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A novel one-pot three-component reaction: Synthesis of triheterocyclic 4*H*-pyrimido[2,1-*b*]benzazoles ring systems

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Abstract—A novel one-pot three-component condensation reaction of an aldehyde, β-ketoester and 2-aminobenzimidazole or 2-aminobenzothiazole in 1,1,3,3-*N*,*N*,*N*′,*N*′-tetramethylguanidinium trifluoroacetate as an ionic liquid is described. During the course of this reaction 4*H*-pyrimido[2,1-*b*]benzimidazoles or 4*H*-pyrimido[2,1-*b*]benzothiazoles are formed in high yields at 100 °C. The ionic liquid can be recovered conveniently and reused efficiently.

1. Introduction

Multicomponent condensation reactions (MCRs) have recently been discovered to be a powerful method for the synthesis of organic compounds, since the products are formed in a single step and diversity can be achieved by simply varying each component.[1]

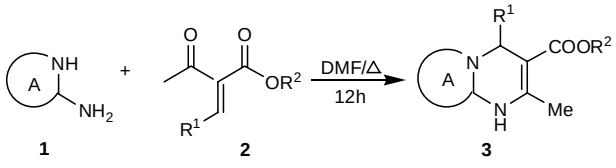
The classic version of the Biginelli three-component condensation reaction,[2] which combines an aldehyde, urea or thiourea and an open-chain β-dicarbonyl compound under acidic conditions in ethanol to give a monocyclic 3,4-dihydropyrimidin-2(1*H*)-one (DHPs), has extended into widespread use for generating large collections of molecules in combinatorial synthesis.[3]

In recent years, there has been increasing interest in the design of new products for the synthesis of Biginelli and Biginelli-like compounds,[3b,4–8] which exhibit a wide range of biological activities.

The bicyclic DHPs such as thiazolopyrimidines and imidazopyrimidines **3**, which have potent vasorelaxant activity, are prepared in two steps by the Atwal modification of Biginelli reaction.[9] As indicated in Scheme 1, in this approach, an enone type 3-benzylidene-2,4-pentanedione **2** is condensed with 2-aminothiazole or various aminoheterocycles **1**, reminiscent of the general procedure for the synthesis of monocyclic Biginelli compounds.

Very recently, Deniaud[10] and co-workers have developed an annulation protocol for the synthesis of tricyclic DHPs such as 4*H*-pyrimido[2,1-*b*]benzothiazoles **4** based on multi-step reaction strategy (Scheme 2).

Due to biological activity of a significant number of compounds containing condensed pyrimidine ring system[11–19] and our interest in MCRs[20] and Biginelli and Biginelli-like reactions,[8a,b,21] we wish to report the synthesis of triheterocyclic DHPs such as 4*H*-pyrimido[2,1-*b*]benzazoles ring systems by the one-pot three-component condensation of an aldehyde **5** and β-ketoester **6** in the presence of 2-aminobenzimidazole or 2-aminobenzothiazole **1**, instead of common urea or thiourea in Biginelli reaction, in 1,1,3,3-*N*,*N*,*N*′,*N*′-tetramethylguanidinium trifluoroacetate (TMGT) as an ionic liquid at 100 °C (Scheme 3).



Scheme 1.

Keywords: Multicomponent; 2-Aminobenzimidazole; 2-Aminobenzothiazole; 4*H*-Pyrimido[2,1-*b*]benzothiazoles; 4*H*-Pyrimido[2,1-*b*]-benzimidazoles.
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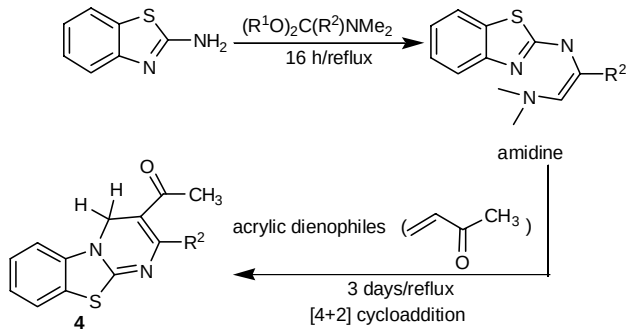


Scheme 2.

