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Simple route to multisubstituted tetrahydropyrimidines

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ABSTRACT

As part of our ongoing investigation into the synthetic application of nitroenamines several new densely substituted pyrimidine and pyrrolo-pyrimidine derivatives were prepared. Thus, 2-nitromethylenepyrrolidine and some open chain nitroenamines of phenyl-(2-nitro-1-phenyl-vinyl)-amine type were reacted with ethyl glyoxylate and a substituted aniline usually in a one-pot procedure to furnish the key intermediates for a subsequent cyclization. These compounds including a molecular fragment of 1,3-diamine type were subjected to a simple ring closure with formaldehyde to give the title compounds in good yields. The protocol reported has the advantages of mild reaction conditions, easy workup and inexpensive reagents.

In an attempted removal of the 4-methoxy-phenyl protecting group from the 4-methoxy-phenyl substituted hexahydropyrrolo[1,2-*c*]pyrimidine derivative, an unexpected periodic acid mediated ring cleavage and phenyl group migration was discovered. The structures of the synthesized new compounds were confirmed by spectral data, and, particularly, the hindered rotation and the unusual ^{1}H NMR characteristics of 4-(4-nitro-phenyl)-but-3-enoic acid ethyl ester derivative were discussed.

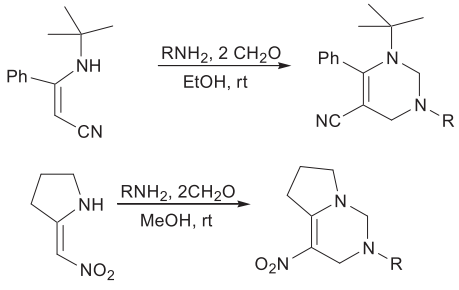
1. Introduction

As many naturally occurring compounds contain a pyrimidine skeleton as a key structural motif[1] in the last two decades we were witnesses to a tremendous increase in the number of publications dealing with the synthesis of multifunctionalized dihydropyrimidines ('Biginellii compounds') and tetrahydropyrimidines[2,3] representing remarkable pharmacological efficiency.[4] A wide range of biological effects,[5] including anticancer,[6] calcium channel modulation,[7] muscarinic agonist,[8] antiviral, antimicrobial,[9] and anti-inflammatory[10] activities have been attributed to this class of heterocyclic compounds.

In our earlier work[11,12] we demonstrated that enaminonitriles and nitroenamines with primary amines and formaldehyde undergo 'double' Mannich reactions to afford tetrahydropyrimidines and hexahydro-pyrrolo-pyrimidines in good yields (Scheme 1).

Recently we have also reported the multi-component catalyst-free reactions of 2-nitromethylenepyrrolidine (**1**) with ethyl glyoxylate and differently substituted anilines[13] to give the adducts **2** (Scheme 2). Our protocol offers considerable benefits, like simple reactants, synthetic work carried out on gram-scale, and access to a large number of new multi-functional compounds for further transformations to polysubstituted heterocyclic scaffolds.

These results prompted us to investigate similar ring closing reactions of **2** with formaldehyde and to synthesize new multi-substituted tetrahydropyrimidines starting from different nitroenamines.[1]



Scheme 1. Mannich reaction with enaminonitrile and nitroenamine.

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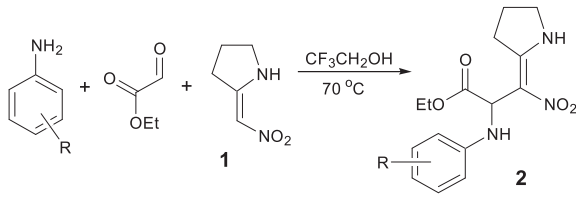
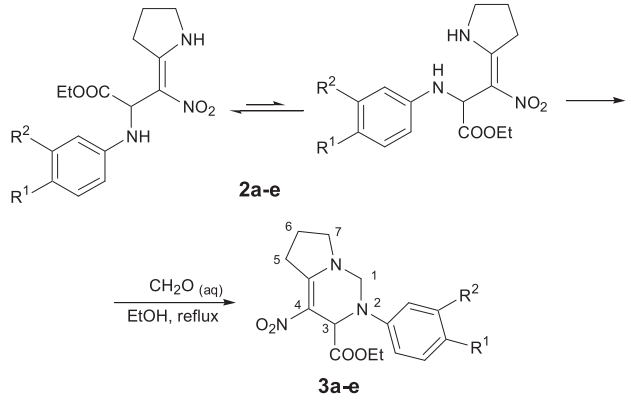


Scheme 2. Three-component reaction with nitroenamine **1**.

2. Results and discussion

First we prepared five Mannich adducts **2a**–**e** according to the procedure described earlier.[13] The products underwent ring closures in ethanol at reflux temperature using 35% formaldehyde solution resulting in **3a**–**e** in low to acceptable yields (Scheme 3, Table 1). Attempts to carry out the reactions with paraformaldehyde were unsuccessful. The *Z* arrangement around the C=C double bond of **2a**–**e** confirmed in the preceding paper[13] has been changed in the ring closure process, which can be evidenced by the unique bonding structure of the push–pull alkenes. In fact, previous studies of nitroenamine models revealed[14] that the low energy barrier (about 15 kcal/mol) of the *Z*–*E* interconversion leads to an equilibrium with the predominance of the former one due to the stabilization through H-bonding. The easy formation of **3a**–**e** can be understood by this relatively free rotation around the C=C bond providing a suitable geometrical position both NH groups to be cyclized with formaldehyde, irrespective of the type of the possible iminium intermediates with either of the NH functionalities.



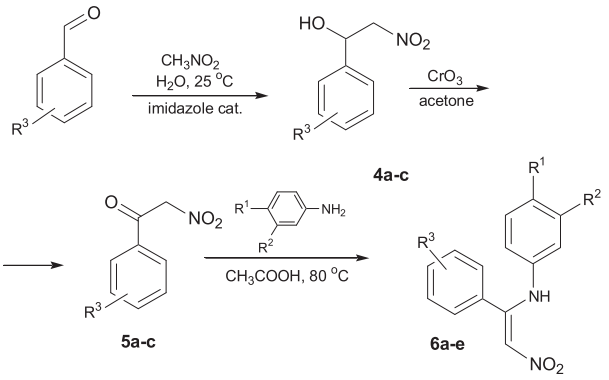
Scheme 3. Ring closure of **2a**–**e** with formaldehyde.

Table 1
Pyrrolo-pyrimidines prepared from **2a**–**e**

Entry	R^1	R^2	Yield (%)
3a	OCH_3	H	40
3b	H	H	30
3c	CH_3	H	60
3d	CH_3	CH_3	25
3e	OPh	H	58

Having this reaction in hand, we attempted to prepare these pyrrolo-pyrimidines in a four-component reaction. After the formation of **2a**–**e** from the three starting materials in trifluoroethanol, without isolation of the intermediate formaldehyde solution was added to the reaction mixture. The desired products **3a**–**e** could be detected by TLC, but after purification the yields were somewhat lower than in the sequential process.

In order to broaden the scope of the Mannich reaction and the subsequent ring closure we synthesized new open chain nitroenamines according to known procedures.[15] Substituted benzaldehydes were reacted with nitromethane at room temperature to give the addition products **4a**–**c**. The replacement of the imidazole catalyst by potassium fluoride simplified the workup procedure, and after evaporation of the solvent the product could be used in the next step. After oxidation of **4a**–**c** to the corresponding acetophenones **5a**–**c**, the nitroenamines **6a**–**e** were obtained with anilines in acceptable yields (Scheme 4, Table 2).

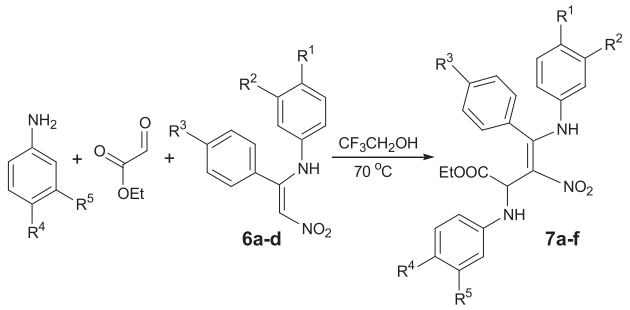


Scheme 4. Synthesis of nitroenamines **6a**–**e** (R^1, R^2, R^3 see Table 2).

Table 2
Open chain nitroenamines **6a**–**e**

Entry	R^1	R^2	R^3	Yield (%)
6a	CH_3	CH_3	4-NO_2	65
6b	F	H	4-NO_2	67
6c	CH_3	CH_3	H	66
6d	H	H	4-NO_2	74
6e	CH_3	CH_3	3-NO_2	62

The new aryl substituted nitroenamines **6a**–**d** readily underwent Mannich reactions with ethyl glyoxylate and anilines to afford the desired products **7a**–**f** in one-pot reactions with acceptable yields (Scheme 5, Table 3).



