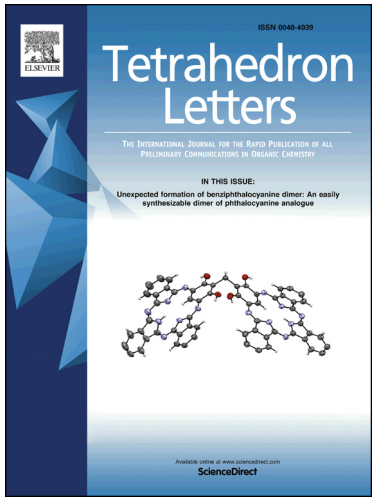

Al(III) Chloride catalyzed Multi-Component Domino Strategy: Synthesis of Library of Dihydrotetrazolo[1,5-*a*]pyrimidines and Tetrahydrotetrazolo[1,5-*a*]quinazolinones

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Al(III) Chloride catalyzed Multi-Component Domino Strategy: Synthesis of Library of Dihydrotetrazolo[1,5-*a*]pyrimidines and Tetrahydrotetrazolo[1,5-*a*]quinazolinones

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Abstract: Tetrazolo[1,5-*a*]pyrimidines are well recognized and valuable scaffolds in drug discovery. In the current manuscript, we demonstrated $AlCl_3$ catalyzed synthesis of series of dihydrotetrazolo[1,5-*a*]pyrimidines and tetrahydrotetrazolo[1,5-*a*]quinazolinones *via* a modified Bignelli type multi-component reaction of 5-aminotetrazole, aldehyde and diverse active methylene components such as acetophenone/alkylacetoacetates/dimedone. This provides an efficient route to construct highly functionalized dihydrotetrazolo[1,5-*a*]pyrimidines and tetrahydrotetrazolo[1,5-*a*]quinazolinones directly from readily available starting materials.

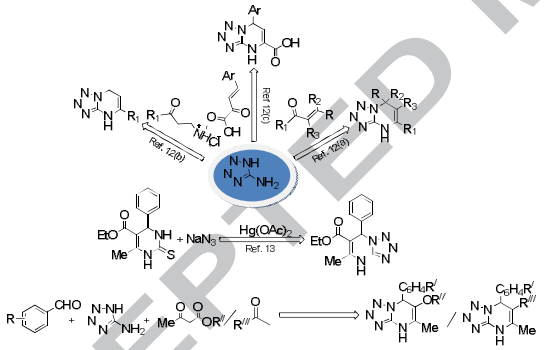
Keywords: Aluminium(III) chloride, multi-component reaction, domino reaction, tetrazolopyrimidines and tetrazoloquinazolinones.

Introduction

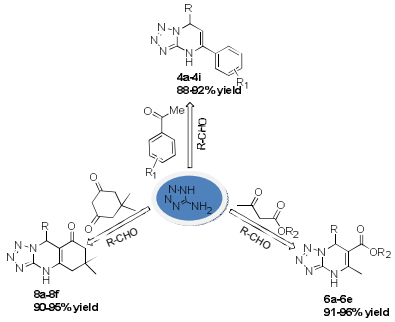
A multi-component domino strategy represents a powerful tool in which three or more reactants participate simultaneously resulting in the quick synthesis of diversified complex structures thus obviating the need for isolation and purification of intermediates, resulting in reduction of waste and reaction time, which also improves the overall yield.[1]
Over the past several years, these reactions have witnessed an extensive development in the field of combinatorial and medicinal chemistry for the synthesis of compound libraries and bioactive heterocycles from small set of readily accessible raw materials.[2]
Pyrimidines are among the privileged class of heterocyclic scaffolds known to exhibit broad range of biological and pharmacological activities, such as antihypertensive,[3] antiviral,[4] antitumor.[5] Minoxidil[6] and Trimethoprim[7] are well known hypertensive and antimalarial drugs containing pyrimidine moiety. Likewise, tetrazoles are an important subunit of many natural and synthetic compounds that exhibit biological activity.[8] Further, tetrazoles fused with pyrimidines are also known to display a broad range of biological properties, which includes antimicrobial,[9] antidepressant,[10] and antituberculosis activities.[11]

Previous methods for the synthesis of tetrazolopyrimidines, involve initial synthesis of chalcones, Mannich bases or arylidenepyruvic acids followed by cyclocondensation with 5-aminotetrazole in overall poor yield (Scheme 1, top).[12] Further, these methods are associated with several drawbacks such as multistep synthesis, tedious work-up procedure, long reaction time, and the use of expensive and toxic acid catalysts that would limit the use of these protocols in accordance with the principles of "Green Chemistry".

