activities, respectively). Furthermore, the comparison of biological activities among **9-11**, **9-13** and **9-2** against *Musca domestica* (values are 33.3%, 5.6% and 65.6% respectively) also give a similar result.

Otherwise, it seems that compounds **9-19** and **9-22**, which contain electron-donating substituents, are found to display better insecticidal activities (the knock down rates were both 100% against *Culex pipiens*) than compounds with electron-withdrawing substituents on the benzene ring (**9-26** and **9-27**: 35.6% and 27.8%, respectively).

Conclusions

In conclusion, more than 28 aryl pyrazole derivatives containing 5-fluorouracil were designed, synthesised and evaluated in this study. The results of bioassays indicate that most of the target compounds exhibited satisfactory insecticidal activities against *Culex pipiens* and *Musca domestica* at the concentration of 0.1%. Furthermore, compounds **9-21** and **9-28** still exhibited excellent insecticidal activities against *Culex pipiens* and *Musca domestica* even at a lower concentration of 0.05%. In particular, compound **9-21** possessed the best insecticidal activity with the lowest KT50 value (4′13″ and 3′40″) and the highest 24 h knock down rate (100%), which is superior to commercial dextral tetramethrin. These findings indicate that the incorporation of the 5-fluorouracil fragment improves the insecticidal activities of the aryl pyrazole derivatives as expected and warrant further studies for designing new molecules with good biological activities. Further studies on structural optimisation and structure–activity relationships of these aryl pyrazole derivatives are in progress.

Experimental

Unless otherwise noted, reagents were purchased from commercial suppliers and are used without further purification. All solvents were analytical reagents and were further purified or dried before use when necessary. Reactions were monitored by TLC with visualisation by UV light. The melting points were determined on an X-4 microscope electrothermal apparatus (Beijing Tech Instruments Co., Beijing, P.R. China) and were corrected in advance. ^{1}H NMR spectra were recorded on a Bruker AV-500 spectrometer and a Bruker AV-300 spectrometer in DMSO-d_6 with tetramethylsilane (TMS) as internal standard. FT-IR spectra in KBr were recorded by a PerkinElmer PE-683 IR spectrometer. Elemental analyses were determined on an Elementer Vario EL III analyser.

*Synthesis of 3-methyl-1-aryl-1H-pyrazole-5-carboxylic acid (**5**); general procedure*

Ethyl 2,4-dioxo pentanoate **2**(3.16 g, 20 mmol) was gradually added to the solution containing aryl hydrazine (20 mmol) in ethanol (20 mL) below 5 °C (see ref. 22 and Scheme 1). The progress of the reaction was monitored by TLC. Upon completion, the solution was evaporated *in vacuo*. The residue **3** was dissolved in tetrahydrofuran (20 mL) and 36.5% hydrochloric acid (15 mL) solution. The reaction was kept at reflux and monitored by TLC. After the evaporation of tetrahydrofuran, water (20 mL)/ethanol (5 mL) was added to the residue **4**. The solution was brought to pH 9–10 with 50% sodium hydroxide solution and heated to reflux for 4 h. After cooling to room temperature, the resulting mixture was brought to pH 1–2 with 36.5% hydrochloric acid. Precipitated solid was filtered and the filter cake was recrystallised from ethanol to obtain white to yellow solids **5-(1-28)**.

1-(4-Chlorophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**5-1**): Yield 74.8%; m.p. 212–213 °C (lit.[23] 212–214 °C).

1-(4-Fluorophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**5-2**): Yield 65.2%; m.p. 194–195 °C; ^{1}H NMR (DMSO-d_6, δ): 2.24 (s, 3H, pyrazole-C**H**$_3$), 6.83 (s, 1H, pyrazole-C**H**), 7.25–7.29 (m, 2H, Ph-**H**), 7.50–7.53 (m, 2H, Ph-**H**), 13.30 (s, 1H, CO–OH). Anal. calcd for $C_{11}H_9FN_2O_2$ (220.06): C, 60.00; H, 4.12; N, 12.72; found: C, 59.97; H, 4.09; N, 12.75%.

*1-(3-Chlorophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (***5-3**): Yield 70.2%; m.p. 190–192 °C; ^{1}H NMR (DMSO-d_6, δ): 2.34 (s, 3H, pyrazole-C**H**$_3$), 6.72 (s, 1H, pyrazole-C**H**), 7.57 (s, 3H, Ph-**H**), 7.68 (s, 1H, Ph-**H**), 13.30 (s, 1H, CO–OH). Anal. calcd for $C_{11}H_9ClN_2O_2$ (236.04): C, 55.83; H, 3.83; N, 11.84; found: C, 55.85; H, 3.85; N, 11.80%.

1-(2,4-Difluorophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**5-4**): Yield 46.5%; m.p. 153–157 °C; ^{1}H NMR (DMSO-d_6, δ): 2.15 (s, 3H, pyrazole-C**H**$_3$), 6.71 (s, 1H, pyrazole-C**H**), 7.27–7.32 (m, 1H, Ph-**H**), 7.65–7.80 (m, 2H, Ph-**H**), 13.30 (s, 1H, CO–OH). Anal. calcd for $C_{11}H_8F_2N_2O_2$ (238.06): C, 55.47; H, 3.39; N, 11.76; found: C, 55.50; H, 3.35; N, 11.69%.

1-(2,6-Difluorophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**5-5):** Yield 56.4%; m.p. 155–161 °C; ^{1}H NMR (DMSO-d_6, δ): 2.13 (s, 3H, pyrazole-C**H**$_3$), 6.75 (s, 1H, pyrazole-C**H**), 7.42 (t, J = 6.0 Hz, 2H, Ph-**H**), 7.69–7.71 (m, 1H, Ph-**H**), 13.29 (s, 1H, CO–OH). Anal. calcd for $C_{11}H_8F_2N_2O_2$ (238.06): C, 55.47; H, 3.39; N, 11.76; found: C, 55.51; H, 3.37; N, 11.71%.

1-(3,4-Difluorophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**5-6**): Yield 56.4%; m.p. 189–193 °C; ^{1}H NMR (DMSO-d_6, δ): 2.33 (s, 3H, pyrazole-C**H**$_3$), 6.70 (s, 1H, pyrazole-C**H**), 7.45–7.47 (m, 1H, Ph-**H**), 7.68–7.71 (m, 1H, Ph-**H**), 7.82–7.87 (m, 1H, Ph-**H**), 13.33 (s, 1H, CO–OH). Anal. calcd for $C_{11}H_8F_2N_2O_2$ (238.06): C, 55.47; H, 3.39; N, 11.76; found: C, 55.42; H, 3.43; N, 11.68%.