Scheme 5. Synthesis of **7a**–**f** with three-component reactions.

Table 3
Mannich products **7a**–**f** from the open chain nitreoenamines **6a**–**d**

Entry	R^1	R^2	R^3	R^4	R^5	Yield (%)
7a	CH_3	CH_3	NO_2	F	H	62
7b	F	H	NO_2	F	H	82
7c	CH_3	CH_3	H	F	H	70
7d	CH_3	CH_3	H	CH_3	CH_3	69
7e	H	H	NO_2	F	H	76
7f	H	H	NO_2	CH_3	CH_3	82

The new compounds **7a**–**f** were fully characterized by NMR spectroscopy. However, an unexpected NMR spectral observation, not found so far according to our knowledge, made a detailed study of **7f** necessary. The 2″-H/6″-H and 3″-H/5″-H atoms of the 3-(*p*-

nitrophenyl) group of **7f** gave, surprisingly, four signals with dd (8.5 Hz, 2.0 Hz) multiplicity at 7.38/7.93 and 8.16/8.35 ppm, respectively, instead of the expected AA′XX′ spectrum pattern. From this observation it can be concluded that the 2″-H/6″-H and 3″-H/5″-H hydrogens became pair-wise diastereotopic showing huge differences, i.e., $\Delta\delta$=329 Hz and 114 Hz, that cannot be explained with the effect of the C-2 stereocenter of the chiral compound **7f**. Interaction of this type, however, manifested itself in the signals of the geminal hydrogen atoms of the ethyl group, resulting in the chemical shifts 4.32dq and 4.25dq ppm (10.7 and 7.1 Hz) in the 600 MHz spectrum with the difference $\Delta\delta$=40 Hz.

In the two-dimensional NOESY spectrum of **7f** (mixing time=300 ms) we managed to observe the NOESY (blue) as well as the exchange (red) cross-peaks separately. The extreme chemical shift of one of the NH hydrogens, i.e., δ 12.05 ppm, indicates a planar structure of chelate type of the nitroenamine moiety that, owing to the extended conjugation, is arranged coplanar with the 4-(*p*-nitrophenyl) ring. The H-6″ signal and its steric proximity to 2-H was assigned by the 4.57/7.93 NOESY peak. Due to steric reasons, confirmed also by models, the aniline-phenyl group is nearly perpendicular to the chelate ring and, consequently, the 2″-H and 3″-H hydrogens are located above the plane of this C_6H_5 ring, explaining their detected diamagnetic shifts (Figs. 1 and 2).

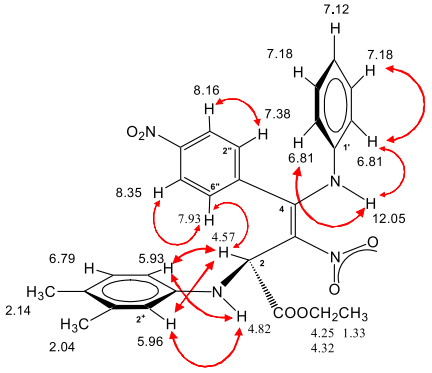


Fig. 1. Stereostructure, ^{1}H chemical shifts, and characteristic NOESY responses of **7f** (Only one of the enantiomeric forms is depicted.).

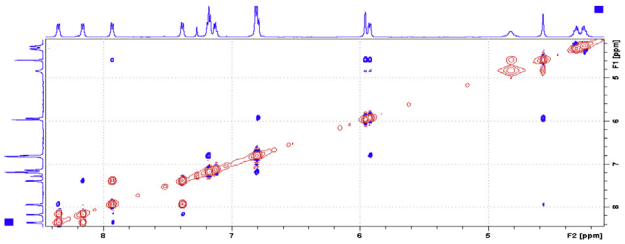
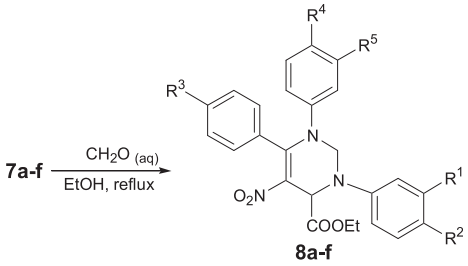


Fig. 2. Section of the NOESY spectrum of **7f**. Blue cross-peaks correspond to the NOESY responses whereas the red ones refer to the exchanges.

The 7.38/7.93 and 8.16/8.35 ppm exchange (red) cross-peaks reveals that during the 300 ms mixing time a slow rotation takes place around the C-1″–C-4 bond that accelerates upon heating. Thus, in a DMSO-d_6 solution we observed a coalescence of the 2″-H/6″-H and 3″-H/5″-H signals, and at about 100 °C a spectrum of AA′XX″ type was registered, accompanied, unfortunately, by a considerable thermal decomposition.

Products **7a**–**f** were utilized in cyclizations with formaldehyde according to the procedure described above to give 5-nitro-1,3,6-triphenyl-1,2,3,4-tetrahydro-pyrimidine-4-carboxylic acid esters **8a**–**f** (Scheme 6, Table 4).

Next we tried to replace the anilines by aliphatic and aralkyl primary amines such as butylamine and benzylamine.

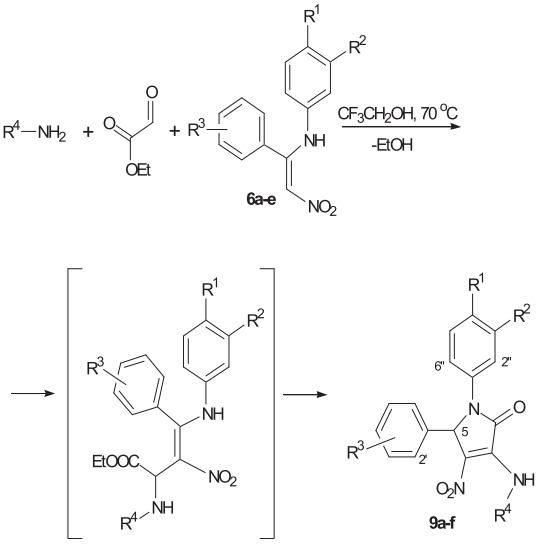


Scheme 6. Ring closure with formaldehyde to 1,2,3,4-tetrahydro-pyrimidines **8a**–**f**.

Table 4
Tetrahydropyrimidines from **7a**–**f**

Entry	R^1	R^2	R^3	R^4	R^5	Yield (%)
8a	CH_3	CH_3	NO_2	F	H	73
8b	F	H	NO_2	F	H	71
8c	CH_3	CH_3	H	F	H	76
8d	CH_3	CH_3	H	CH_3	CH_3	67
8e	H	H	NO_2	F	H	82
8f	H	H	NO_2	CH_3	CH_3	77

Unfortunately, these experiments led to complex mixtures from which pure products could not be separated. On the other hand, use of cyclopentyl-, cyclohexyl-, adamantyl-, and *tert*-butylamine furnished new compounds, which were isolated and purified with column chromatography in moderate yields. The missing ^{1}H NMR signals of the ethyl protons indicated a spontaneous cyclization leading to formation of 1,5-dihydropyrrolones **9a**–**f** and not allowing the isolation of the expected intermediate (Scheme 7, Table 5). The ring closure was accompanied with a double bond shift, which is evidenced by a strong HMBC cross peak, e.g., H-5(δ 5.87s)/C-2″,6″(δ 127.8) for compound **9a** and H-5(δ 5.98s)/C-2″(δ 122.7) and C-6″(δ 134.0) for compound **9e**.

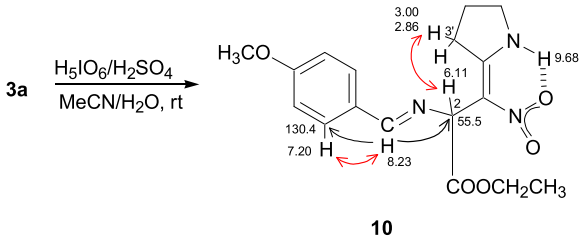


Scheme 7. Spontaneous ring closure to 1,5-dihydropyrrolone derivatives **9a**–**f**.