2. Results and discussions

The reaction of aldehydes with β-ketoesters and 2-aminobenzimidazole or 2-aminobenzothiazole afforded triheterocyclic 4*H*-pyrimido[2,1-*b*]benzazoles ring systems in TMGT as a promoter in relatively high yields. The structure of the products **4a**–**n** was deduced from their IR, ^{1}H NMR and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m*/*z* values.

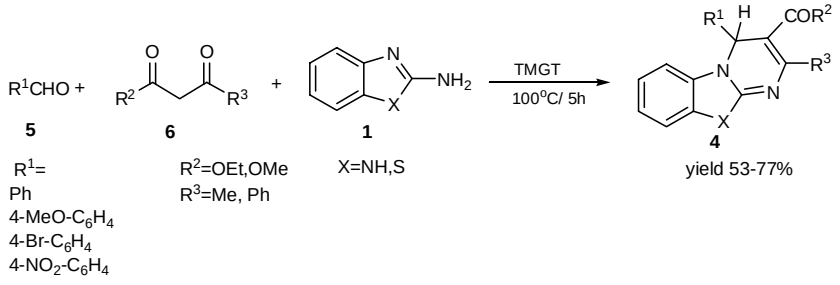
The ^{1}H NMR spectrum of **4a** exhibited three sharp lines readily recognized as arising from two methyl (δ = 2.46 and 3.70) and a Ph-C*H* (δ = 6.39) protons. A multiplet appeared at δ = 7.06–7.44 for the aromatic hydrogens. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 17 distinct resonances in agreement with the suggested structures. The ^{1}H and ^{13}C NMR spectra of **4b**–**n** are similar to those of **4a**, except for the R^1, R^2 and R^3 groups, which exhibit characteristic signals with appropriate chemical shifts.

We have not established a mechanism for the formation of 4*H*-pyrimido[2,1-*b*]benzazoles ring systems, but a reasonable possibility is indicated in Scheme 4.

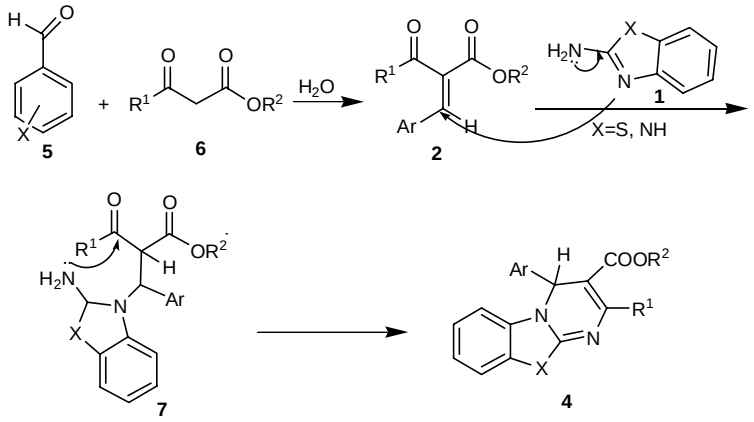
The reaction presumably proceeds in two steps: condensation of aldehyde **5** and β-ketoester **6** by standard Knoevenagel reaction produces 3-benzylidene-2,4-pentanedione **2**.[22] Then 2-aminobenzimidazole or 2-aminobenzothiazole **1** is reacted with compound **2** through a Michael addition and produces product type of **7** and after cyclisation to afford 4*H*-pyrimido[2,1-*b*]benzazoles ring systems **4**.[9a]

To explore the scope and limitations of this reaction further, we have extended it to various *para*-substituted benzaldehydes in the presence of 2-aminobenzimidazole and 2-aminobenzothiazole. As indicated in Table 1, the reaction proceeds efficiently with benzaldehyde and electron-withdrawing and electron-releasing *para*-substituted benzaldehydes.

One of the other advantages of this IL is its ability to be recyclable as reaction medium. We were easily able to separate TMGT from reaction medium by washing it with water and evaporating the solvent under vacuum,



Scheme 3.



Scheme 4.

