# Four-Component Tandem Reaction to Synthesize Dihydrotetrazolopyrimidinyl Carbamides



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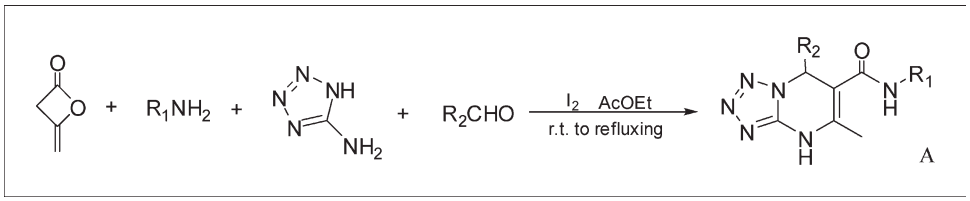


Four-component tandem procedure to prepare a series of dihydrotetrazolopyrimidinyl carbamides starting from diketene, amine, 5-aminotetrazole, and aldehyde was newly developed in the presence of iodine. Most of the products were obtained in moderate to good yield after simple workup of the final reaction mixture, the scope and limitation was also probed into.

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## INTRODUCTION

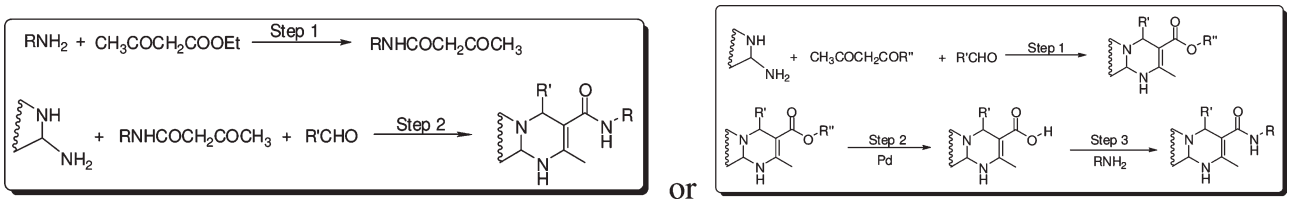
Over the years, considerable attention has been focused on the synthesis and selective multifunctionalization of dihydropyrimidines owing to the pharmacological properties associated with many derivatives of this privileged heterocyclic core [1]. Based on the Biginelli scaffold, dihydropyrimidines were largely extended by varying the aldehydes and 1,3-dicarbonyl compounds including β-ketoesters and cyclic β-diketones [2]. However, we noted that the dihydropyrimidinyl carbamides evaluated as $\alpha_{1A}$-adrenergic receptor antagonists for the treatment of benign prostatis hyperplasia [3] were rarely investigated because of a paucity of efficient synthetic route. According to the literature survey, the construction of the amide bond encountered either the prerequisite of initial β-ketoamides formation to participate the following Biginelli reaction [3,4], or the stepwise synthetic route [5] involving the synthesis of dihydropyrimidinyl ester firstly, deallylation of ester to dihydropyrimidinyl carboxylic acid secondly, and condensation the carboxylic acid with selected amine lastly (Scheme 1). These reported methods obviously complicated the generation of library diversity needed for the drug discovery. Therefore, a valuable and facile approach is desired.

In times where a premium is always put on speed, diversity and efficiency, simultaneous molecular interaction of three or more component namely multicomponent reactions (MCRs) offering significant advantages over conventional linear-type syntheses are of great interest for both chemists and biologists. Accordingly, adding the amine to the classical Biginelli MCR directly is extremely costly leading to dihydropyrimidinyl carbamides. To complete the one-pot reaction, the usual 1,3-dicarbonyl compound used in classical Biginelli reaction was replaced by diketene which could be readily ring-opened to afford acetoacetic derivatives [6] for the furnishment of target structure in a tandem manner.