Table 5
1,5-Dihydropyrrolones formed from **6a**–**e**

Entry	R^1	R^2	R^3	R^4	Yield (%)
9a	CH_3	CH_3	H	Cyclohexyl	52
9b	CH_3	CH_3	4-NO_2	Cyclohexyl	38
9c	F	H	4-NO_2	Cyclopentyl	20
9d	F	H	4-NO_2	*tert*-Butyl	17
9e	CH_3	CH_3	3-NO_2	Adamantyl	44
9f	H	H	4-NO_2	Adamantyl	32

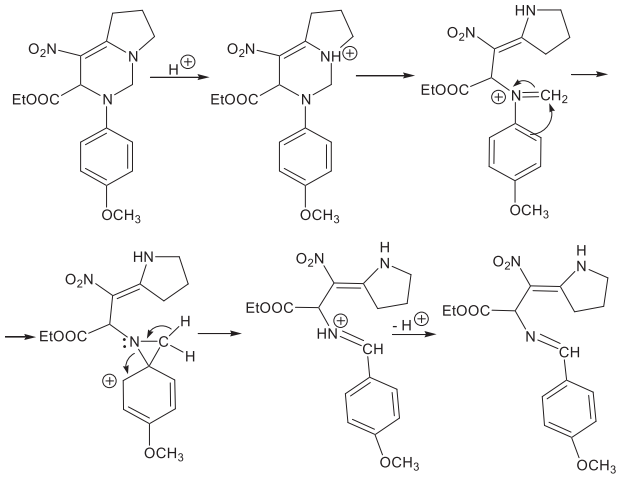
As our attempts to prepare the *N*-benzyl derivatives of **3** were unsuccessful we tried to remove the PMP moiety of **3a** in order to prepare pyrimidines with a secondary nitrogen in the ring, thus opening the route to further functionalization. Strictly adapting the standardized reaction conditions of the oxidative deprotection with periodic acid/sulfuric acid the expected product was, however, not obtained. Instead a ring opening accompanied by phenyl group migration took place, and a compound of aldimine type **10** was formed as a single product in excellent yield (Scheme 8), whose structure was proven by detailed NMR measurements.



Scheme 8. Formation of **10** through ring opening rearrangement of **3a**. Characteristic NOESY steric proximity is indicated with red, the HMBC correlations with black arrows.

The cyclic structure of **3a** is proven by the presence of the characteristic NMR signals of the NCH_2N moiety at 60.2; 4.77d/4.50dd. The absence of these signals and the appearance of a new NH singlet at 9.68s in the spectra of **10** indicate the opening of the tetrahydropyrimidine ring and simultaneously the emergence of a hydrogen bonding with the nitro group. The *Z*-configuration around the C=C double bond is further proven by the 2-H/3′-H_2 NOESY cross-peaks. The presence of a N=CH aldimine moiety in compound **10** is verified by the characteristic shifts (8.23s, 1H, 163.3) and coupling constant (^1J(C,H)=200 Hz). Furthermore, the HMBC cross-peaks (8.23/130.4 (C-2″,6″) and 8.23/55.5(C-2)) and the NOESY response (8.23/7.20(2″,6″-H)) provided unambiguous evidences that the carbon atom of the azomethine group is directly connected to the 4-methoxyphenyl group.

A plausible proposal for the mechanism of this transformation is depicted in Scheme 9. It can be supposed that, due to the decreased basicity, the enamine-nitrogen in the ring cannot tolerate protonation and leads to the cleavage of the tetrahydropyrimidine ring followed by the phenyl migration adopting the favored *Z*-configuration as explained above.



Scheme 9. Mechanistic proposal for the ring opening rearrangement process.

Since no oxidation occurred, we tried to carry out the reaction without periodic acid, either in an aqueous solution of sulfuric or trifluoroacetic acid, but **3a** remained unchanged. On the other hand, in a periodic acid solution without sulfuric acid the reaction took place slower, but also with excellent yield.

3. Conclusion

In summary, an efficient and simple synthesis was elaborated for the preparation of highly substituted tetrahydropyrimidines and hexahydropyrrolo-pyrimidines. These new compounds were obtained from the Mannich adducts of versatile nitroenamines, ethyl glyoxylate, and anilines in a simple ring closure with formaldehyde. The products are suitable for further transformations to afford complex heterocyclic scaffolds and alkaloid analogues. An interesting with N→C phenyl migration accompanied acid catalyzed ring opening reaction of a hexahydropyrrolo-pyrimidine derivative was discovered.

4. Experimental section

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded at room temperature on Bruker Avance 300, 500, 600 and Varian Unity 300 spectrometers. Chemical shifts, given on the δ scale, were referenced to the solvent ($CDCl_3$: δ_C=77.0 and δ_H=7.27). In the 1D measurements (^{1}H, ^{13}C, DEPTQ, DEPT-135, sel-NOE), 64K data points were used for the FID. The pulse programs (gradient-selected HSQC, HMBC, and NOESY) were taken from the Bruker software library. The NMR signals of the products were assigned by comprehensive one- and two-dimensional NMR methods using widely accepted strategies.[16] The HRMS analyses were performed with an Agilent 5230 TOF instrument. IR spectra were recorded on a Perkin Elmer 1600 FT IR spectrometer. TLC precoated sheets (Merck DC-Alufolien Kieselgel $60F_{254}$) were used. Melting points were determined on an Electrothermal 9100 apparatus.

4.2. General procedure for the synthesis of 3a–e

A solution of formaldehyde (37% w/w *aq* solution, 0.2 mL, 3.2 mmol), and **2a**–**e** (1.0 mmol) in EtOH (6 mL) were heated at reflux temperature until the starting material was consumed. The reaction mixture was concentrated under reduced pressure and the oily residue was dissolved in CH_2Cl_2 (10 mL). The solution was washed with H_2O (3×10 mL), dried over Na_2SO_4, and then evaporated under reduced pressure to give the crude product.

*4.2.1. 2-(4-Methoxy-phenyl)-4-nitro-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-c]pyrimidine-3-carboxylic acid ethyl ester (**3a**).* Purification of the product by column chromatography (*n*-hexane/EtOAc/^{i}Pr-amine 59:33:8) gave yellowish solid (278 mg, 40%), mp 86–88 °C (decomp.); R_f (*n*-hexane/EtOAc/^{i}Pr-amine 59:33:8) 0.40. ν_{max} (KBr) 1737, 1592, 1511, 1342, 1288, 1229, 1093, 836 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.92 (2H, d, *J* 10.0 Hz, 2′-H, 6′-H), 6.82 (2H, d, *J* 10.0 Hz, 3′-H, 5′-H), 5.24 (1H, s, 3-H), 4.77 (1H, d, *J* 13.1 Hz, 1-H), 4.50 (1H, d, *J* 13.1 Hz, 1-H), 4.28–4.20 (2H, m, CH_2–CH_3), 3.76 (3H, s, OCH_3), 3.64–3.58 (2H, m, 7-H), 3.54–3.50 (2H, m, 5-H), 2.18–2.08 (2H, m, 6-H), 1.28 (3H, t, *J* 7.0 Hz, CH_2–CH_3); δ_C (125 MHz, $CDCl_3$) 170.6, 160.9, 155.8, 142.2, 121.0, 114.6, 114.0, 61.6, 61.0, 60.2, 55.5, 52.1, 34.3, 20.1, 14.1. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{17}H_{22}N_3O_5$: 348.1559. Found: 348.1563.

*4.2.2. 4-Nitro-2-phenyl-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-c]pyrimidine-3-carboxylic acid ethyl ester (**3b**).* Purification of the product by column chromatography (^{t}Bu-Me-ether/^{i}Pr-amine 9:1) gave white solid (190 mg, 30%), mp 123–125 °C (decomp.); R_f (^{t}Bu-Me-ether/^{i}Pr-amine 9:1) 0.70. ν_{max} (KBr) 1739, 1597, 1342, 1285, 1233, 1098, 1026 cm^{-1}; δ_H (500 MHz $CDCl_3$) 7.30–6.98 (5H, m, Ar), 5.43

(1H, s, 3-H), 4.81 (1H, d, *J* 9.0 Hz, 1-H), 4.62 (1H, d, *J* 9.0 Hz, 1-H), 4.28–4.22 (2H, m, C*H*$_2$–CH$_3$), 3.64–3.58 (2H, m, 7-H), 3.54–3.50 (2H, m, 5-H), 2.20–2.09 (2H, m, 6-H), 1.30 (3H, t, *J* 7.0 Hz, CH$_2$–C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 170.6, 160.9, 148.3, 129.5, 122.9, 118.8, 114.1, 61.7, 59.9, 59.7, 52.1, 34.3, 20.1, 14.1. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{16}H_{20}N_3O_4$: 318.1454. Found: 318.1452.