Table 1. One-pot synthesis of triheterocyclic 4*H*-pyrimido[2,1-*b*]benzazoles by the condensation reaction of an aldehyde, β-ketoester and 2-aminobenzimidazole or 2-aminobenzothiazole in TMGT at 100 °C after 5 h

Product	R^1	R^2	R^3	X	Yield (%)[a]	Mp (°C)
4a	C_6H_5	OMe	Me	S	58	143–145
4b	4-MeO-C_6H_4	OMe	Me	S	59	150–153
4c	4-NO_2-C_6H_4	OMe	Me	S	57	78–81
4d	C_6H_5	OEt	Me	S	66, 60[b], 58[b], 55[b], 25[c]	173–175
4e	4-MeO-C_6H_4	OEt	Me	S	65	140–143
4f	4-Br-C_6H_4	OEt	Me	S	77	110–114
4g	4-NO_2-C_6H_4	OEt	Me	S	53	150–152
4h	C_6H_5	OEt	Ph	S	61	77–80
4i	4-NO_2-C_6H_4	OEt	Ph	S	55	158 dec
4j	C_6H_5	OEt	Me	N	73	>260
4k	4-MeO-C_6H_4	OEt	Me	N	67	250–253
4l	4-NO_2-C_6H_4	OEt	Me	N	60	225 dec
4m	4-MeO-C_6H_4	OEt	Ph	N	56	117–120
4n	4-NO_2-C_6H_4	OEt	Ph	N	61	248 dec

[a] Isolated yield.
[b] The same TMGT was used for each of the four runs.
[c] In the absence of TMGT.

and reusing it for subsequent reaction. As indicated in Table 1, no considerable loss of efficiency was observed with regard to reaction time and yield after four times (**4d** in Table 1). However, fresh IL can be added after four reuses for comparison in subsequent runs.

It is important to note, in the absence of TMGT, the yield of reaction decreased up to 25% after the 5 h (**4d** in Table 1).

In conclusion, we have developed a novel three-component condensation reaction of an aldehyde, β-ketoester and 2-aminobenzimidazole or 2-aminobenzothiazole for the efficient synthesis of 4*H*-pyrimido[2,1-*b*]benzazoles ring systems. The one-pot nature and the use of the ionic liquid as an eco-friendly promoter make it an interesting alternative to multi-step approaches.[9,10]

3. Experimental

3.1. Typical procedure for the synthesis of ethyl-2-methyl-4-(phenyl)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxylate

A mixture of ethylacetoacetate (0.130 g, 1 mmol), benzaldehyde (0.106 g, 1 mmol), TMGT (0.080 g, 0.3 mmol) and 2-aminobenzthiazole (0.150 g, 1 mmol) was successively added to a screw-capped vial containing a magnetic stirring bar and was heated at 100 °C in a preheated oil bath for 5 h. Then the reaction mixture was washed with cold water (2× 10 ml) and the solid residue was crystallized from acetone/water 1:3 to yield 0.231 g of **4d** as a yellow powder (66%).

All the products are new compounds, which were characterized by IR and ^{1}H NMR, ^{13}C NMR and mass spectral data.

3.1.1. Compound 4a: Methyl-2-methyl-4-(phenyl)-4*H*-primido[2,1-*b*][1,3]benzothiazole-3-carboxylate. Yellow powder; mp 143–145 °C; IR (KBr) (ν_{max}, cm^{-1}): 3055, 1666, 1581, 1428, 1238, 742; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.46 (3H, s), 3.70 (3H, s), 6.39 (1H, s), 7.06–7.44 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 166.96, 163.53, 154.87, 141.37, 137.94, 128.73, 128.41, 127.08, 126.68, 124.02, 123.80, 122.18, 111.78, 102.89, 57.73, 51.16, 23.71; MS (EI, 70 eV) (*m*/*z*, %) 337 ($(M+1)^+$, 11), 336 (M^+, 40), 277 (35), 259 (100), 199 (21), 175 (12), 134 (12).