## RESULTS AND DISCUSSION

As part of our on going interests in tetrazolopyrimidines [7], 5-aminotetrazole (5-AT) bearing both endocyclic nitrogen and exocyclic amino group which could participate the construction of pyrimidine-ring simultaneously was initially chosen as the 1,3-binucleophile synthon. Our study commenced with the model reaction of *N*-benzyl-3-oxobutanamide M, which was generated from benzyl amine and diketene in situ at room temperature, with 4-chlorobenzaldehyde and 5-AT in AcOEt as depicted in Scheme 2. Fortunately, the anticipated product A1 was obtained after refluxing the materials in AcOEt for 24 hours, the structure was proved by means of Ms and NMR, wherein a molecular ion peak displayed at *m*/*z* 379 in the mass spectrum, the sharp singlet signals at $\delta = 2.2$, 6.75 ppm arising from 5-Me, 7-CH, and the two doublet signals at $\delta = 4.09$–4.14, 4.30–4.35 ($J = 15$ Hz) arising from N—$CH_2$ exhibited distinctly in $^1$H NMR. However, the yield was poor (16%). Meanwhile, iodine, as a mild, cheap, less toxic

**Scheme 1.** Traditional methods to dihydropyrimidinyl carbamides.




and easily accessible metal-free catalyst, has entered into widespread use for promoting the MCR-heterocyclization in recent years [8]. We have effectively validated the high activity in our previous work [7,8c,h,i]. Thereupon, 25 mol % of iodine as a Lewis acid catalyst was added into the model reaction (Scheme 2). To our delight, the yield was increased up to 56%, and the reaction time was shortened to 8 hours. The catalyst concentration was ultimately fixed on 30 mol %, because the anticipated product could be yielded in 63% in the presence of 30 mol % of iodine and further increasing the amount of iodine didn't improve the yield.

Since there were limited publications devoted to the synthesis of dihydrotetrazolopyrimidinyl carbamides, especially in one-pot tandem fashion starting from amine directly, the success of the preliminary experimentation encouraged us to further explore the scope and limitation of this four-compound condensation via varying aldehydes and amines. The results were collected in Table 1. All of the representative aromatic aldehydes bearing either electron-withdrawing group (such as chloro, nitro) or electron-donating group and amines including aromatic and aliphatic amines were smoothly transformed into the target products in moderate to good yields after refluxing no more than 12 hours. Impressively, electron-deficient aldehydes and electro-rich amines were favorable for the transformation, the 4-methoxybenzaldehyde delivered lower yields (Entry 2, Table 1), while the expected product was not detected in the final mixture in the case of aniline (Entry 9, Table 1), moreover, we failed completely to apply this iodine-catalyzed system to aliphatic aldehyde such as butyraldehyde and 4-chloroaniline respectively. Similar results were obtained when 5-AT was replaced by urea or thiourea, and the data has been reported while our research was in progress [9]. On the other hand, the steric factor made limited impact on the reaction, inasmuch as the 2-chlorobenzaldeheyde and 2-fluorobenzyl amine (Entries 4 and 8, Table 1) were converted to the corresponding products successfully in slightly lower yield of 46 and 49%, respectively.

In summary, we have successfully designed a tandem reaction involving an initial addition of amine to diketene followed by a Biginelli-like condensation with 5-AT and aldehyde in one-pot in the presence of iodine for the first time. The dihydrotetrazolopyrimidinyl carbamide and derivatives were produced in moderate to good yield, and the limitation was disclosed when the system was applied to electron-rich aldehydes and electro-deficient amines. The simplicity and efficiency of the present procedure make it an interesting alternative to the complex multistep approach.

## EXPERIMENTAL

Starting material 5-AT was prepared according to literature procedure [10], others were obtained from commercial suppliers and used without further purification. All melting points were uncorrected. The purity was analyzed qualitatively by high performance liquid chromatography (HPLC) on Waters 600E chromatograph, 2487 detector. Mass spectra were taken on an Finnigan TSQ Quantum-LC/MS/MS instrument in the

**Scheme 2.** Iodine catalyzed four-component tandem reaction to synthesize *N*-benzyl-7-(4-chlorophenyl)-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide A1.