*4.2.3. 4-Nitro-2-p-tolyl-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-c]pyrimidine-3-carboxylic acid ethyl ester (**3c**).* Purification of the product by column chromatography (EtOAc/*n*-hexane 1:1) gave white solid (400 mg, 60%), mp 114–115 °C; R_f (EtOAc) 0.70. ν_{max} (KBr) 1737, 1592, 1513, 1342, 1290, 1229, 1098 cm^{-1}; δ_H (500 MHz $CDCl_3$) 7.09 (2H, d, *J* 10.0 Hz, 3′-H, 5′-H), 6.88 (2H, d, *J* 10.0 Hz, 2′-H, 6′-H), 5.37 (1H, s, 3-H), 4.78 (1H, d, *J* 12.0 Hz, 1-H), 4.60 (1H, d, *J* 12.0 Hz, 1-H), 4.27–4.21 (2H, m, C*H*$_2$–CH$_3$), 3.64–3.58 (2H, m, 7-H), 3.54–3.50 (2H, m, 5-H), 2.29 (3H, s, CH$_3$), 2.19–2.09 (2H, m, 6-H), 1.29 (3H, t, *J* 7.0 Hz, CH$_2$–C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 170.6, 160.9, 146.0, 132.6, 130.0, 119.0, 114.1, 61.6, 60.3, 59.8, 52.1, 34.3, 22.8, 20.5, 14.1. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{17}H_{22}N_3O_4$: 332.1610. Found: 332.1611.

*4.2.4. 2-(3,4-Dimethyl-phenyl)-4-nitro-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-c]pyrimidine-3-carboxylic acid ethyl ester (**3d**).* Purification of the product by column chromatography (EtOAc/cyclohexane 6:4) gave white solid (173 mg, 25%), mp 176–178 °C; R_f (EtOAc/cyclohexane 1:1) 0.40. ν_{max} (KBr) 1737, 1588, 1518, 1344, 1285, 1242, 1211, 1096 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.04 (1H, d, *J* 8.1 Hz, 5′-H), 6.81 (1H, s, 2′-H), 6.69 (1H, dd, *J* 8.1, 2.1 Hz, 6′-H), 5.39 (1H, s, 3-H), 4.79 (1H, d, *J* 13.2 Hz, 1-H), 4.62 (1H, d, *J* 13.2 Hz, 1-H), 4.31–4.20 (2H, m, C*H*$_2$–CH$_3$), 3.65 (2H, m, 7-H), 3.53 (2H, m, 5-H), 2.14–2.06 (2H, m, 6-H), 2.24 (3H, s, Ph–C*H*$_3$), 2.21 (3H, s, Ph–C*H*$_3$), 1.31 (3H, t, *J* 7.1 Hz, CH$_2$–C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 170.8, 161.0, 146.4, 137.9, 131.4, 130.5, 120.7, 116.0, 114.2, 61.8, 60.4, 59.8, 52.2, 34.4, 20.2, 20.1, 19.0, 14.2. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{18}H_{24}N_3O_4$: 346.1769. Found: 346.1765.

*4.2.5. 4-Nitro-2-(4-phenoxy-phenyl)-1,2,3,5,6,7-hexahydro-pyrrolo[1,2-c]pyrimidine-3-carboxylic acid ethyl ester (**3e**).* Purification of the product by column chromatography (EtOAc/cyclohexane 1:5) gave white solid (456 mg, 58%), mp 129–130 °C; R_f (EtOAc/cyclohexane 1:9) 0.55. ν_{max} (KBr) 1739, 1592, 1506, 1342, 1290, 1233, 1093 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36–7.28 (2H, m, Ar–H), 7.12–7.07 (1H, m, Ar–H), 6.99–6.97 (5H, m, Ar–H), 5.33 (1H, s, 3-H), 4.81 (1H, d, *J* 12.9 Hz, 1-H), 4.57 (1H, d, *J* 12.9 Hz, 1-H), 4.29–4.22 (2H, m, C*H*$_2$–CH$_3$), 3.68–3.62 (2H, m, 7-H), 3.56–3.52 (2H, m, 5-H), 2.23–2.11 (2H, m, 6-H), 1.31 (3H, t, *J* 7.1 Hz, CH$_2$–C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 170.6, 161.0, 157.6, 152.7, 144.4, 129.8, 123.2, 120.8, 120.2, 118.4, 114.1, 61.8, 60.5, 60.3, 52.1, 34.4, 20.2, 14.2. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{22}H_{24}N_3O_5$: 410.1716. Found: 411.1708.

4.3. General procedure for the synthesis of 6a–e

A mixture of α-nitro ketone **5a**–**c** (25 mmol), substituted aniline (50 mmol), and acetic acid (50 mmol) was stirred at 80 °C under nitrogen atmosphere until TLC indicated the total consumption of the α-nitro ketone. The reaction mixture was concentrated at reduced pressure and the residue was purified by column chromatography (hexane/EtOAc 5:2).

*4.3.1. (3,4-Dimethyl-phenyl)-[2-nitro-1-(4-nitro-phenyl)-vinyl]-amine (**6a**).* Yellow solid (5.09 g, 65%), mp 150 °C; R_f (hexane/EtOAc 5:2) 0.63. ν_{max} (KBr) 2362, 1700, 1652, 1578, 1526, 1350, 1202 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 11.28 (1H, br s, NH), 8.17 (2H, d, *J* 8.6 Hz, *Ph*(*p*-NO_2)), 7.49 (2H, d, *J* 8.6 Hz, *Ph*(*p*-NO_2)), 6.88 (1H, d, *J* 8.0 Hz, *Ph*(3,4-$(CH_3)_2$)), 6.70 (1H, s, =CH–NO_2), 6.68 (1H, s, *Ph*(3,4–$(CH_3)_2$)), 6.43 (1H, d, *J* 8.0 Hz, *Ph*(3,4–$(CH_3)_2$)), 2.15 (3H, s, CH_3), 2.12 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 153.3, 149.0, 138.5, 138.3, 135.6, 134.7, 130.5, 130.0, 125.5, 124.2, 121.9, 114.3, 19.9, 19.4. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{16}H_{16}N_3O_4$: 314.1140. Found: 314.1144.

*4.3.2. (4-Fluoro-phenyl)-[2-nitro-1-(4-nitro-phenyl)-vinyl]-amine (**6b**).* Yellow solid (5.07 g, 67%), mp 183 °C; R_f (hexane/EtOAc 5:2) 0.54. ν_{max} (KBr) 1584, 1529, 1512, 1349, 1193, 860 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 11.21 (1H, br s, NH), 8.18 (2H, d, *J* 8.4 Hz, *Ph*(*p*-NO_2)), 7.47 (2H, d, *J* 8.4 Hz, *Ph*(*p*-NO_2)), 6.88–6.80 (4H, m, *Ph*(*p*-F)), 6.72 (1H, s, =CH–NO_2); δ_C (75 MHz, $CDCl_3$) 162.6, 159.3, 153.2, 149.1, 137.9, 133.3, 133.2, 130.1, 126.5, 126.3, 124.4, 116.8, 116.6, 114.8. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{14}H_{11}FN_3O_4$: 304.0734. Found: 304.0737.

*4.3.3. (3,4-Dimethyl-phenyl)-(2-nitro-1-phenyl-vinyl)-amine (**6c**).* Yellow solid (4.42 g, 66%), mp 167 °C; R_f (hexane/EtOAc 5:2) 0.69. ν_{max} (KBr) 2367, 1700, 1596, 1568, 1358, 1200 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 11.51 (1H, br s, NH), 8.35–7.24 (5H, m, *Ph*), 6.85 (1H, d, *J* 8.1 Hz, *Ph*(3,4-$(CH_3)_2$)), 6.73 (1H, s, =C*H*–NO_2), 6.64 (1H, s, *Ph*(3,4-$(CH_3)_2$)), 6.43 (1H, d, *J* 8.1 Hz, *Ph*(3,4-$(CH_3)_2$)), 2.13 (3H, s, CH_3), 2.09 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 156.1, 137.8, 135.3, 134.8, 131.9, 130.9, 130.2, 129.1, 128.7, 125.1, 121.4, 113.9, 19.9, 19.4. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{16}H_{17}N_2O_2$: 269.1290. Found: 269.1288.

*4.3.4. [2-Nitro-1-(4-nitro-phenyl)-vinyl]-phenyl-amine (**6d**).* Yellow solid (5.28 g, 74%), mp 179 °C; R_f (hexane/EtOAc 5:2) 0.32. ν_{max} (KBr) 1581, 1529, 1351, 1288, 1197, 857 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 11.28 (1H, br s, NH), 8.18 (2H, d, *J* 8.7 Hz, Ph(*p*-NO_2)), 7.51 (2H, d, *J* 8.7 Hz, *Ph*(*p*-NO_2)), 7.20–7.13 (3H, m, *Ph*), 6.82–6.73 (2H, m, *Ph*), 6.73 (1H, s, =C*H*–NO_2); δ_C (75 MHz, $CDCl_3$) 153.0, 149.1, 138.2, 137.2, 130.1, 129.7, 126.8, 124.4, 124.3, 114.9. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{14}H_{12}N_3O_4$: 286.0828. Found: 286.0835.