1-(3,5-Difluorophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**5-7**): Yield 62.3%; m.p. 187–189 °C; ^{1}H NMR (DMSO-d_6, δ): 2.38 (s, 3H, pyrazole-C**H**$_3$), 6.72 (s, 1H, pyrazole-C**H**), 7.40–7.50 (m, 3H, Ph-**H**), 13.29 (s, 1H, CO–OH). Anal. calcd for $C_{11}H_8F_2N_2O_2$ (238.06): C, 55.47; H, 3.39; N, 11.76; found: C, 55.49; H, 3.42; N, 11.80%.

1-(2-Bromophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**5-8**): Yield 67.5%; m.p. 189–191 °C; ^{1}H NMR (DMSO-d_6, δ): 2.08 (s, 3H, pyrazole-C**H**$_3$), 6.73 (s, 1H, pyrazole-C**H**), 7.51–7.56 (m, 3H, Ph-**H**), 7.97 (d, J = 5.6 Hz, 1H, Ph-**H**), 13.30 (s, 1H, CO–OH). Anal. calcd for $C_{11}H_9BrN_2O_2$ (278.98): C, 47.00; H, 3.23; N, 9.97; found: C, 46.97; H, 3.25; N, 10.01%.

1-(3-Bromophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**5-9):** Yield 70.6%; m.p. 176–180 °C; ^{1}H NMR (DMSO-d_6, δ): 2.39 (s, 3H, pyrazole-C**H**$_3$), 6.77 (s, 1H, pyrazole-C**H**), 7.52–7.55 (m, 1H, Ph-**H**), 7.83 (d, J = 5.2 Hz, 1H, Ph-**H**), 7.91 (d, J = 5.2 Hz, 1H, Ph-**H**), 7.85 (s, 1H, Ph-**H**), 13.39 (s, 1H, CO–OH). Anal. calcd for $C_{11}H_9BrN_2O_2$ (278.98): C, 47.00; H, 3.23; N, 9.97; found: C, 47.07; H, 3.26; N, 9.91%.

1-(2,6-Dichlorophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid **(5-10)**: Yield 52.9%; m.p. 120–123 °C; ^{1}H NMR (DMSO-d_6, δ): 2.12 (s, 3H, pyrazole-C**H**$_3$), 6.81 (s, 1H, pyrazole-C**H**), 7.59–7.61 (m, 1H, Ph-**H**), 7.65–7.80 (m, 2H, Ph-**H**), 13.31 (s, 1H, CO–OH). Anal. calcd for $C_{11}H_8Cl_2N_2O_2$ (270.00): C, 48.73; H, 2.97; N, 10.33; found: C, 48.75; H, 2.94; N, 10.40%.

1-(2-Fluorophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid **(5-11)**: Yield 52.8%; m.p. 183–185 °C; ^{1}H NMR (DMSO-d_6, δ): 2.16 (s, 3H, pyrazole-C**H**$_3$), 6.71 (s, 1H, pyrazole-C**H**), 7.40 (d, J = 6.5 Hz, 1H, Ph-**H**), 7.49–7.53 (m, 1H, Ph-**H**), 7.56–7.61 (m, 2H, Ph-**H**), 13.30 (s, 1H, CO–OH). Anal. calcd for $C_{11}H_9FN_2O_2$ (220.06): C, 60.00; H, 4.12; N, 12.72; found: C, 60.07; H, 4.17; N, 12.70%.

1-(2,4-Dichlorophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid **(5-12)**: Yield 67.9%; m.p. 224–225 °C (lit.[24] 195–205 °C).

1-(3-Fluorophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**5-13)**: Yield 61.5%; m.p. 188–191 °C; ^{1}H NMR (DMSO-d_6, δ): 2.35 (s, 3H, pyrazole-C**H**$_3$), 6.71 (s, 1H, pyrazole-C**H**), 7.33–7.35 (m, 1H, Ph-**H**), 7.50 (d, J = 7.9 Hz, 1H, Ph-**H**), 7.58 (d, J = 8.7 Hz, 1H, Ph-**H**), 7.67–7.70 (m, 1H, Ph-**H**), 13.30 (s, 1H, CO–OH). Anal. calcd for $C_{11}H_9FN_2O_2$ (220.06): C, 60.00; H, 4.12; N, 12.72; found: C, 59.95; H, 4.17; N, 12.68%.

1-(2,3,4-Trifluorophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid **(5-14)**: Yield 59.0%; m.p. 177–180 °C, ^{1}H NMR (DMSO-d_6, δ): 2.19 (s, 3H, pyrazole-C**H**$_3$), 6.73 (s, 1H, pyrazole-C**H**), 7.49–7.56 (m, 2H, Ph-**H**), 13.31 (s, 1H, CO–OH). Anal. calcd for $C_{11}H_7F_3N_2O_2$ (256.05): C, 51.57; H, 2.75; N, 10.94; found: C, 51.60; H, 2.79; N, 10.90%.

1-(4-Bromophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid **(5-15)**: Yield 52.8%; m.p. 185–187 °C (lit.[25] 182–184 °C).

1-(2-Chlorophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid **(5-16)**: Yield 64.4%; m.p. 188–191 °C; ^{1}H NMR (DMSO-d_6, δ): 2.08 (s, 3H, pyrazole-C**H**$_3$), 6.72 (s, 1H, pyrazole-C**H**), 7.50–7.59 (m, 3H, Ph-**H**), 7.66–7.70 (m, 1H, Ph-**H**), 13.32 (s, 1H, CO–OH). Anal. calcd for $C_{11}H_9ClN_2O_2$ (236.04): C, 55.83; H, 3.83; N, 11.84; found: C, 55.78; H, 3.80; N, 11.78%.

1-Phenyl-3-methyl-1H-pyrazole-5-carboxylic acid (**5-17)**: Yield 58.2%; m.p. 192–194 °C (lit.[25] 181–182 °C).

1-(4-Methoxyphenyl)-3-methyl-1H-pyrazole-5-carboxylic acid **(5-18)**: Yield 60.2%; m.p. 164–168 °C; ^{1}H NMR (DMSO-d_6, δ): 2.24 (s, 3H, pyrazole-C**H**$_3$), 3.80 (s, 3H, C**H**$_3$-O), 6.79 (s, 1H, pyrazole-C**H**), 6.90 (d, J = 6.9 Hz, 2H, Ph-**H**), 7.41 (d, J = 5.7 Hz, 2H, Ph-**H**), 13.31 (s, 1H, CO–OH). Anal. calcd for $C_{12}H_{12}N_2O_3$ (232.08): C, 62.06; H, 5.21; N, 12.06; found: C, 62.10; H, 5.19; N, 12.10%.

1-(4-Methylphenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**5-19**: Yield 59.4%; m.p. 203–206 °C (lit.[27] 203 °C).

1-(4-Nitrophenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**5-20)**: Yield 58.4%; m.p. 231–233 °C (lit.[28] 237–238 °C).