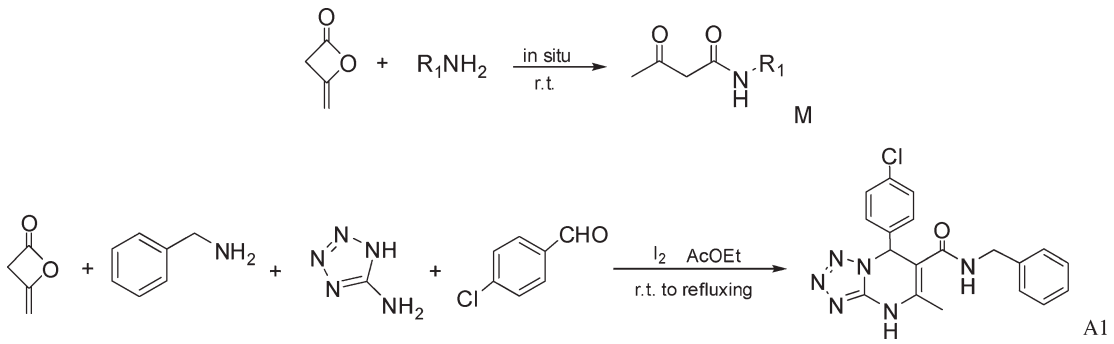
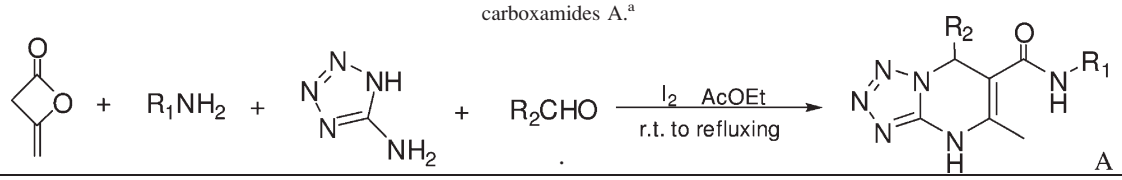


**Table 1**

Iodine catalyzed four-component tandem reaction to synthesize the *N*,7-disubstituted-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamides A.[a]




| Entry | $R_1$ | $R_2$ | T (h)[b] | Product | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 | $C_6H_5CH_2$ | 4-$ClC_6H_4$ | 8 | A1 | 63 |
| 2 | $C_6H_5CH_2$ | 4-$MeOC_6H_4$ | 9 | A2 | 31 |
| 3 | $C_6H_5CH_2$ | 4-$NO_2C_6H_4$ | 8 | A3 | 73 |
| 4 | $C_6H_5CH_2$ | 2-$ClC_6H_4$ | 12 | A4 | 46 |
| 5 | $C_6H_5CH_2$ | $C_6H_5$ | 10 | A5 | 54 |
| 6 | 4-$FC_6H_4CH_2$ | 4-$ClC_6H_4$ | 8 | A6 | 54 |
| 7 | 4-$MeOC_6H_4CH_2$ | 4-$ClC_6H_4$ | 8 | A7 | 61 |
| 8 | 2-$FC_6H_4CH_2$ | 4-$ClC_6H_4$ | 10 | A8 | 49 |
| 9 | $C_6H_5$ | 4-$ClC_6H_4$ | 24 | A9 | – |
| 10 | $CH_3(CH_2)_3$ | 4-$ClC_6H_4$ | 6 | A10 | 61 |

[a] Reaction conditions: after 2 mmol of diketene and amine were stirred in 3 mL of AcOEt at room temperature for 2 hours, 2 mmol of aldehyde and 5-AT, 0.6 mmol of iodine were then added and the reaction finally proceeded at 78°C.
[b] The time since 5-AT was added.
[c] Isolated yield.

electrospray ionization (negative) mode. The IR spectra were recorded on KBr pellets on Shimadzu IR Prestige-21 spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded at 300 or 500 MHz and 75 or 125 MHz, respectively, in DMSO-*d*6, and chemical shifts were reported in ppm from internal TMS (δ). Elemental analyses were performed on a Yanagimoto MT3CHN recorder.

**The typical procedure for the synthesis of *N*,7-disubstituted-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamides A.** A solution of amine (2 mmol) and diketene (2 mmol) was stirred in 3 mL of AcOEt at room temperature for 2 hours. Then, the aldehyde (2 mmol), 5-AT (2 mmol) and iodine (0.6 mmol) were added, and the temperature was increased to 78°C. The precipitate appeared gradually after 2 hours, the reaction was terminated till the mixture was solidified after several hours (Table 1). After the reaction mixture was cooled to room temperature, 3 mL of AcOEt was added, and then the solid precipitated was filtrated, washed with a solution of sodium thiosulfate followed by water and EtOH. White powder was obtained after drying, the further purification was needless as the purity of the corresponding product was high up to 98% based on the analysis of HPLC.

All of the products were new, and have been fully characterized by $^1$H NMR, $^{13}$C NMR, IR, Mass and elemental analysis.