3.1.2. Compound 4b: Methyl-2-methyl-4-(4-methoxyphenyl)-4*H*-primido[2,1-*b*][1,3]benzothiazole-3-carboxylate. Yellow powder; mp 150–153 °C; IR (KBr) (ν_{max}, cm^{-1}): 3060, 1660, 1576, 1400, 1242, 739; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.46 (3H, s), 3.71 (3H, s), 3.72 (3H, s), 6.37 (1H, s), 6.76–7.44 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 166.95, 163.22, 159.55, 137.95, 133.58, 128.38, 126.70, 124.10, 124.00, 122.23, 114.06, 111.95, 103.24, 57.30, 55.22, 51.15, 23.35; MS (EI, 70 eV) (*m*/*z*, %) 367 ($(M+1)^+$, 19), 366 (50), 307 (75), 259 (100), 199 (14), 134 (12).

3.1.3. Compound 4c: Methyl-2-methyl-4-(4-nitrophenyl)-4*H*-primido[2,1-*b*][1,3]benzothiazole-3-carboxylate. Yellow powder; mp 78–81 °C; IR (KBr) (ν_{max}, cm^{-1}): 3420, 1698, 1514, 1492, 1238, 745; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.45 (3H, s), 3.73 (3H, s), 6.53 (1H, s), 7.01–7.61 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 166.73, 163.73, 147.82, 147.73, 137.39, 127.98, 127.02, 124.63, 124.18, 123.85, 122.59, 111.46, 101.93, 57.11, 51.51, 23.85; MS (EI, 70 eV) (*m*/*z*, %) 382 ($(M+1)^+$, 19), 381 (M^+, 35), 322 (16), 259 (100), 199 (19), 150 (19), 43 (16).

3.1.4. Compound 4d: Ethyl-2-methyl-4-(phenyl)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxylate. Yellow powder; mp 173–175 °C; IR (KBr) (ν_{max}, cm^{-1}): 3425, 3030, 1664, 1588, 1456, 1236, 746; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.30 (3H, t, $^3J_{HH}$ = 7.1 Hz), 2.48 (3H, s), 4.17 (2H, m), 6.43 (1H, s), 7.12–7.46 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 166.39, 163.24,

141.16, 137.87, 128.65, 128.41, 127.17, 126.70, 124.08, 123.88, 122.20, 111.85, 103.09, 60.14, 57.82, 23.40, 14.33; MS (EI, 70 eV) (*m*/*z*, %) 351 ($(M+1)^+$, 10), 350 (M^+, 24), 321 (12), 273 (100), 245 (54), 199 (21), 175 (21), 150 (12), 134 (20), 77 (20).

3.1.5. Compound 4e: Ethyl-2-methyl-4-(4-methoxyphenyl)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxylate. Yellow powder; mp 140–143 °C; IR (KBr) (υ_{max}, cm^{-1}): 3415, 1695, 1504, 1238, 745; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.20 (3H, t, $^3J_{HH}$ = 9 Hz), 2.38 (3H, s), 3.62 (3H, s), 4.05–4.10 (2H, m), 6.26 (1H, s), 6.67–7.35 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 164.54, 161.15, 157.40, 152.12, 135.95, 131.67, 126.48, 124.59, 121.93, 121.81, 120.13, 111.87, 109.82, 101.24, 58.07, 55.19, 53.15, 21.54, 12.36; MS (EI, 70 eV) (*m*/*z*, %) 381($(M+1)^+$, 25), 380 (M^+, 70), 351 (26), 307 (100), 273 (90), 245 (45), 199 (15), 175 (15), 135 (19), 77 (12).

3.1.6. Compound 4f: Ethyl-2-methyl-4-(4-bromophenyl)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxylate. Yellow powder; mp 110–114 °C; IR (KBr) (υ_{max}, cm^{-1}): 3405, 3110, 1665, 1497, 1238; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.30 (3H, t, $^3J_{HH}$ = 7.1 Hz), 2.47 (3H, s), 4.16–4.21 (2H, m), 6.40 (1H, s), 7.09–7.51 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 166.20, 163.14, 139.98, 137.51, 131.91, 128.84, 126.91, 124.50, 123.99, 122.56, 122.44, 111.85, 102.84, 60.38, 57.35, 23.21, 14.36; MS (EI, 70 eV) (*m*/*z*, %) 430 (M^+, 15), 429 ($(M-1)^+$, 10), 401 (5), 355 (5), 273 (100), 245 (45), 199 (15), 175 (19), 150 (20), 134 (19), 75 (12), 43 (21).