*4.3.5. (3,4-Dimethyl-phenyl)-[2-nitro-1-(3-nitro-phenyl)-vinyl]-amine (**6e**).* Yellow solid (4.43 g, 62%), mp 168 °C; R_f (hexane/EtOAc 5:2) 0.52. ν_{max} (KBr) 1580, 1529, 1349, 1288, 1194, 865 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 11.28 (1H, br s, NH), 8.25 (1H, d, *J* 8.2 Hz, 4′-H), 8.20 (1H, s, 2′-H), 7.62 (1H, d, *J* 8.2 Hz, 6′-H), 7.53 (1H, t, *J* 7.8 Hz, 5′-H), 6.89 (1H, d, *J* 7.8 Hz, 5″-H), 6.73 (1H, s, =CH–NO_2), 6.70 (1H, d, *J* 2.1 Hz, 2″-H), 6.46 (1H, dd, *J* 7.8, 2.1 Hz, 6″-H), 2.15 (3H, s, CH_3), 2.13 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 153.2, 148.4, 138.4, 135.6, 134.7, 134.6, 130.9, 130.5, 130.3, 125.6, 125.5, 123.8, 122.1, 114.3, 19.9, 19.5. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{14}H_{12}N_3O_4$: 314.1141. Found: 314.1145.

4.4. General procedure for the one-pot synthesis of compounds 7a–f

Nitroenamine **6a**–**d** (2 mmol), ethyl glyoxylate (1.1 mL 50% solution in toluene, 5.5 mmol), and the corresponding aniline (5.5 mmol) were stirred in 8 mL trifluoroethanol at 70 °C until the nitroenamine was consumed. The solvent was then removed in vacuum and the crude product was purified by column chromatography on silica gel using hexane/EtOAc (5:2) as eluent to give a crystalline product.

*4.4.1. 4-(3,4-Dimethyl-phenylamino)-2-(4-fluoro-phenylamino)-3-nitro-4-(4-nitro-phenyl)-but-3-enoic acid ethyl ester (**7a**).* Yellow solid (629 mg, 62%), mp 158 °C; R_f (hexane/EtOAc 5:2) 0.50. ν_{max} (KBr) 2364, 1752, 1700, 1652, 1559, 1509, 1350 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 12.06 (1H, s, NH), 8.32 (1H, dd, *J* 8.5, 2.1 Hz, Ph(*p*-NO_2)), 8.15 (1H, dd, *J* 8.5, 2.1 Hz, Ph(*p*-NO_2)), 7.85 (1H, dd, *J* 8.5, 1.5 Hz, Ph(*p*-NO_2)), 7.35 (1H, dd, *J* 8.5, 1.5 Hz, Ph(*p*-NO_2)), 6.84 (1H, d, *J* 8.0 Hz, Ph$(CH_3)_2$), 6.76 (1H, d, *J* 8.5 Hz, Ph(*p*-F)), 6.72 (1H, d, *J* 8.5 Hz, Ph(*p*-F)), 6.68 (1H, s, Ph$(CH_3)_2$), 6.42 (1H, d, *J* 8.0 Hz, Ph$(CH_3)_2$), 6.14 (1H, d, *J* 8.8 Hz, Ph(*p*-F)), 6.12 (1H, d, *J* 8.5 Hz, Ph(*p*-F)), 4.87 (1H, d, *J* 9.9 Hz,

NH), 4.46 (1H, d, *J* 9.9 Hz, C*H*–COOEt), 4.25 (2H, q, *J* 7.1 Hz, CH_2–CH_3), 2.13 (3H, s, CH_3), 2.10 (3H, s, CH_3), 1.14 (3H, t, *J* 7.1 Hz, CH_2–CH_3); δ_C (75 MHz, $CDCl_3$) 170.5, 155.3, 149.1, 142.7, 142.6, 138.4, 138.3, 136.4, 134.7, 131.2, 131.1, 130.7, 126.5, 124.4, 124.2, 123.6, 122.8, 116.2, 116.2, 116.0, 115.9, 62.7, 58.5, 20.1, 19.6, 14.6. HRMS (ITTOF) *m*/*z*: $[M-H]^+$ calcd for $C_{26}H_{26}FN_4O_6$: 509.1836. Found: 509.1840.

*4.4.2. 2,4-Bis-(4-fluoro-phenylamino)-3-nitro-4-(4-nitro-phenyl)-but-3-enoic acid ethyl ester (**7b**).* Yellow solid (817 mg, 82%), mp 129 °C; R_f (hexane/EtOAc 5:2) 0.51. ν_{max} (KBr) 2362, 1700, 1652, 1578, 1526, 1350, 1202 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 11.93 (1H, s, NH), 8.32 (1H, dd, *J* 8.5, 1.9 Hz, Ph(*p*-NO_2)), 8.17 (1H, dd, *J* 8.5, 1.9 Hz, Ph(*p*-NO_2)), 7.83 (1H, dd, *J* 8.2, 1.3 Hz, Ph(*p*-NO_2)), 7.35 (1H, dd, *J* 8.2, 1.3 Hz, Ph(*p*-NO_2)), 6.90–6.72 (6H, m, Ar), 6.15–6.12 (2H, m, Ar), 4.85 (1H, d, *J* 10.0 Hz, NH), 4.47 (1H, d, *J* 10.0 Hz, C*H*–COOEt), 4.26 (2H, q, *J* 7.0 Hz, CH_2–CH_3), 1.30 (3H, t, *J* 7.0 Hz, CH_2–CH_3); δ_C (75 MHz, $CDCl_3$) 170.2, 162.9, 159.6, 158.5, 155.3, 154.9, 149.1, 142.5, 142.4, 137.7, 133.1, 133.0, 131.1, 130.9, 127.5, 127.3, 124.5, 124.1, 116.8, 116.5, 116.1, 116.0, 115.8, 62.6, 58.3, 14.4. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{24}H_{21}F_2N_4O_6$: 499.1429. Found: 499.1429.

*4.4.3. 4-(3,4-Dimethyl-phenylamino)-2-(4-fluoro-phenylamino)-3-nitro-4-phenyl-but-3-enoic acid ethyl ester (**7c**).* Yellow solid (649 mg, 70%), mp 115 °C; R_f (hexane/EtOAc 5:2) 0.45. ν_{max} (KBr) 2362, 1699, 1650, 1557, 1539, 1522, 1505 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 12.40 (1H, s, NH), 7.64 (1H, d, *J* 8.0 Hz, Ph(CH_3)$_2$), 7.52–7.49 (2H, m, Ph), 7.39–7.32 (1H, m, Ph), 7.16 (1H, d, *J* 7.5 Hz, Ph(*p*-F)), 6.85 (1H, d, *J* 7.5 Hz, Ph(*p*-F)), 6.73 (1H, d, *J* 8.5 Hz, Ph(*p*-F)), 6.70 (1H, d, *J* 8.5 Hz, Ph(*p*-F)), 6.62 (1H, s, Ph(CH_3)$_2$), 6.43 (1H, d, *J* 7.5 Hz, Ph(CH_3)$_2$), 6.14–6.10 (2H, m, Ph), 4.93 (1H, d, *J* 9.6 Hz, NH), 4.70 (1H, d, *J* 9.6 Hz, C*H*–COOEt), 4.27 (2H, q, *J* 7.1 Hz, CH_2–CH_3), 2.14 (3H, s, CH_3), 2.10 (3H, s, CH_3), 1.31 (3H, t, *J* 7.1 Hz, CH_2–CH_3); δ_C (75 MHz, $CDCl_3$) 170.7, 158.0, 157.3, 154.9, 142.9, 137.6, 135.1, 135.0, 131.7, 130.8, 130.0, 129.4, 129.2, 129.1, 129.0, 125.5, 123.3, 121.7, 115.6, 115.5, 115.3, 62.1, 58.0, 19.7. 19.2, 14.3. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{26}H_{27}FN_3O_4$: 464.1986. Found: 464.1978.

*4.4.4. 2,4-Bis-(3,4-dimethyl-phenylamino)-3-nitro-4-phenyl-but-3-enoic acid ethyl ester (**7d**).* Yellow solid (653 mg, 69%), mp 134 °C; R_f (hexane/EtOAc 5:2) 0.53. ν_{max} (KBr) 2367, 1734, 1701, 1652, 1559, 1540, 1509 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 12.40 (1H, s, NH), 7.72–5.97 (11H, m, Ar), 4.91 (1H, d, *J* 9.5 Hz, NH), 4.83 (1H, d, *J* 9.5 Hz, C*H*–COOEt), 4.26 (2H, q, *J* 7.1 Hz, CH_2–CH_3), 2.19 (3H, s, CH_3), 2.15 (3H, s, CH_3), 2.11 (3H, s, CH_3), 2.06 (3H, s, CH_3), 1.34 (3H, t, *J* 7.1 Hz, CH_2–CH_3); δ_C (75 MHz, $CDCl_3$) 170.4, 157.0, 144.5, 137.2, 137.1, 135.1, 134.9, 131.8, 130.7, 130.2, 130.1, 129.9, 129.7, 126.5, 125.4, 123.8, 121.6, 115.7, 111.9, 62.0, 57.5, 19.8, 19.7. 19.2, 19.0, 14.3. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{28}H_{32}N_3O_4$: 474.2393. Found: 474.2394.