***N*-benzyl-7-(4-chlorophenyl)-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (A1).** (Table 1, Entry 1): Yield 0.48g (63%) of white powder, 99% pure by HPLC. Mp 254-256°C; IR (KBr): 3343, 3065, 2944, 1670, 1625, 1600, 1555, 1521, 1489, 1420, 1318, 1011, 840; $^1$H NMR (300 MHz DMSO-$d_6$): δ = 2.17 (3H, s, $CH_3$), 4.09-4.14 (1H, m, $BnCH_2$), 4.30-4.35 (1H, m, $BnCH_2$) 6.74 (1H, s, CH), 6.77-7.79 (2H, m, Ar-H), 7.14-7.17 (3H, m, Ar-H), 7.32-7.35 (2H, d, Ar-H), 7.42-7.45 (2H, d, Ar-H), 8.35 (1H, s, NH); $^{13}$C NMR (75 MHz DMSO-$d_6$):δ = 17.64, 42.32, 59.28, 103.50, 126.92, 127.08, 128.32, 129.16, 130.04, 133.84, 135.37, 138.54, 139.402, 165.67; Ms (ESI) *m/z* 379 [M – H]; Anal. Calcd for $C_{19}H_{17}ClN_6O$: C, 59.92; H, 4.50; N, 22.07. Found: C, 60.07; H, 4.65; N, 22.00.

***N*-benzyl-7-(4-methoxyphenyl)-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (A2).** (Table 1, Entry 2): Yield 0.23g (31%) of light yellow powder, 98% pure by HPLC. Mp 238-240°C; IR (KBr): 3352, 3204, 3062, 2951, 2836, 1676, 1625, 1518, 1447, 1412, 1311, 996, 846; $^1$H NMR (500 MHz DMSO-$d_6$): δ = 2.18 (3H, s, $CH_3$), 3.74 (3H, s, $CH_3O$), 4.14-4.18 (1H, m, $BnCH_2$), 4.29-4.33 (1H, m, $BnCH_2$), 6.70 (1H, s, CH), 6.76-6.83 (2H, m, Ar-H), 6.91-7.00 (2H, m, Ar-H), 7.12-7.17 (3H, m, Ar-H), 7.24-7.30 (2H, m, Ar-H), 8.39-8.41 (1H, m, NH), 10.54 (1H, s, NH); $^{13}$C NMR (125 MHz DMSO-$d_6$): δ = 17.74, 42.42, 55.66, 59.52, 104.14, 114.49, 126.96, 127.21, 128.42, 128.62, 129.20, 129.40, 131.95, 135.27, 139.56,159.99, 149.36, 165.98; Ms (ESI) *m/z* 375 [M – H]; Anal. Calcd for $C_{20}H_{20}N_6O_2$: C, 63.82; H, 5.36; N, 22.33. Found: C, 63.17; H, 5.69; N, 22.13.

***N*-benzyl-5-methyl-7-(4-nitrophenyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (A3).** (Table 1, Entry 3): Yield 0.57g (73%) of yellow powder, 99% pure by HPLC. Mp 231-233°C; IR (KBr): 3460, 3076, 2953, 2860, 1670, 1622, 1597, 1525, 1435, 1352, 999, 831; $^1$H NMR (500 MHz DMSO-$d_6$): δ = 2.19 (3H, s, $CH_3$), 4.09-4.13 (1H, m, $BnCH_2$), 4.28-4.32 (1H, m, $BnCH_2$), 6.90 (1H, s, CH), 6.84-6.86 (2H, d, Ar-H), 7.05-7.17 (3H, m, Ar-H), 7.56-7.57 (2H, d, Ar-H), 8.18-8.19 (2H, d, Ar-H), 8.44-8.46 (1H, m, NH), 10.81 (1H, s, NH); $^{13}$C NMR (125 MHz DMSO-$d_6$):δ = 17.74, 42.42, 55.66, 59.52, 104.14, 114.49, 126.96, 127.21, 128.42, 128.62, 129.20, 129.40, 131.95, 135.27, 139.56, 159.99, 149.36, 165.98; Ms (ESI) *m/z* 390 [M – H]; Anal. Calcd for $C_{19}H_{17}N_7O_3$: C, 58.31; H, 4.38; N, 25.05. Found: C, 58.49; H, 4.24; N, 25.96.