3.1.7. Compound 4g: Ethyl-2-methyl-4-(4-nitrophenyl)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxylate. Yellow powder; mp 150–152 °C; IR (KBr) (υ_{max}, cm^{-1}): 3410, 3105, 1576, 1497, 1341, 1237, 746; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.31 (3H, t, $^3J_{HH}$ = 6.9 Hz), 2.50 (3H, s), 4.15–4.26 (2H, m), 6.57 (1H, s), 7.08–7.56 (4H, m), 7.61 (2H, d, $^3J_{HH}$ = 8.7 Hz), 8.15 (2H, d, $^3J_{HH}$ = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 165.97, 163.25, 147.82, 147.32, 137.07, 128.08, 127.21, 124.98, 124.18, 124.07, 122.74, 111.71, 102.31, 60.71, 57.28, 23.07, 14.36; MS (EI, 70 eV) (*m*/*z*, %) 396 ($(M+1)^+$, 5), 395 (M^+, 5), 366 (10), 322 (20), 273 (100), 245 (50), 199 (25), 175 (15), 134 (16).

3.1.8. Compound 4h: Ethyl-4-(phenyl)-2-phenyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxylate. Yellow powder; mp 77–80 °C; IR (KBr) (υ_{max}, cm^{-1}): 3055, 1669, 1504, 1476, 1211, 744; ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.85 (3H, t, $^3J_{HH}$ = 7.1 Hz), 3.86–3.94 (2H, m), 6.58 (1H, s), 7.22–7.56 (14H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 166.36, 163.06, 140.74, 137.52, 130.13, 128.99, 128.79, 128.30, 127.83, 127.13, 124.54, 122.41, 112.20, 103.40, 60.24, 58.47, 13.51; MS (EI, 70 eV) (*m*/*z*, %) 412 (M^+, 21), 339 (45), 307 (16), 134 (21), 105 (100), 77 (64), 43 (40).

3.1.9. Compound 4i: Ethyl-4-(4-nitrophenyl)-2-phenyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxylate. Yellow powder; mp 158 °C dec; IR (KBr) (υ_{max}, cm^{-1}): 3440, 1608, 1514, 1346, 1267, 1218; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.08 (3H, t, $^3J_{HH}$ = 7.0 Hz), 4.16–4.27 (2H, m), 7.18 (1H, s), 7.26–8.21 (13H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 168.36, 165.07, 132.74, 130.52, 130.13, 128.99, 128.79, 128.30, 126.83, 126.13, 124.55, 122.41, 112.20, 101.40, 61.24, 58.47, 12.5; MS (EI, 70 eV) (*m*/*z*, %) 456 (M^+, 19), 427 (100), 398 (28), 351 (64), 323 (21), 305 (75), 277 (16), 237 (70), 190 (12), 150 (40), 129 (42), 104 (66), 76 (64), 50 (30).

3.1.10. Compound 4j: Ethyl-2-methyl-4-(phenyl)-4,10-dihydropyrimido[1,2-*a*][1,3]benzimidazole-3-carboxylate. Yellow powder; mp >260 °C; IR (KBr) (υ_{max}, cm^{-1}): 3400, 3105, 1693, 1567, 1451, 1396, 1249; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.13 (3H, t, $^3J_{HH}$ = 7.0 Hz), 2.62 (3H, s), 4.01–4.04 (2H, m), 6.32 (1H, s), 6.90–7.38 (9H, m), 10.80 (1H, br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 165.91, 146.51, 146.12, 141.35, 140.37, 131.37, 128.54, 128.15, 127.44, 122.74, 121.24, 116.14, 109.95, 99.43, 60.14, 57.05, 1950, 14.31; MS (EI, 70 eV) (*m*/*z*, %) 334 ($(M+1)^+$, 30), 333 (M^+,100), 304 (30), 256 (90), 228 (35), 182 (14), 133 (14), 77 (16), 43 (23).