*4.4.5. 2-(4-Fluoro-phenylamino)-3-nitro-4-(4-nitro-phenyl)-4-phenylamino-but-3-enoic acid ethyl ester (**7e**).* Recrystallization of the crude product (EtOAc) gave a yellow solid (730 mg, 76%), mp 168 °C; R_f (hexane/EtOAc 5:2) 0.50. ν_{max} (KBr) 2361, 1751, 1574, 1511, 1350, 1141 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 12.07 (1H, s, NH), 8.33 (1H, dd, *J* 8.4, 2.0 Hz, Ph(*p*-NO_2)), 8.16 (1H, dd, *J* 8.4, 2.0 Hz, Ph(*p*-NO_2)), 7.88 (1H, dd, *J* 8.3, 1.3 Hz, Ph(*p*-NO_2)), 7.36 (1H, dd, *J* 8.3, 1.3 Hz, Ph(*p*-NO_2)), 7.21–7.13 (3H, m, Ph), 6.83–6.73 (4H, m, Ph(*p*-F)), 6.17–6.11 (2H, m, Ph), 4.89 (1H, d, *J* 10.2 Hz, NH), 4.50 (1H, d, *J* 10.2 Hz, C*H*–COOEt), 4.28 (2H, q, *J* 7.1 Hz, CH_2–CH_3), 1.32 (3H, t, *J* 7.1 Hz, CH_2–CH_3); δ_C (75 MHz, $CDCl_3$) 170.1, 158.3, 155.1, 154.6, 148.9, 142.3, 142.2, 137.8, 136.8, 131.0, 130.8, 129.5, 127.2, 125.2, 124.2, 123.9, 123.8, 115.9, 115.8, 115.7, 115.6, 62.5, 58.1, 14.3. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{24}H_{22}FN_4O_6$: 481.1523. Found: 481.1531.

*4.4.6. 2-(3,4-Dimethyl-phenylamino)-3-nitro-4-(4-nitro-phenyl)-4-phenylamino-but-3-enoic acid ethyl ester (**7f**).* Yellow solid (800 mg, 82%), mp 152 °C; R_f (hexane/EtOAc 5:2) 0.40. ν_{max} (KBr) 2362, 1572, 1529, 1348, 1134, 857 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 12.05 (1H, s, NH), 8.35 (1H, dd, *J* 8.5, 2.0 Hz, 3″-H), 8.16 (1H, dd, *J* 8.5, 2.0 Hz, 5″-H), 7.93 (1H, dd, *J* 8.5, 2.0 Hz, 2″-H), 7.38 (1H, dd, *J* 8.5, 2.0 Hz, 6″-H), 7.18 (2H, t, *J* 7.3 Hz, 3′,5′-H), 7.12 (1H, t, *J* 7.3 Hz, 4′-H), 6.81 (2H, d, *J* 7.3 Hz, 2′,6′-H), 6.79 (1H, d, *J* 8.1 Hz, 5^+-H), 5.96 (1H, d, *J* 2.0 Hz, 2^+-H), 5.93 (1H, dd, *J* 8.1, 2.0 Hz, 6^+-H), 4.82 (1H, br, NH), 4.57 (1H, s, C*H*–COOEt), 4.32, 4.25 (2H, dq, *J* 10.7, 7.1 Hz, CH_2–CH_3), 2.14 (3H, s, 4^+–CH_3), 2.04 (3H, s, 3^+-CH_3), 1.33 (3H, t, *J* 7.1 Hz, CH_2–CH_3); δ_C (150 MHz, $CDCl_3$) 170.3 (C=O), 154.1 (C-4), 148.7 (C-4″), 143.8 (C-1^+), 137.8 (C-1″), 137.2 (C-2^+), 136.8 (C-1′), 131.1 (C-6″), 130.9 (C-2″), 130.1 (C-5^+), 129.3 (C-3′,5′), 127.1 (C-4^+), 127.0 (C-4′), 125.0 (C-2′,6′), 124.2 (C-3), 124.1 (C-3″), 123.8 (C-5″), 115.8 (C-1^+), 111.7 (C-6^+), 62.3 (OCH_2), 57.4 (C-2), 19.8 (CH_3-5^+), 18.6 (CH_3-4^+), 14.2 (CH_3CH_2). HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{26}H_{27}N_4O_6$: 491.1931. Found: 491.1937.

4.5. Compounds 8a–f were prepared as described above for 3a–e

*4.5.1. 1-(3,4-Dimethyl-phenyl)-3-(4-fluoro-phenyl)-5-nitro-6-(4-nitro-phenyl)-1,2,3,4-tetrahydro-pyrimidine-4-carboxylic acid ethyl ester (**8a**).* Recrystallization of the crude product (EtOAc) gave a yellow solid (380 mg, 73%), mp 168 °C; R_f (hexane/EtOAc 5:2) 0.51. ν_{max} (KBr) 2362, 1700, 1652, 1578, 1526, 1350, 1202 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.05 (2H, d, *J* 7.6 Hz, Ph(*p*-NO_2)), 7.33 (2H, d, *J* 7.6 Hz, Ph(*p*-NO_2)), 7.01–6.98 (4H, m, Ar), 6.79 (1H, d, *J* 7.9 Hz, Ph(CH_3)$_2$), 6.48 (1H, s, Ph(CH_3)$_2$), 6.33 (1H, d, *J* 7.9 Hz, Ph(CH_3)$_2$), 5.55 (1H, s, C*H*–COOEt), 5.33 (1H, d, *J* 13.1 Hz, N–CH_2–N), 4.83 (1H, d, *J* 13.1 Hz, N–CH_2–N), 4.31 (2H, q, *J* 7.1 Hz, CH_2–CH_3), 2.09 (3H, s, CH_3), 2.05 (3H, s, CH_3), 1.34 (3H, t, *J* 7.1 Hz, CH_2–CH_3); δ_C (75 MHz, $CDCl_3$) 170.1, 161.0, 157.2, 154.3, 148.2, 144.2, 144.1, 139.8, 139.6, 138.5, 136.9, 130.8, 130.3, 128.0, 124.6, 123.8, 121.4, 120.9, 120.8, 116.7, 116.4, 67.9, 62.5, 61.7, 20.0, 19.7, 14.5. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{27}H_{26}FN_4O_6$: 521.1836. Found: 521.1839.

*4.5.2. 1,3-Bis-(4-fluoro-phenyl)-5-nitro-6-(4-nitro-phenyl)-1,2,3,4-tetrahydro-pyrimidine-4-carboxylic acid ethyl ester (**8b**).* Recrystallization of the crude product (EtOAc) gave a yellow solid (724 mg, 71%), mp 184 °C; R_f (hexane/EtOAc 5:2) 0.56. ν_{max} (KBr) 1737, 1572, 1511, 1348, 1297, 1231, 839 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.04 (2H, d, *J* 7.1 Hz, Ph(*p*-NO_2)), 7.33 (2H, d, *J* 7.6 Hz, Ph(*p*-NO_2)), 7.00–6.60 (8H, m, Ph(*p*-F)), 5.53 (1H, s, C*H*–COOEt), 5.32 (1H, d, *J* 13.0 Hz, N–CH_2–N), 4.80 (1H, d, *J* 13.0 Hz, N–CH_2–N), 4.29 (2H, q, *J* 7.1 Hz, CH_2–CH_3), 1.31 (3H, t, *J* 7.1 Hz, CH_2–CH_3); δ_C (75 MHz, $CDCl_3$) 169.8, 162.9, 160.6, 159.6, 157.4, 153.5, 148.1, 143.8, 143.7, 139.2, 138.0, 137.9, 130.1, 129.0, 128.9, 123.8, 122.1, 120.8, 120.7, 116.9, 116.7, 116.6, 116.4, 68.1, 62.5, 61.2, 14.3. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{25}H_{21}F_2N_4O_6$: 511.1429. Found: 511.1430.