***N*-benzyl-7-(2-chlorophenyl)-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (A4).** (Table 1, Entry 4): Yield 0.35g (46%) of white powder, 99% pure by HPLC. Mp

218-221°C; IR (KBr): 3313, 3059, 2943, 1666, 1625, 1600, 1537, 1442, 1333, 1001, 754; $^1$H NMR (500 MHz DMSO-$d_6$): δ = 2.18 (3H, s, $CH_3$), 4.08-4.12 (1H, m, $BnCH_2$), 4.32-4.37 (1H, m, $BnCH_2$), 7.07 (1H, s, CH), 6.77-6.80 (2H, d, Ar-H), 7.14-7.15 (3H, m, Ar-H), 7.31-7.36 (1H, m, Ar-H), 7.41-7.44 (2H, m, Ar-H), 7.48-7.50 (1H, m, Ar-H), 8.42-8.44 (1H, m, NH), 10.64 (1H, s, NH); $^{13}$C NMR (125 MHz DMSO-$d_6$): δ = 17.69, 42.46, 58.10, 102.91, 126.96, 127.10, 128.14, 128.52, 130.55, 131.06, 131.50, 133.17, 135.51, 136.22, 139.47, 149.63, 165.79; Ms (ESI) *m/z* 379 [M – H]; Anal. Calcd for $C_{19}H_{17}ClN_6O$: C, 59.92; H, 4.50; N, 22.07. Found: C, 59.21; H, 4.03; N, 22.91.

***N*-benzyl-5-methyl-7-phenyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (A5).** (Table 1, Entry 5): Yield 0.38g (54%) of white powder, 99% pure by HPLC. Mp 232-234°C; IR (KBr): 3282, 3062, 2945, 2839, 1674, 1604, 1585, 1496, 1388, 1323, 999, 746, 698; $^1$H NMR (500 MHz DMSO-$d_6$): δ = 2.10 (3H, s, $CH_3$), 4.14-4.18 (1H, m, $BnCH_2$), 4.29-4.33 (1H, m, $BnCH_2$), 6.76 (1H, s, CH), 6.82-6.83 (2H, d, Ar-H), 7.12-7.15 (3H, m, Ar-H), 7.30-7.31 (2H, m, Ar-H), 7.34-7.39 (3H, m, Ar-H), 8.42-8.44 (1H, m, NH), 10.59 (1H, s, NH); $^{13}$C NMR (125 MHz DMSO-$d_6$): δ = 17.76, 42.48, 60.62, 103.97, 126.95, 127.20, 128.05, 128.51, 128.62, 129.20, 129.40, 135,51, 135.52, 139.80, 149.50, 165.91; Ms (ESI) *m/z* 345 [M – H]; Anal. Calcd for $C_{19}H_{17}N_6O$: C, 65.88; H, 5.24; N, 24.26. Found: C, 66.06; H, 5.71; N, 24.17.

**7-(4-chlorophenyl)-*N*-(4-fluorobenzyl)-5-methyl-4,7-dihy-drotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (A6).** (Ta-ble 1, Entry 6): Yield 0.43g (54%) of white powder, 99% pure by HPLC. Mp 254-257°C; IR (KBr): 3294, 3064, 2973, 1672, 1630, 1539, 1510, 1492, 1413, 1380, 993, 825; $^1$H NMR (500 MHz DMSO-$d_6$): δ = 2.176 (3H, s, $CH_3$), 4.11-4.14 (1H, m, $BnCH_2$), 4.27-4.31 (1H, m, $BnCH_2$), 6.71 (1H, s, CH), 6.79-6.85 (2H, d, Ar-H), 6.95-6.98 (2H, d, Ar-H), 7.32-7.39 (2H, m, Ar-H), 7.42-7.44 (2H, m, Ar-H), 8.44 (1H, s, NH), 10.66 (1H, s, NH); $^{13}$C NMR (125 MHz DMSO-$d_6$):δ = 17.80, 41.77, 59.35, 103.5, 114.98, 115.15, 129.20, 129.24, 130.08, 133.91, 135.77, 138.65, 160.44, 162.39, 149.37, 165.78; Ms (ESI) *m/z* 397 [M – H]; Anal. Calcd for $C_{19}H_{16}ClFN_6O$: C, 57.22; H, 4.04; N, 21.07. Found: C, 57.45; H, 4.27; N, 21.53.