1-(2,6-Dichloro-4-(trifluoromethyl)phenyl-3-methyl-1H-pyrazole-5-carboxylic acid (**5-21)**: Yield 50.3%; m.p. 202–204 °C; ^{1}H NMR (DMSO-d_6, δ): 2.27 (s, 3H, pyrazole-C**H**$_3$), 6.83 (s, 1H, pyrazole-C**H**), 7.62–7.64 (m, 2H, Ph-**H**), 13.30 (s, 1H, COO-**H**). Anal. calcd for $C_{12}H_7F_3Cl_2N_2O_2$ (337.98): C, 42.50; H, 2.08; N, 8.26; found: C, 42.58; H, 2.01; N, 8.20%.

1-(3-Methylphenyl)-3-methyl-1H-pyrazole-5-carboxylic acid **(5-22)**: Yield 56.3%; m.p. 158–160 °C, ^{1}H NMR (DMSO-d_6, δ): 2.25 (s, 3H, Ph-C**H**$_3$), 2.33 (s, 3H, pyrazole-C**H**$_3$), 6.81 (s, 1H, pyrazole-C**H**), 7.17–7.22 (m, 3H, Ph-**H**), 7.40–7.42 (m, 1H, Ph-**H**), 13.30 (s, 1H, CO–OH). Anal. calcd for $C_{12}H_{12}N_2O_2$ (216.09): C, 66.65; H, 5.59; N, 12.69; found: C, 66.60; H, 5.62; N, 12.60%.

1-(2-Methylphenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**5-23)**: Yield 63.5%; m.p. 164–166 °C; ^{1}H NMR (DMSO-d_6, δ): 1.95 (s, 3H, Ph-C**H**$_3$), 2.06 (s, 3H, pyrazole-C**H**$_3$), 6.69 (s, 1H, pyrazole-C**H**), 7.31 (d, J = 6.5 Hz, 1H, Ph-**H**), 7.43 (t, J = 6.8 Hz, 1H, Ph-**H**), 7.49–7.55 (m, 2H, Ph-**H**), 13.29 (s, 1H, CO–OH). Anal. calcd for $C_{12}H_{12}N_2O_2$ (216.09): C, 66.65; H, 5.59; N, 12.69; found: C, 66.69; H, 5.55; N, 12.72%.

1-(3,5-Dimethylphenyl)-3-methyl-1H-pyrazole-5-carboxylic acid **(5-24)**: Yield 54.3%; m.p. 162–164 °C; ^{1}H NMR (DMSO-d_6, δ): 2.33 (s, 3H, pyrazole-C**H**$_3$), 2.48 (s, 6H, Ph-C**H**$_3$), 6.67 (s, 1H, pyrazole-C**H**), 7.01–7.10 (m, 3H, Ph-**H**), 13.30 (s, 1H, CO–OH). Anal. calcd for $C_{13}H_{14}N_2O_2$ (230.11): C, 67.81; H, 6.13; N, 12.17; found: C, 67.75; H, 6.19; N, 12.20%.

1-(4-Trifluoromethoxyphenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**5-25)**: Yield 65.2%; m.p. 167–173 °C; ^{1}H NMR (DMSO-d_6, δ): 2.33 (s, 3H, pyrazole-C**H**$_3$), 6.71 (s, 1H, pyrazole-C**H**), 7.52–7.56 (m, 2H, Ph-**H**), 7.82–7.85 (m, 2H, Ph-**H**), 13.31 (s, 1H, CO–OH). Anal. calcd for $C_{12}H_9F_3N_2O_3$ (286.21): C, 50.36; H, 3.17; N, 9.79; found: C, 50.31; H, 3.21; N, 9.82%.

1-(4-Trifluoromethylphenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**5-26)**: Yield 71.5%; m.p. 172–175 °C; ^{1}H NMR (DMSO-d_6, δ): 2.43 (s, 3H, pyrazole-C**H**$_3$), 6.80 (s, 1H, pyrazole-C**H**), 7.86–7.88 (m, 2H, Ph-**H**), 8.03–8.06 (m, 2H, Ph-**H**), 13.34 (s, 1H, CO–OH). Anal. calcd for $C_{12}H_9F_3N_2O_2$ (270.06): C, 53.34; H, 3.36; F, 21.09; N, 10.37; found: C, 53.30; H, 3.39; N, 10.30%.

1-(3-Trifluoromethylphenyl)-3-methyl-1H-pyrazole-5-carboxylic acid (**5-27)**: Yield 56.9%; m.p. 183–187 °C; ^{1}H NMR (DMSO-d_6, δ): 2.38 (s, 3H, pyrazole-C**H**$_3$), 6.77 (s, 1H, pyrazole-C**H**), 7.80 (t, J = 7.2 Hz, 1H, Ph-**H**), 7.85 (s, 1H, Ph-**H**), 7.89 (s, 1H, Ph-**H**), 7.93 (s, 1H, Ph-**H**), 13.32 (s, 1H, CO–OH). Anal. calcd for $C_{12}H_9F_3N_2O_2$ (270.06): C, 53.34; H, 3.36; F, 21.09; N, 10.37; found: C, 53.40; H, 3.31; N, 10.42%.

1-(3-Chloropyridin-2-yl)-3-methyl-1H-pyrazole-5-carboxylic acid **(5-28)**: Yield 55.3%. m.p. 171–174 °C, ^{1}H NMR (DMSO-d_6, δ): 2.28 (s, 3H, pyrazole-C**H**$_3$), 6.85 (s, 1H, pyrazole-C**H**), 7.60–7.62 (m, 1H, pyridine-**H**), 8.17 (d, J = 6.8 Hz, 1H, pyridine-**H**), 8.52 (dd, J = 4.6 Hz, 1H, pyridine-**H**), 13.29 (s, 1H, CO–OH). Anal. calcd for $C_{10}H_8ClN_3O_2$ (237.03): C, 50.54; H, 3.39; N, 17.68; found: C, 50.60; H, 3.43; N, 17.63%.

Synthesis of 2-(5-fluorouracil-1-yl)-N-(2-hydroxyethyl)acetamide **8**

2-Aminoethanol (2.14 g, 35 mmol) was added dropwise to a stirred solution of 2-(5-fluorouracil-1-yl) acetic acid **7** (which was synthesised according to the literature)[19] (5.0 g, 27 mmol), PDCP (32.4 mmol) and anhydrous DMF (133 mL) at room temperature. The mixture was stirred for half an hour. Triethylamine (78 mmol) was added dropwise to the reaction solution. The reaction was carried out at room temperature and monitored by TLC. Upon completion, the reaction solution was evaporated *in vacuo* and water (50 mL) was added. The resulting precipitate was collected by filtration. The filter cake was washed with water, dried, and recrystallised from EtOH: DMF = 10 : 1 to give white crystals (5.24 g, 85%), m.p. 230–233 °C (lit.[29] 245–247 °C).