*4.5.3. 1-(3,4-Dimethyl-phenyl)-3-(4-fluoro-phenyl)-5-nitro-6-phenyl-1,2,3,4-tetrahydro-pyrimidine-4-carboxylic acid ethyl ester (**8c**).* Recrystallization of the crude product (EtOAc) gave a yellow solid (722 mg, 76%), mp 158 °C; R_f (hexane/EtOAc 5:2) 0.30. ν_{max} (KBr) 1737, 1558, 1508, 1292, 1208, 737 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.11–6.97 (9H, m, Ar), 6.79 (1H, d, *J* 7.8 Hz, Ph(CH_3)$_2$), 6.37 (1H, s, Ph(CH_3)$_2$), 6.34 (1H, d, *J* 7.8 Hz, Ph(CH_3)$_2$), 5.56 (1H, s, C*H*–COOEt), 5.34 (1H, d, *J* 13.0 Hz, N–CH_2–N), 4.85 (1H, d, *J* 13.0 Hz, N–CH_2–N), 4.33 (2H, q, *J* 7.1 Hz, CH_2–CH_3), 2.10 (3H, s, CH_3), 2.05 (3H, s, CH_3), 1.36 (3H, t, *J* 7.1 Hz, CH_2–CH_3); δ_C (75 MHz, $CDCl_3$) 170.0, 160.2, 156.9, 156.6, 144.1, 144.0, 140.3, 137.6, 135.5, 132.4, 130.0, 129.3, 129.1, 1283, 127.6, 124.1, 120.8, 120.5, 120.4, 116.2, 115.9, 67.4, 62.0, 61.8, 19.6, 19.3, 14.2. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{27}H_{27}FN_3O_4$: 476.1986. Found: 476.1979.

*4.5.4. 1,3-Bis-(3,4-dimethyl-phenyl)-5-nitro-6-phenyl-1,2,3,4-tetrahydro-pyrimidine-4-carboxylic acid ethyl ester (**8d**).* Recrystallization of the crude product (EtOAc) gave a yellow solid

(650 mg, 67%), mp 136 °C; R_f (hexane/EtOAc 5:2) 0.50. ν_{max} (KBr) 2368, 1736, 1699, 1650, 1555, 1542, 1507, 1458, 1285 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.20–6.43 (11H, m, Ar), 5.68 (1H, s, C*H*–COOEt), 5.34 (1H, d, *J* 13.0 Hz, N–C*H*$_2$–N), 4.93 (1H, d, *J* 13.0 Hz, N–C*H*$_2$–N), 4.34 (2H, q, *J* 7.0 Hz, C*H*$_2$–CH_3), 2.21 (3H, s, CH_3), 2.18 (3H, s, CH_3), 2.12 (3H, s, CH_3), 2.06 (3H, s, CH_3), 1.37 (3H, t, *J* 7.0 Hz, CH_2–C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 170.3, 156.7, 145.6, 140.4, 137.7, 137.4, 135.4, 132.7, 130.7, 130.5, 129.9, 129.2, 129.1, 128.2, 127.8, 124.3, 120.9, 120.2, 115.8, 66.7, 61.9, 61.8, 20.1, 19.6, 19.3, 18.4, 14.2. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{29}H_{32}N_3O_4$: 486.2393. Found: 486.2398.

*4.5.5. 3-(4-Fluoro-phenyl)-5-nitro-6-(4-nitro-phenyl)-1-phenyl-1,2,3,4-tetrahydro-pyrimidine-4-carboxylic acid ethyl ester (**8e**).* Recrystallization of the crude product (EtOAc) gave a yellow solid (807 mg, 82%), mp 110 °C; R_f (hexane/EtOAc 5:2) 0.44. ν_{max} (KBr) 1739, 1565, 1511, 1351, 1299, 1215, 861 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.07 (2H, d, *J* 6.9 Hz, Ph(*p*-NO_2)), 7.35 (2H, d, *J* 6.9 Hz, Ph(*p*-NO_2)), 7.15–7.00 (7H, m, Ar), 6.70–6.65 (2H, m, Ph), 5.58 (1H, s, C*H*–COOEt), 5.38 (1H, d, *J* 13.0 Hz, N–C*H*$_2$–N), 4.89 (1H, d, *J* 13.0 Hz, N–C*H*$_2$–N), 4.34 (2H, q, *J* 7.1 Hz, C*H*$_2$–CH_3), 1.37 (3H, t, *J* 7.1 Hz, CH_2–C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 169.7, 160.4, 157.2, 153.5, 147.9, 143.7, 143.6, 141.7, 139.2, 130.1, 129.6, 127.7, 126.9, 123.5, 121.7, 120.5, 120.4, 116.5, 116.2, 67.5, 62.3, 61.3, 14.2. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{25}H_{22}FN_4O_6$: 493.1523. Found: 493.1529.

*4.5.6. 3-(3,4-Dimethyl-phenyl)-5-nitro-6-(4-nitro-phenyl)-1-phenyl-1,2,3,4-tetrahydro-pyrimidine-4-carboxylic acid ethyl ester (**8f**).* Recrystallization of the crude product (EtOAc) gave a yellow solid (773 mg, 77%), mp 113 °C; R_f (hexane/EtOAc 5:2) 0.54. ν_{max} (KBr) 2368, 1736, 1700, 1650, 1550, 1539, 1502, 1460, 1288 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.05 (1H, d, *J* 7.1 Hz, Ph(*p*-NO_2)), 7.34 (2H, d, *J* 7.1 Hz, Ph(*p*-NO_2)), 7.06–6.71 (8H, m, Ar), 5.65 (1H, s, C*H*–COOEt), 5.37 (1H, d, *J* 13.0 Hz, N–C*H*$_2$–N), 4.95 (1H, d, *J* 13.0 Hz, N–C*H*$_2$–N), 4.35 (2H, q, *J* 7.1 Hz, C*H*$_2$–CH_3), 2.18 (3H, s, CH_3), 2.14 (3H, s, CH_3), 1.37 (3H, t, *J* 7.1 Hz, CH_2–C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 170.2, 153.5, 147.8, 145.2, 141.9, 139.4, 138.0, 131.3, 130.6, 130.1, 129.4, 127.6, 127.0, 123.5, 121.9, 120.1, 115.7, 66.8, 62.1, 61.4, 20.2, 18.9, 14.2. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{27}H_{27}N_4O_6$: 503.1931. Found: 503.1928.

4.6. General procedure for the one-pot synthesis of compounds 9a–f

Nitroenamine **6a–e** (2 mmol), ethyl glyoxylate (1.1 mL 50% solution in toluene, 5.5 mmol), and the corresponding primary amine (5.5 mmol) were stirred in 8 mL trifluoroethanol at 70 °C until the nitroenamine was consumed. The solvent was then removed in vacuum and the crude product was purified by column chromatography on silica.

*4.6.1. 3-Cyclohexylamino-1-(3,4-dimethyl-phenyl)-4-nitro-5-phenyl-1,5-dihydro-pyrrol-2-one (**9a**).* Purification by column chromatography (hexane/EtOAc 5:1), yellow solid (842 mg, 52%), mp 156 °C; R_f (hexane/EtOAc 5:2) 0.73. ν_{max} (KBr) 1703, 1647, 1513, 1454, 1396 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.47 (1H, d, *J* 8.6 Hz, NH), 7.35–7.20 (5H, m, Ph-5), 7.17 (1H, d, *J* 2.0 Hz, 2″-H), 7.03 (1H, d, *J* 8.3 Hz, 5″-H), 7.00 (1H, dd, *J* 8.3, 2.0 Hz, 6″-H), 5.87 (1H, s, 5-H), 2.18 (3H, s, 3″-CH_3), 2.16 (3H, s, 4″-CH_3), cyclohexyl: 4.99 (1H, m, CH–N), 2.20–1.20 (10H, m, C_6H_{11}); δ_C (125 MHz, $CDCl_3$) 161.3 (C-2), 142.4 (C-3), 137.5 (C-3″), 135.7 (C-4″), 134.7 (C-1′), 133.0 (C-1″), 130.2 (C-5″), 128.8 (C-4′), 128.6 (C-3′,5′), 127.8 (C-2′,6′), 125.2 (C-2″), 123.6 (C-4), 121.3 (C-6″), 61.9 (C-5), 20.0 (CH_3-3″), 19.4 (CH_3-4″), cyclohexyl: 51.6 (C–N), 34.9/34.4, 24.7/24.6 and 25.2 (CH_2). HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{24}H_{28}N_3O_3$: 406.2131. Found: 406.2138.