3.1.11. Compound 4k: Ethyl-2-methyl-4-(4-methoxyphenyl)-4,10-dihydropyrimido[1,2-*a*][1,3]benzimidazole-3-carboxylate. Yellow powder; mp 250–253 °C; IR (KBr) (υ_{max}, cm^{-1}): 3410, 3105, 1698, 1396, 1239, 751; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.29 (3H, t, $^3J_{HH}$ = 7.1 Hz), 2.75 (3H, s), 3.74 (3H, s), 4.13–4.21 (2H, m), 6.42 (1H, s), 6.78–7.51 (8H, m), 10.40 (1H, br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 165.94, 159.28, 146.36, 145.62, 139.97, 133.55, 131.23, 128.62, 122.79, 121.30, 116.00, 113.84, 110.04, 99.79, 60.14, 56.50, 55.19, 19.46, 14.33; MS (EI, 70 eV) (*m*/*z*, %) 364 ($(M+1)^+$, 21), 363 (M^+, 70), 334 (50), 290 (35), 256 (100), 228 (45), 182 (25), 133 (12), 115 (28), 77 (23).

3.1.12. Compound 4l: Ethyl-2-methyl-4-(4-nitrophenyl)-4,10-dihydropyrimido[1,2-*a*][1,3]benzimidazole-3-carboxylate. Yellow powder; mp 225 °C dec; IR (KBr) (υ_{max}, cm^{-1}): 3105, 1693, 1566, 1433, 1249, 753; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.29 (3H, t, $^3J_{HH}$ = 7.0 Hz), 2.74 (3H, s), 4.13–4.23 (2H, m), 6.59 (1H, s), 7.14–8.16 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 166.93, 156.94, 146.94, 145.62, 139.97, 133.55, 131.23, 127.62, 123.79, 121.30, 116.00, 113.84, 109.04, 98.80, 60.14, 55.19, 20.46, 13.33; MS (EI, 70 eV) (*m*/*z*, %) 378 (M^+, 64), 349 (26), 308 (14), 256 (100), 228 (64), 182 (30), 133 (31), 90 (28).

3.1.13. Compound 4m: Ethyl-4-(4-methoxyphenyl)-2-phenyl-4,10-dihydropyrimido[1,2-*a*][1,3]benzimidazole-3-carboxylate. Yellow powder; mp 117–120 °C; IR (KBr) (υ_{max}, cm^{-1}): 3120, 1675, 1554, 1450, 1248, 740; ^1H NMR(300 MHz, $CDCl_3$): δ_H 0.69 (3H, t, $^3J_{HH}$ = 7.05 Hz), 3.61 (3H, s), 3.68–3.75 (2H, m), 6.36 (1H, s), 6.68–7.39 (13H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 165.33, 159.63, 145.43, 145.22, 135.06, 132.67, 129.82, 128.63, 128.59, 128.28, 123.30, 122.16, 115.66, 114.19, 109.98, 101.38, 60.23, 56.86, 55.25, 13.55; MS (EI, 70 eV) (*m*/*z*, %) 426 ($(M+1)^+$, 95), 425 (M^+, 100), 396 (74), 352 (85), 318 (77), 129 (54), 105 (35), 77 (80).

3.1.14. Compound 4n: Ethyl-4-(4-nitrophenyl)-2-phenyl-4,10-dihydropyrimido[1,2-*a*][1,3]benzimidazole-3-carboxylate. Yellow powder; mp 248 °C dec; IR (KBr) (υ_{max}, cm^{-1}): 3405, 1675, 1558, 1341, 1249, 752; ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.82 (3H, t, $^3J_{HH}$ = 6.13 Hz), 3.85–3.87 (2H, m), 5.87 (1H, s), 6.65–8.19 (13H, m), 9.30–10.30 (1H, br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 165.38, 147.95, 147.73, 145.80, 135.33, 130.27, 129.84, 128.70, 128.65. 128.16, 124.12, 122.97, 121.80, 116.79, 109.01, 99.24, 60.28, 56.53, 13.47; MS (EI, 70 eV) (*m*/*z*, %) 393 (70), 367 (19), 318 (100), 291 (30), 278 (22), 244 (30), 172 (20), 111 (10), 87 (23), 69 (50).

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