Synthesis of 2-(2-(5-fluorouracil-1-yl) acetamido) ethyl 1-(arylphenyl)-3-methyl-1H-pyrazole-5-carboxylate **9***; general procedure*

A solution of compound **5-(1-28)** (5 mmol), CDI (6 mmol), DMAP (6 mmol) and anhydrous DMF (30 mL) was added to a 50 mL round-bottom flask fitted with a magnetic stirrer. The mixture was stirred for half an hour and then compound **8** was added to the reaction solution in portions. The reaction was monitored by TLC. The solution was evaporated under a reduced pressure to get the crude product which was purified *via* silica gel column chromatography using ethyl acetate as the eluting solution to obtain title compounds **9-(1-28)**.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(4-chlorophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-1**): Yield 68.4%; m.p. 248–250 °C; IR (KBr): 3340, 2848, 1741, 1716, 1697, 1670, 1558, 1226 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.27 (s, 3H, pyrazole-C**H**$_3$), 3.35–3.36 (m, 2H, CONH–CH$_2$), 4.15 (t, J = 5.6 Hz, 2H, COO–CH$_2$), 4.28 (s, 2H, N–CH$_2$–CO), 6.92 (s, 1H, pyrazole-C**H**), 7.42–7.43 (m, 2H, Ph-**H**), 7.67–7.70 (m, 2H, Ph-**H**), 7.97 (d, J = 6.8 Hz, 1H, CF=C**H**), 8.30 (s, 1H, CO–NH), 11.80 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{17}ClFN_5O_5$ (449.09): C, 50.73; H, 3.81; N, 15.57; found: C, 50.75; H, 3.80; N, 15.53%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(4-fluorophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-2**): Yield 74.2%; m.p. 225–228 °C; IR (KBr): 3346, 2827, 1743, 1704, 1670, 1660, 1558, 1230 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.27 (s, 3H, pyrazole-C**H**$_3$), 3.35–3.36 (m, 2H, CONH–CH$_2$), 4.15 (t, J = 5.6 Hz, 2H, COO–CH$_2$), 4.28 (s, 2H, N–CH$_2$–CO), 6.92 (s, 1H, pyrazole-C**H**), 7.28–7.31(m,

2H, Ph-**H**), 7.47–7.50 (m, 2H, Ph-**H**), 7.98 (d, J = 6.8 Hz, 1H, CF=C**H**), 8.30 (s, 1H, CO–NH), 11.81 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{17}F_2N_5O_5$ (433.12): C, 52.66; H, 3.95; N, 16.16; found: C, 52.70; H, 3.89; N, 16.11%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(3-chlorophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-3**): Yield 69.5%; m.p. 205–211 °C. IR (KBr): 3344, 2847, 1724, 1715, 1701, 1675, 1549, 1239 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.36 (s, 3H, pyrazole-C**H**$_3$), 3.44–3.46 (m, 2H, CO–NH–CH$_2$), 4.26 (t, J = 5.4 Hz, 2H, COO–CH$_2$), 4.29 (s, 2H, N–CH$_2$–CO), 6.80 (s, 1H, pyrazole-C**H**), 7.59 (s, 3H, Ph-**H**), 7.70 (s, 1H, Ph-**H**), 7.99 (d, J = 6.6 Hz, 1H, CF=C**H**), 8.39 (t, J = 4.8 Hz, 1H, CO–NH), 11.80 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{17}ClFN_5O_5$ (449.09): C, 50.73; H, 3.81; N, 15.57; found: C, 50.65; H, 3.85; N, 15.60%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(2,4-difluorophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-4**): Yield 68.4%; m.p. 169–172 °C; IR (KBr): 3420, 2829, 1728, 1710, 1666, 1659, 1577, 1221 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.18 (s, 3H, pyrazole-C**H**$_3$), 3.43–3.45 (m, 2H, CO–NH–CH$_2$), 4.25 (t, J = 5.7 Hz, 2H, COO–CH$_2$), 4.29 (s, 2H, N–CH$_2$–CO), 6.80 (s, 1H, pyrazole-C**H**), 7.30–7.36 (m, 1H, Ph-**H**), 7.59–7.75 (m, 2H, Ph-**H**), 7.99 (d, J = 3.0 Hz, 1H, CF=C**H**), 8.41 (t, J = 5.7 Hz, 1H, CO–NH), 11.80 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{16}F_3N_5O_5$ (451.11): C, 50.56; H, 3.57; N, 15.52; found: C, 50.60; H, 3.65; N, 15.59%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(2,6-difluorophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-5**): Yield 70.1%; m.p. 167–169 °C; IR (KBr): 3413, 2829, 1737, 1707, 1689, 1666, 1552, 1240 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.16 (s, 3H, pyrazole-C**H**$_3$), 3.41–3.44 (m, 2H, CO–NH–CH$_2$), 4.24 (t, J = 5.6 Hz, 2H, COO–CH$_2$), 4.28 (s, 2H, N–CH$_2$–CO), 6.84 (s, 1H, pyrazole-C**H**), 7.45 (t, J = 6.0 Hz, 2H, Ph-**H**), 7.72–7.76 (m, 1H, Ph-**H**), 7.99 (d, J = 3.0 Hz, 1H, CF=C**H**), 8.43 (t, J = 3.9 Hz, 1H, CO–NH), 11.85 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{16}F_3N_5O_5$ (451.11): C, 50.56; H, 3.57; N, 15.52; found: C, 50.49; H, 3.50; N, 15.71%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(3,4-difluorophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-6**): Yield 67.5%; m.p. 236–240 °C; IR (KBr): 3420, 2820, 1752, 1717, 1688, 1663, 1580, 1221 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.35 (s, 3H, pyrazole-C**H**$_3$), 3.44–3.45 (m, 2H, CONH–CH$_2$), 4.25 (t, J = 5.7 Hz, 2H, COO–CH$_2$), 4.29 (s, 2H, N–CH$_2$–CO), 6.79 (s, 1H, pyrazole-C**H**), 7.46–7.49 (m, 1H, Ph-**H**), 7.61–7.70 (m, 1H, Ph-**H**), 7.76–7.83 (m, 1H, Ph-**H**), 7.99 (d, J = 2.4 Hz, 1H, CF=C**H**), 8.39 (t, J = 5.4 Hz, 1H, CO–NH), 11.81 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{16}F_3N_5O_5$ (451.11): C, 50.56; H, 3.57; N, 15.52; found: C, 50.70; H, 3.67; N, 15.70%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(3,5-difluorophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-7**): Yield 71.6%; m.p. 190–193 °C; IR (KBr): 3343, 2849, 1722, 1702, 1674, 1654, 1552, 1248 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.41 (s, 3H, pyrazole-C**H**$_3$), 3.43–3.47 (m, 2H, CONH–CH$_2$), 4.26 (t, J = 6.0 Hz, 2H, COO–CH$_2$), 4.29 (s, 2H, N–CH$_2$–CO), 6.81 (s, 1H, pyrazole-C**H**), 7.43–7.47 (m, 3H, Ph-**H**), 7.99 (d, J = 7.0 Hz, 1H, CF=C**H**), 8.39 (t, J = 5.5 Hz, 1H, CO–NH), 11.80 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{16}F_3N_5O_5$ (451.11): C, 50.56; H, 3.57; N, 15.52; found: C, 50.69; H, 3.53; N, 15.45%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(2-bromophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-8**): Yield 72.1%; m.p. 201–202 °C; IR (KBr): 3410, 2828, 1717, 1703, 1697, 1663, 1563, 1225 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.12 (s, 3H, pyrazole-C**H**$_3$), 3.42–3.46 (m, 2H, CONH–CH$_2$), 4.25 (t, J = 5.6 Hz, 2H, COO–CH$_2$), 4.30 (s, 2H, N–CH$_2$–CO), 6.81 (s, 1H, pyrazole-C**H**), 7.56–7.62 (m, 3H, Ph-**H**), 7.90 (d, J = 8.0 Hz, 1H, Ph-**H**), 8.02 (d, J = 6.8 Hz, 1H, CF=C**H**), 8.46 (t, J = 5.6 Hz, 1H, CO–NH), 11.86 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{17}BrFN_5O_5$ (493.04): C, 46.17; H, 3.47; N, 14.17; found: C, 46.29; H, 3.44; N, 14.09%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(3-bromophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-9**): Yield 75.3%; m.p. 202–203 °C; IR (KBr): 3343, 2848, 1724, 1703, 1683, 1676, 1549, 1237 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.41 (s, 3H, pyrazole-C**H**$_3$), 3.48–3.50 (m, 2H, CONH–CH$_2$), 4.30 (t, J = 5.6 Hz, 2H, COO–CH$_2$), 4.34 (s, 2H, N–CH$_2$–CO), 6.85 (s, 1H, pyrazole-C**H**), 7.56–7.60 (m, 1H, Ph-**H**), 7.67 (d, J = 8.0 Hz, 1H, Ph-**H**), 7.77 (d, J = 8.0 Hz, 1H, Ph-**H**), 7.87 (s, 1H, Ph-**H**), 8.06 (d, J = 6.8 Hz, 1H, CF=C**H**), 8.48 (t, J = 5.6 Hz, 1H, CO–NH), 11.90 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{17}BrFN_5O_5$ (493.04): C, 46.17; H, 3.47; N, 14.17; found: C, 46.26; H, 3.40; N, 14.23%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(2,6-dichlorophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-10**): Yield 56.8%; m.p. 186–188 °C; IR (KBr): 3410, 2828, 1727, 1701, 1667, 1649, 1569, 1244 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.15 (s, 3H, pyrazole-C**H**$_3$), 3.45–3.47 (m, 2H, CONH–CH$_2$), 4.31 (t, J = 5.6 Hz, 2H, COO–CH$_2$), 4.33 (s, 2H, N–CH$_2$–CO), 6.90 (s, 1H, pyrazole-C**H**), 7.60–7.63 (m, 1H, Ph-**H**), 7.65–7.85 (m, 2H, Ph-**H**), 8.05 (d, J = 4.0 Hz, 1H, CF=C**H**), 8.52 (t, J = 4.0 Hz, 1H, CO–NH), 11.81 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{16}Cl_2FN_5O_5$ (483.05): C, 47.12; H, 3.33; N, 14.46; found: C, 47.25; H, 3.36; N, 14.50%.