**7-(4-chlorophenyl)-*N*-(4-methoxybenzyl)-5-methyl-4,7-dihy-drotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (A7).** (Table 1, Entry 7): Yield 0.50g (61%) of white powder, 99% pure by HPLC. Mp 220-224°C; IR (KBr): 3430, 3072, 2956, 2835, 1678, 1620, 1527, 1490, 1460, 1382, 1001, 821; $^1$H NMR (500 MHz DMSO-$d_6$): δ = 2.15 (3H, s, $CH_3$), 3.75 (3H, s, $CH_3$), 4.03-4.07 (1H, m, $BnCH_2$), 4.23-4.27 (1H, m, $BnCH_2$), 6.76 (1H, s, CH), 6.68-6.73 (4H, m, Ar-H), 7.31-7.33 (2H, d, Ar-H), 7.42-7.43 (2H, d, Ar-H), 8.36-8.38 (1H, m, NH), 10.62 (1H, s, NH); $^{13}$C NMR (125 MHz DMSO-$d_6$):δ = 17.76, 41.86, 55.63, 59.40, 103.69, 109.59, 113.81, 128.52, 129.21, 129.41, 130.08, 131.45, 133.89, 135.45, 138.65, 159.45,149.39, 165.67; Ms (ESI) *m/z* 409 [M – H]; Anal. Calcd for $C_{20}H_{19}ClN_6O_2$: C, 58.47; H, 4.66; N, 20.45. Found: C, 58.03; H, 4.56; N, 20.41.

**7-(4-chlorophenyl)-*N*-(2-fluorobenzyl)-5-methyl-4,7-dihy-drotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (A8).** (Ta-ble 1, Entry 8): Yield 0.39g (49%) of white powder, 99% pure by HPLC. Mp 238-242°C; IR (KBr): 3308, 3058, 2957, 2843, 1676, 1625, 1605, 1548, 1489, 1370, 1004, 761; $^1$H NMR (500 MHz DMSO-$d_6$): δ = 2.18 (3H, s, $CH_3$), 4.20-4.24 (1H, m, $BnCH_2$), 4.28-4.32 (1H, m, $BnCH_2$), 6.76 (1H, s, CH), 6.54-6.57 (1H, m, Ar-H), 6.89-6.92 (1H, m, Ar-H), 7.09-9.11 (1H, m, Ar-H), 7.16-7.26 (1H, m, Ar-H), 7.32-7.37 (2H, m, Ar-H), 7.42-7.48 (2H, m, Ar-H), 8.41-8.44 (1H, m, NH), 10.66 (1H, s, NH); $^{13}$C NMR (125 MHz DMSO-$d_6$): δ = 17.77, 59.32, 103.38, 115.24, 124.26, 126.02, 129.06, 129.12, 129.28, 130.04, 133.94, 136.06, 138.67, 159.31, 161.25, 149.37, 165.89; Ms (ESI) *m/z* 397 [M – H]; Anal. Calcd for $C_{19}H_{16}ClFN_6O$: C, 57.22; H, 4.04; N, 21.07. Found: C, 57.91; H, 4.15; N, 21.32.

***N*-butyl-7-(4-chlorophenyl)-5-methyl-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidine-6-carboxamide (A10).** (Table 1, Entry 10): Yield 0.42g (61%) of white powder, 99% pure by HPLC. Mp 230-232°C; IR (KBr): 3293, 3080, 2957, 2865, 1676, 1605, 1540, 1490, 1432, 1383, 1325, 1001, 829; $^1$H NMR (500 MHz DMSO-$d_6$): δ = 0.70-0.75 (3H, m, $CH_3$), 0.94-1.02 (2H, m, $CH_2$), 1.14-1.21 (2H, m, $CH_2$), 2.13 (3H, s, $CH_3$), 2.94-3.00 (2H, m, $CH_2$), 6.71 (1H, s, CH), 7.30-7.31 (2H, d, Ar-H), 7.41-7.43 (2H, d, Ar-H), 7.85 (1H, d, NH), 10.57 (1H, s, NH); $^{13}$C NMR (125 MHz DMSO-$d_6$):δ = 14.02, 17.66, 19.77, 31.44, 38.64, 59.33, 103.91, 129.09, 129.84, 133.81, 135.08, 138.61, 149.48, 165.52; Ms (ESI) *m/z* 345 [M – H]; Anal. Calcd for $C_{16}H_{19}ClN_6O$: C, 55.41; H, 5.52; N, 24.23. Found: C, 55.14; H, 5.78, N, 24.39.

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