*4.6.2. 3-Cyclohexylamino-1-(3,4-dimethyl-phenyl)-4-nitro-5-(4-nitro-phenyl)-1,5-dihydro-pyrrol-2-one (**9b**).* Purification by column chromatography (hexane/EtOAc 5:2), yellow solid (684 mg, 38%), mp 124 °C; R_f (hexane/EtOAc 5:2) 0.54. ν_{max} (KBr) 1714, 1645, 1520, 1458, 1350 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.47 (1H, s, NH), 8.07 (2H, d, *J* 8.4 Hz, Ph(*p*-NO_2)), 7.42 (2H, d, *J* 8.4 Hz, Ph(*p*-NO_2)), 7.14–6.97 (3H, m, Ph(CH_3)$_2$), 5.98 (1H, s, H-5), 4.96–4.93 (1H, m, NH–C*H*), 2.15 (3H, s, C*H*$_3$), 2.13 (3H, s, C*H*$_3$), 1.81–1.23 (10H, m, C_6H_{11}); δ_C (75 MHz, $CDCl_3$) 160.8, 148.0, 142.4, 142.3, 137.9, 136.2, 132.4, 130.3, 128.8, 128.7, 124.8, 123.8, 120.9, 60.7, 51.7, 34.7, 34.2, 26.9, 25.1, 24.6, 19.9, 19.3. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{24}H_{27}N_4O_5$: 451.1981. Found: 451.1983.

*4.6.3. 3-Cyclopentylamino-1-(4-fluoro-phenyl)-4-nitro-5-(4-nitro-phenyl)-1,5-dihydro-pyrrol-2-one (**9c**).* Purification by column chromatography (hexane/EtOAc 2:1) gave an oil (342 mg, 20%); R_f (cyclohexane/EtOAc 2:1) 0.51; δ_H (300 MHz, $CDCl_3$) 8.50 (1H, d, *J* 9.0 Hz, NH), 8.15–6.98 (8H, m, Ar), 5.99 (1H, s, H-5), 5.38–5.35 (1H, m, NH–C*H*), 1.85–1.13 (8H, m, C_5H_9); δ_C (75 MHz, $CDCl_3$) 162.9, 161.3, 159.6, 148.4, 142.4, 141.9, 131.0, 129.0, 125.8, 125.7, 124.2, 122.7, 116.8, 116.5, 61.2, 61.1, 54.9, 35.4, 34.9, 24.1, 24.0. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{21}H_{20}FN_4O_5$: 427.1418. Found: 427.1414.

*4.6.4. 3-tert-Butylamino-1-(4-fluoro-phenyl)-4-nitro-5-(4-nitro-phenyl)-1,5-dihydro-pyrrol-2-one (**9d**).* Purification by column chromatography (hexane/EtOAc 2:1) gave an oil (114 mg, 17%); R_f (cyclohexane/EtOAc 2:1) 0.55; δ_H (300 MHz, $CDCl_3$) 9.15 (1H, s, NH), 8.15–7.01 (8H, m, Ar), 5.99 (1H, s, H-5), 1.68 (9H, s, C_4H_9); δ_C (75 MHz, $CDCl_3$) 162.9, 161.3, 148.4, 144.6, 142.0, 131.1, 128.9, 125.9, 125.8, 124.2, 122.7, 116.8, 116.5, 61.5, 56.3, 30.8. HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{20}H_{20}FN_4O_5$: 415.1418. Found: 415.1417.

*4.6.5. 3-(Adamant-1-ylamino)-1-(3,4-dimethyl-phenyl)-4-nitro-5-(3-nitro-phenyl)-1,5-dihydro-pyrrol-2-one (**9e**).* Purification by column chromatography (hexane/EtOAc 2:1), yellow solid (442 mg, 44%), mp 221 °C; R_f (cyclohexane/EtOAc 2:1) 0.60. ν_{max} (KBr) 1716, 1640, 1520, 1457, 1352 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 9.14 (1H, s, NH), 8.10 (1H, d, *J* 8.3 Hz, 4′-H), 8.09 (1H, s, 2′-H), 7.60 (1H, d, *J* 8.3 Hz, 6′-H), 7.46 (1H, t, *J* 8.3 Hz, 5′-H), 7.12 (1H, d, *J* 2.0 Hz, 2″-H), 7.05 (1H, d, *J* 8.3 Hz, 5″-H), 6.97 (1H, dd, *J* 8.3, 2.0 Hz, 6″-H), 5.98 (1H, s, 5-H), 2.19 (3H, s, 3″-CH_3), 2.16 (3H, s, 4″-CH_3), adamantyl: 2.32/2.28 (6H, d, *J* 12.0 Hz, CH_2), 1.78–1.72 (6H, d, *J* 12.0 Hz, CH), 2.19 (3H, s); δ_C (150 MHz, $CDCl_3$) 160.3 (C-2), 148.3 (C-3′), 145.2 (C-3), 138.0 (C-3″), 137.3 (C-2′), 136.4 (C-4″), 134.0 (C-6′), 132.3 (C-1″), 130.4 (C-5″), 129.5 (C-5′), 125.4 (C-2″), 123.8 (C-4), 123.8 (C-4′), 122.7 (C-2′), 121.5 (C-6″), 19.9 (CH_3-3″), 19.3 (CH_3-4″), adamantyl: 56.6 (C–N), 42.6 and 35.7 (CH_2), 29.7 (CH) (The C-4 and C-4′ appeared as overlapped signals at 123.8 ppm, proven by ed-HSQC and HMBC measurements. For differentiation of 3″-CH_3 and 4″-CH_3 signals selective NOESY experiment (irradiation at 7.12) was applied.). HRMS (ITTOF) *m*/*z*: $[M+H]^+$ calcd for $C_{28}H_{31}N_4O_5$: 503.2294. Found: 503.2301.

*4.6.6. 3-(Adamant-1-ylamino)-1-phenyl-4-nitro-5-(4-nitro-phenyl)-1,5-dihydro-pyrrol-2-one (**9f**).* Purification by column chromatography (hexane/EtOAc 2:1), yellow solid; (304 mg, 32%), mp 213-214 °C; R_f (cyclohexane/EtOAc 5:2) 0.63. ν_{max} (KBr) 1712, 1638, 1522, 1457, 1357 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.10 (1H, s, NH), 8.12 (2H, d, *J* 8.7 Hz, Ph(*p*-NO_2)), 7.43 (2H, d, *J* 8.7 Hz, Ph(*p*-NO_2)), 7.35–7.29 (3H, m, Ph), 7.21–7.16 (2H, m, Ph), 6.03 (1H, s, 5-H), adamantyl: 2.30/2.25 (6H, d, *J* 12.0 Hz, CH_2), 1.78–1.75 (6H, d, *J* 12.0 Hz, CH), 2.19 (3H, s); δ_C (75 MHz, $CDCl_3$) 160.7, 148.3, 142.3, 135.2, 129.6, 128.9, 127.6, 124.1, 68.6, 61.5, 56.8, 42.9, 36.0, 30.0, 23.1, 20.3. HRMS

(ITTOF) m/z: $[M+H]^+$ calcd for $C_{26}H_{26}N_4O_5$. 475.1981. Found: 475.1988.

4.7. 2-[(4-Methoxy-benzylidene)-amino]-3-nitro-3-pyrrolidin-2-ylidene-propionic acid ethyl ester (10)

A mixture of **3a** (300 mg 0.86 mmol), periodic acid (197 mg 0.86 mmol), and sulfuric acid (0.86 mL, 1 M, 0.86 mmol) in acetonitrile/water (16 mL 1:1) was stirred at room temperature. The complete conversion was indicated by TLC analysis after 48 h reaction time. Then, potassium carbonate (3 g) was added, and the organic phase was separated. The aqueous phase was extracted with diethyl ether, and the combined organic phases were treated with charcoal, dried (Na_2SO_4), and evaporated to furnish a fairly pure product (290 mg, 97%) as a red oil that solidified upon standing. Flash column chromatography on silica (*tert*-butyl-methyl-ether/EtOAc/isopropylamine 72:20:8) gave an analytical sample; yellow solid, mp >200 °C dec; R_f (*tert*-butyl-methyl-ether/isopropylamine 9:1) 0.31. δ_H (600 MHz, $CDCl_3$) 9.68 (1H, br s, NH), 8.23 (1H, s, CH=), 7.20 (2H, d, 2′,6′-H), 6.81 (2H, d, 3′,5′-H), 6.11 (1H, s, C(2)-H), 4.24 (2H, m, CH_3CH_2), 3.81 (2H, t, t, J 7.2 Hz, 5″-H_2), 3.78 (3H, s, OCH_3), 3.00 and 2.86 (2H, m, 3″-H_2), 2.22 (2H, m, 4″-H_2), 1.28 (3H, t, J 7.2 Hz, CH_3CH_2); δ_C (150 MHz, $CDCl_3$) 167.9, 164.6, 163.3, 159.6, 130.4, 130.3, 114.0, 113.2, 62.0, 55.5, 55.3, 49.2, 32.7, 21.4, 14.1. HRMS (ITTOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{20}N_3O_5$: 347.1481. Found: 347.1478.

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