2-(2-(5-Fluorouracil-1-yl) acetamido)ethyl-1-(2-fluorophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-11**): Yield 68.4%; m.p. 228–230 °C; yield, 57.4%; m.p. 230–233 °C. IR (KBr): 3349, 2837, 1738, 1722, 1706, 1681, 1580, 1242 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.19 (s, 3H, pyrazole-C**H**$_3$), 3.42–3.47 (m, 2H, CONH–CH$_2$), 4.26 (t, J = 5.7 Hz, 2H, COO–CH$_2$), 4.31 (s, 2H, N–CH$_2$–CO), 6.80 (s, 1H, pyrazole-C**H**), 7.43 (d, J = 6.9 Hz, 1H, Ph-**H**), 7.52–7.58 (m, 1H, Ph-**H**), 7.60–7.68 (m, 2H, Ph-**H**), 7.99 (d, J = 6.9 Hz, 1H, CF=C**H**), 8.39 (t, J = 5.1 Hz, 1H, CO–NH), 11.80 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{17}F_2N_5O_5$ (433.12): C, 52.66; H, 3.95; N, 16.16; found: C, 52.55; H, 3.91; N, 16.10%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(2,4-dichlorophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-12**): Yield 58.4%; m.p. 227–230 °C; IR (KBr): 3442, 2824, 1735, 1700, 1681, 1658, 1581, 1219 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.13 (s, 3H, pyrazole-C**H**$_3$), 3.41–3.47 (m, 2H, CONH–CH$_2$), 4.25 (t, J = 5.7 Hz, 2H, COO–CH$_2$), 4.30 (s, 2H, N–CH$_2$–CO), 6.80 (s, 1H, pyrazole-C**H**), 7.66 (s, 1H, Ph-**H**), 7.95–7.97 (m, 2H, Ph-**H**), 7.99 (d, J = 6.6 Hz, 1H, CF=C**H**), 8.40 (s, 1H, CO–NH), 11.81 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{16}Cl_2FN_5O_5$ (483.05): C, 47.12; H, 3.33; N, 14.46; found: C, 47.23; H, 3.38; N, 14.52%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(3-fluorophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-13**): Yield 57.4%; m.p. 230–233 °C; IR (KBr): 3412, 2828, 1714, 1703, 1685, 1660, 1570, 1228 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.37 (s, 3H, pyrazole-C**H**$_3$), 3.44–3.45 (m, 2H, CONH–CH$_2$), 4.26 (s, 2H, COO–CH$_2$), 4.30 (s, 2H, N–CH$_2$–CO), 6.80 (s, 1H, pyrazole-C**H**), 7.36–7.39 (m, 1H, Ph-**H**), 7.44 (d, J = 7.5 Hz, 1H, Ph-**H**), 7.50 (d, J = 9.5 Hz, 1H, Ph-**H**), 7.60–7.64 (m, 1H, Ph-**H**), 7.99 (d, J = 6.5 Hz, 1H, CF=C**H**), 8.39 (s, 1H, CO–NH), 11.80 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{17}F_2N_5O_5$ (433.12): C, 52.66; H, 3.95; N, 16.16; found: C, 52.60; H, 3.99; N, 16.20%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(2,3,4-trifluorophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-14**): Yield 62.4%; m.p. 203–205 °C; IR (KBr): 3302, 2839, 1739, 1697, 1674, 1662, 1558, 1229 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.22 (s, 3H, pyrazole-C**H**$_3$), 3.41–3.47 (m, 2H, CONH–CH$_2$), 4.26 (t, J = 8.0 Hz, 2H, COO–CH$_2$), 4.29 (s, 2H, N–CH$_2$–CO), 6.82 (s, 1H, pyrazole-C**H**), 7.52–7.62 (m, 2H, Ph-**H**), 8.00 (d, J = 3.0 Hz, 1H, CF=C**H**), 8.40 (t, J = 6.0 Hz, 1H, CO–NH), 11.82 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{15}F_4N_5O_5$ (469.10): C, 48.62%; H, 3.22%; N, 14.92%; found: C, 48.75; H, 3.31; N, 14.81%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(4-bromophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-15**): Yield 64.1%; m.p. 147–150 °C; IR (KBr): 3413, 2824, 1719, 1703, 1681, 1661, 1578, 1229 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.35 (s, 3H, pyrazole-C**H**$_3$), 3.43–3.45 (m, 2H, CONH–CH$_2$), 4.26 (t, J = 5.4 Hz, 2H, COO–CH$_2$), 4.29 (s, 2H, N–CH$_2$–CO), 6.79 (s, 1H, pyrazole-C**H**), 7.55 (d, J = 8.7 Hz, 2H, Ph-**H**), 7.77 (d, J = 8.7 Hz, 2H, Ph-**H**), 7.99 (d, J = 6.9 Hz, 1H, CF=C**H**), 8.40 (t, J = 5.7 Hz, 1H, CO–NH), 11.82 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{17}BrFN_5O_5$ (493.04): C, 46.17; H, 3.47; N, 14.17; found: C, 46.23; H, 3.51; N, 14.19%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(2-chlorophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-16**): Yield 56.3%; m.p.

225–228 °C; IR (KBr): 3337, 2843, 1741, 1706, 1674, 1645, 1553, 1223 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.12 (s, 3H, pyrazole-C**H**$_3$), 3.40–3.49 (m, 2H, CONH–CH$_2$), 4.25 (t, J = 5.7 Hz, 2H, COO–CH$_2$), 4.30 (s, 2H, N–CH$_2$–CO), 6.80 (s, 1H, pyrazole-C**H**), 7.57–7.67 (m, 3H, Ph-**H**), 7.74–7.77 (m, 1H, Ph-**H**), 7.99 (d, J = 6.6 Hz, 1H, CF=C**H**), 8.42 (t, J = 5.4 Hz, 1H, CO–NH), 11.82 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{17}ClFN_5O_5$ (449.09): C, 50.73; H, 3.81; N, 15.57; found: C, 50.63; H, 3.85; N, 15.63%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-phenyl-3-methyl-1H-pyrazole-5-carboxylate (**9-17**): Yield 68.4%; m.p. 176–178 °C; IR (KBr): 3346, 2840, 1739, 1697, 1674, 1662, 1558, 1236 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.28 (s, 3H, pyrazole-C**H**$_3$), 3.35–3.37 (m, 2H, CONH–CH$_2$), 4.15 (t, J = 5.6 Hz, 2H, COO–CH$_2$), 4.29 (s, 2H, N–CH$_2$–CO), 6.92 (s, 1H, pyrazole-C**H**), 7.42–7.49 (m, 5H, Ph-**H**), 7.98 (d, J = 6.8 Hz, 1H, CF=C**H**), 8.30 (t, J = 5.6 Hz, 1H, CO–NH), 11.82 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{18}FN_5O_5$ (415.13): C, 54.94; H, 4.37; N, 16.86; found: C, 54.85; H, 4.34; N, 16.81%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(4-methoxyphenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-18**): Yield 71.1%; m.p. 202–203 °C. IR (KBr): 3314, 2827, 1731, 1697, 1670, 1660, 1558, 1230 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.26 (s, 3H, pyrazole-C**H**$_3$), 3.35–3.36 (m, 2H, CONH–CH$_2$), 3.81 (s, 3H, O–CH$_3$), 4.14 (t, J = 5.5 Hz, 2H, COO–CH$_2$), 4.29 (s, 2H, N–CH$_2$–CO), 6.88 (s, 1H, pyrazole-C**H**), 6.99 (d, J = 8.9 Hz, 2H, Ph-**H**), 7.33 (d, J = 8.9 Hz, 2H, Ph-**H**), 7.97 (d, J = 6.8 Hz, 1H, CF=C**H**), 8.30 (s, 1H, CO–NH), 11.82 (s, 1H, CO–NH–CO). Anal. calcd for $C_{20}H_{20}FN_5O_6$ (445.14): C, 53.93; H, 4.53; N, 15.72; found: C, 53.82; H, 4.45; N, 15.81%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(4-methylphenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-19**): Yield 65.9%; m.p. 198–201 °C; IR (KBr): 3250, 2840, 1731, 1716, 1697, 1670, 1580, 1226 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.27 (s, 3H, pyrazole-C**H**$_3$), 2.49–2.51 (m, 3H, Ph-C**H**$_3$), 3.35–3.36 (m, 2H, CONH–CH$_2$), 4.14 (t, J = 5.5 Hz, 2H, COO–CH$_2$), 4.28 (s, 2H, N–CH$_2$–CO), 6.89 (s, 1H, pyrazole-C**H**), 7.25–7.26 (m, 2H, Ph-**H**), 7.28–7.30 (m, 2H, Ph-**H**), 7.97 (d, J = 5.4 Hz, 1H, CF=C**H**), 8.29 (s, 1H, CO–NH), 11.81 (s, 1H, CO–NH–CO). Anal. calcd for $C_{20}H_{20}FN_5O_5$ (429.14): C, 55.94; H, 4.69; N, 16.31; found: C, 55.75; H, 4.64; N, 14.40%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(4-nitrophenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-20**): Yield 62.1%; m.p. 289–292 °C. IR (KBr): 3348, 2825, 1739, 1697, 1674, 1662, 1558, 1232 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.27 (s, 3H, pyrazole-C**H**$_3$), 3.35–3.36 (m, 2H, CONH–CH$_2$), 4.15 (s, 2H, COO–CH$_2$), 4.28 (s, 2H, N–CH$_2$–CO), 6.92 (s, 1H, pyrazole-C**H**), 7.94 (m, 1H, Ph-**H**), 8.05–8.06 (m, 2H, Ph-**H**), 8.30 (s, 1H, Ph-**H**), 8.39 (d, J = 0.2 Hz, 1H, CF=C**H**), 8.39 (s, 1H, CO–NH), 11.81 (s, 1H, CO–NH–CO). Anal. calcd for $C_{19}H_{17}FN_6O_7$ (460.11): C, 49.57; H, 3.72; N, 18.25; found: C, 49.75; H, 3.74; N, 18.19%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(2,6-dichloro-4-(trifluoromethyl)phenyl phenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-21**): Yield 78.9%; m.p. 195–198 °C. IR (KBr): 3350, 2827, 1739, 1697, 1674, 1662, 1558, 1236 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.28 (s, 3H, Ph-C**H**$_3$), 3.35–3.37 (m, 2H, CONH–CH$_2$), 4.15 (t, J = 5.6 Hz, 2H, COO–CH$_2$), 4.29 (s, 2H, N–CH$_2$–CO), 6.92 (s, 1H, pyrazole-C**H**), 7.63–7.65 (m, 2H, Ph-**H**), 7.98 (d, J = 0.65 Hz, 1H, CF=C**H**), 8.30 (t, J = 5.8 Hz,1H, CO–NH), 11.81 (s, 1H, CO–NH–CO). Anal. calcd for $C_{20}H_{15}F_4Cl_2N_5O_5$ (551.04): C, 43.50; H, 2.74; N, 12.68; found: C, 43.42; H, 2.71; N, 12.52%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(3-methylphenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-22**): Yield 64.2%; m.p. 184–187 °C; IR (KBr): 3348, 2829, 1739, 1701, 1676, 1663, 1542, 1237 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.27 (s, 3H, Ph-C**H**$_3$), 2.35 (s, 3H, pyrazole-C**H**$_3$), 3.35–3.37 (m, 2H, CONH–CH$_2$), 4.14 (m, 2H, COO–CH$_2$), 4.28 (s, 2H, N–CH$_2$–CO), 6.90 (s, 1H, pyrazole-C**H**), 7.19–7.25 (m, 3H, Ph-**H**), 7.32–7.35 (m, 1H, Ph-**H**), 7.98 (d, J = 6.5 Hz, 1H, CF=C**H**), 8.30 (s, 1H, CO–NH), 11.82 (s, 1H, CO–NH–CO). Anal. calcd for $C_{20}H_{20}FN_5O_5$ (429.14): C, 55.94; H, 4.69; N, 16.31; found: C, 56.02; H, 4.65; N, 16.29%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(2-metnylphenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-23**): Yield 75.3%; m.p. 187–189 °C; IR (KBr): 3420, 2815, 1730, 1712, 1697, 1679, 1568, 1241 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 1.96 (s, 3H, Ph-C**H**$_3$), 2.08 (s, 3H, pyrazole-C**H**$_3$), 3.42–3.46 (m, 2H, CONH–CH$_2$), 4.24 (t, J = 6.0 Hz, 2H, COO–CH$_2$), 4.30 (s, 2H, N–CH$_2$–CO), 6.78 (s, 1H, pyrazole-C**H**), 7.32 (d, J = 7.5 Hz, 1H, Ph-**H**), 7.39 (t, J = 7.0 Hz, 1H, Ph-**H**), 7.45–7.50 (m, 2H, Ph-**H**), 7.99 (d, J = 7.0 Hz, 1H, CF=C**H**), 8.40 (t, J = 5.5 Hz, 1H, CO–NH), 11.80 (s, 1H, CO–NH–CO). Anal. calcd for $C_{20}H_{20}FN_5O_5$ (429.14): C, 55.94; H, 4.69; N, 16.31; found: C, 55.82; H, 4.72; N, 16.42%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(3,5-dimethylphenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-24**): Yield 65.9%; m.p. 223–226 °C; IR (KBr): 3302, 2826, 1713, 1702, 1687, 1661, 1570, 1228 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.36 (s, 3H, pyrazole-C**H**$_3$), 2.50 (s, 6H, Ph-C**H**$_3$), 3.44–3.46 (m, 2H, CONH–CH$_2$), 4.25 (t, J = 5.5 Hz, 2H, COO–CH$_2$), 4.28 (s, 2H, N–CH$_2$–CO), 6.76 (s, 1H, pyrazole-C**H**), 7.02–7.15 (m, 3H, Ph-**H**), 7.99 (d, J = 6.5 Hz, 1H, CF=C**H**), 8.39 (t, J = 5.5 Hz, 1H, CO–NH), 11.81 (s, 1H, CO–NH–CO). Anal. calcd for $C_{21}H_{22}FN_5O_5$ (443.16): C, 56.88; H, 5.00; N, 15.79; found: C, 56.79; H, 4.94; N, 15.89%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(4-trifluoromethoxyphenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-25**): Yield 71.5%; m.p. 172–175 °C; IR (KBr): 3412, 2825, 1722, 1702, 1680, 1662, 1577, 1226 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.36 (s, 3H, pyrazole-C**H**$_3$), 3.42–3.46 (m, 2H, CONH–CH$_2$), 4.26 (t, J = 5.7 Hz, 2H, COO–CH$_2$), 4.29 (s, 2H, N–CH$_2$–CO), 6.80 (s, 1H, pyrazole-C**H**), 7.56–7.59 (m, 2H, Ph-**H**), 7.72–7.75 (m, 2H, Ph-**H**), 7.99 (d, J = 6.9 Hz, 1H, CF=C**H**), 8.39 (t, J = 5.4 Hz, 1H, CO–NH), 11.81 (s, 1H, CO–NH–CO). Anal. calcd for $C_{20}H_{17}F_4N_5O_6$ (499.11): C, 48.10; H, 3.43; N, 14.02; found: C, 48.01; H, 3.46; N, 14.11%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(4-trifluoromethylphenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-26**): Yield 60.2%; m.p. 145–148 °C; IR (KBr): 3411, 2825, 1720, 1698, 1685, 1660, 1578, 1227 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.47 (s, 3H, pyrazole-C**H**$_3$), 3.48–3.53 (m, 2H, CONH–CH$_2$), 4.32 (t, J = 5.6 Hz, 2H, COO–CH$_2$), 4.35 (s, 2H, N–CH$_2$–CO), 6.89 (s, 1H, pyrazole-C**H**), 7.89–7.91 (m, 2H, Ph-**H**), 7.99–8.01 (m, 2H, Ph-**H**), 8.05 (d, J = 4.0 Hz, 1H, CF=C**H**), 8.46 (t, J = 4.0 Hz, 1H, CO–NH), 11.88 (s, 1H, CO–NH–CO). Anal. calcd for $C_{20}H_{17}F_4N_5O_5$ (483.12): C, 49.70; H, 3.54; N, 14.49; found: C, 49.65; H, 3.64; N, 14.56%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(3-trifluoromethylphenyl)-3-methyl-1H-pyrazole-5-carboxylate (**9-27**): Yield 61.6%; m.p. 226–228 °C; IR (KBr): 3347, 2849, 1729, 1703, 1677, 1676, 1552, 1226 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ): 2.39 (s, 3H, pyrazole-C**H**$_3$), 3.43–3.46 (m, 2H, CONH–CH$_2$), 4.27 (t, J = 5.6 Hz, 2H, COO–CH$_2$), 4.30 (s, 2H, N–CH$_2$–CO), 6.84 (s, 1H, pyrazole-C**H**), 7.83 (t, J = 8.0 Hz, 1H, Ph-**H**), 7.90 (s, 1H, Ph-**H**), 7.93 (s, 1H, Ph-**H**), 7.96 (s, 1H, Ph-**H**), 8.02 (d, J = 6.8 Hz, 1H, CF=C**H**), 8.44 (t, J = 5.6 Hz, 1H, CO–NH), 11.85 (s, 1H, CO–NH–CO). Anal. calcd for $C_{20}H_{17}F_4N_5O_5$ (483.12): C, 49.70; H, 3.54; N, 14.49; found: C, 49.79; H, 3.44; N, 14.53%.

2-(2-(5-Fluorouracil-1-yl)acetamido)ethyl-1-(3-chloropyridin-2-yl)-3-methyl-1H-pyrazole-5-carboxylate (**9-28**): Yield 70.2%; m.p. 158–160 °C; IR (KBr): 3343, 2839, 1739, 1697, 1674, 1662, 1558, 1232 cm^{-1}; ^{1}H NMR (DMSO-d_6, δ):2.31 (s, 3H, pyrazole-C**H**$_3$), 3.28–3.30 (m, 2H, CONH–CH$_2$), 4.12 (t, J = 5.6 Hz, 2H, COO–CH$_2$), 4.28 (s, 2H, N–CH$_2$–CO), 6.96 (s, 1H, pyrazole-C**H**), 7.63–7.66 (m, 1H, pyridine-**H**), 7.98 (d, J = 6.8 Hz, 1H, pyridine-**H**), 8.20–8.22 (m, 1H, pyridine-**H**), 8.29–8.31 (m, 1H, CF=C**H**), 8.54 (d, J = 6.2 Hz, 1H, CO–NH), 11.81 (s, 1H, CO–NH–CO). Anal. calcd for $C_{18}H_{16}ClFN_6O_5$ (450.08): C, 47.96; H, 3.58; N, 18.64; found: C, 47.84; H, 3.48; N, 18.57%.

Biological assay

All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C and 60% relative humidity according to statistical requirements. Evaluations are

based on KT50 and knock down rate (24 h). The standard deviations of the tested biological values were ± 5%.

Insecticidal activities against Culex pipiens *and* Musca domestica: The bioassays were performed according to the literature.[30] Pests (20) were released into the cylinder from an orifice and the aerosol insecticide was sprayed into the cylinder from the spraying hole. After 1 minute, the numbers of the test pests knocked down at regular time intervals were counted. For each compound, insecticidal activities were expressed as the mean of values obtained in three independent experiments.

This work was supported by the Key Technology R&D Program of the Science and Technology Department of Jiangsu Province (No. BE2011352) for financial support. We thank Jiangsu Pesticide Research Institute Co., Ltd, and Jiangsu Yangnong Chemical Co., Ltd for facilities for testing the insecticidal activity.

Received 22 December 2012; accepted 1 March 2014
Paper 1302359 doi: 10.3184/174751914X13955977912102
Published online: 6 May 2014

References

1 G.P. Lahm, T.M. Stevenson, T.P. Selby, *Bioorg. Med. Chem. Lett*., 2007, **17**, 6274.
2 Y.F. Sun, H.L. Qiao, Yun. L.S.X. Yang, C.H. Rui, P. Pelosi and X.L. Yang, *J. Agric. Food Chem.,* 2011, **59**, 2456.
3 F.B. Lawrence, L.G. Pilip, M.S. Frederick, S. Ying and S.T. Martin, WO 03016284, 2003.
4 L. Olivier, D. Patricia, T. Stephan, E. Andrew and J. Andre, WO 2007093402, 2007.
5 C.D. Alan and L.G. Pilip, WO 2003062226, 2003.
6 Q.Q. Zhan, Y.Q. Li, L.X. Xiong and Q.Q. Wang, *J. Agric. Food Chem*., 2010, **58**, 4992.
7 C.D. The-wei, B.H.M. Martinus, K. Anke, T. Maria-Theresia, S. Stefan, D. Uwe, H. Jamin and S. Karl, WO 2003074493, 2003.
8 H. Markus, L. Norbert, E. Christoph, W.-N. Ulrike and D.H. Wilhelm, DE 4405207, 1995.
9 F.B. Lawrence, T.A. Edmund, L.J. Keith, WO 2008124092, 2008.
10 S. Mio, E. Okui and T. Imai, JP 2008260706, 2008.
11 M. Hiroshi, I. Tomoaki, T. Shinji and M. Masayuki, JP 2005008628, 2005.
12 E. Yasuhiro and S. Yuichi, WO 2013015429, 2013.
13 D.B. Longley, D.P. Harkin and P.G. Johnston, *Nat. Rev. Cancer,* 2003, **3**, 330.
14 C.Y. Cheng, Y.H. Lin and C.C. Su, *Mol. Med. Rep.,* 2010, **3**, 227.
15 S.C. Lee, J.Y. Chan and S. Pervaiz, *Cancer. Lett.,* 2010, **288**, 36.
16 G. Saroj, *J. Surg. Oncol*., 1982, **21**, 94.
17 H.J. Won, T.K. Ha and C.H. Sung, *Anti-Cancer Drugs,* 2010, **21**, 270.
18 M. Zemanova, L. Petruzelka and A. Pazdro, *Diseas. Esophagus,* 2010, **23**, 160.
19 R. Wan, J.Q. Zhang, F. Han, P. Wang, P. Yu and Q. He, *Nucleosides, Nucleotides Nucleic Acids,* 2011, **30**, 280.
20 R. Wan, Y. Chen, H.P. Mu, Y. Yang, X.D. Fu, X.F. Qin and C. Shen, CN 103214465, 2013.
21 I.L. Finar and R.J. Hurlock, *J. Chem. Soc.,* 1958, 3259.
22 A.C. Boris and J.W. William, *J. Label Compd. Radiopharm.,* 2005, **48**, 407.
23 C. Gyogyszer, NL 6613374, 1965.
24 S. Erich, EP 333131, 1989.
25 M. Carlo, *Gazz. Chim. Ital.,* 1949, **79**, 666.
26 B.A. Tertov, *Khim. Geterotsikl. Soed*., 1975, 392.
27 N. Tetsuo, *Bull. Chem. Soc. Japan,* 1965, **38**, 362.
28 K.C. Chang, *Austral. J. Chem.,* 1979, **32**, 1727.
29 P. Helmut, *Coll. Czech. Chem. Commun.,* 1982, **47**, 2806.
30 M.Z. Qi and J.W. Zhao, CN 101632381, 2010.