However, Wang and co-workers have reported the synthesis of dihydrotetrazolo[1,5-*a*]pyrimidines and tetrahydrotetrazolo[1,5-a]quinazolinones *via* $Hg2^{+}$-induced desulfurization and cyclization of entirely different substrate, dihydropyridine-2-thiones with sodium azide utilizing mercuric acetate (Scheme 1, middle).[13] However, a very convenient strategy which attracted our attention is the one pot three-component reaction of 5-aminotetrazole, aromatic aldehyde and acetophenone/related active methylene building blocks to generate diverse dihydrotetrazolo[1,5-*a*]pyrimidines and tetrahydrotetrazolo[1,5-*a*]quinazolinones (Scheme 1, bottom). A variety of catalysts like boiling acetic acid,[14] Iodine,[15] $[bmim^{+}][BF^{-}_{4}]$,[16] TBBDA,[17] have been used to mediate this reaction. Recently, diisopropylammonium trifluoroacetate mediated synthesis and antimicrobial and antioxidant activity of these scaffolds have also been recognized.[18] Even though, three-component reactions have been able to raise the overall yield, however, most of these methods are plagued with the use of corrosive catalyst, low yield, and limited substrate scope. Iodine[15a] mediated synthesis has been successful for the construction of library of these heterocyclic core using a broad range of active methylene building blocks but the was ver low especially when substituted acetophenone acts as an active methylene partner (0-61%). In spite of the latest developments, it remains extremely challenging to develop a sustainable route for the synthesis of diverse dihydrotetrazolo[1,5-*a*]pyrimidines and tetrahydrotetrazolo[1,5-*a*]quinazolinones which could avoid tedious job of isolation/purification of intermediates and final products. Therefore, we intended to develop an expedient, effective, mild and sustainable synthetic route that could be compatible with wide range of substrates to afford library of dihydrotetrazolo[1,5-*a*]pyrimidines and tetrahydrotetrazolo[1,5-*a*]quinazolinones.



Scheme 1. Previous reports to access dihydrotetrazolo[1,5-*a*]pyrimidines.



Scheme 2. Present work: One-pot domino MCR's approach.

Recently, $AlCl_3$ has received considerable attention in the literature as a potent Lewis acid catalyst in organic synthesis owing to its special attributes such as safe, economical, easy handling, mild and of course its recyclability.[19]

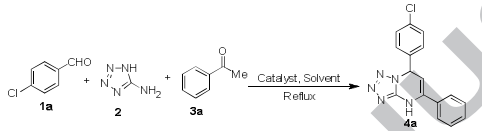
In view of above stated valid points and following our persistent desire to develop new synthetic routes,[20] we herein report $AlCl_3$ as mild and powerful Lewis acid catalyst for synthesis of diverse dihydrotetrazolo[1,5-*a*]pyrimidines and tetrahydrotetrazolo[1,5-*a*]quinazolinones *via* three-component domino strategy as outlined in Scheme 2.

Results and Discussion

At the outset, *p*-chlorobenzaldehyde (**1a**), 5-aminotetrazole (**2**) and acetophenone (**3a**) were chosen as model substrates to investigate one-pot three-component approach to construct diverse 5,7-diaryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidines. As summarized in table 1 (Entries 1-7),

several catalysts (10 mol%) such as $AlCl_3$, LiBr, $FeCl_3$, nano-YO, nano-CuO, $ZnCl_2$, $ZrOCl_2$ were screened in acetonitrile under reflux conditions to determine the best catalytic system. Surprisingly, $AlCl_3$ gave (**4a)** in 75% yield after 5 h. Under similar reaction condition, LiBr, $FeCl_3$, nano-YO, nano-CuO, $ZnCl_2$ and $ZrOCl_2$ gave (**4a)** in 20%, 34%, 40%, 38%, 25% and 33% respectively after 5 h. Next, concentration of $AlCl_3$ was optimized and at 15 and 20 mol% loading yields increased (85% and 92%) and reaction time was decreased to 4 and 3 h respectively (Entries 8 and 9). Importantly, when the reaction was investigated without any catalyst no product formation was observed even after prolonged reaction time. Subsequently, the evaluation of different solvents revealed that acetonitrile gave the best yield (92%) in minimum (3 hrs). Contrary to acetonitrile, $CHCl_3$ furnished the minimum yield (Table 1, entry-10) among the tested solvents. The structure of the product, (**4a)** was confirmed by ^{1}HNMR analysis and comparison with reported data[15a] as summarized in Supporting Information.

Table 1 Optimization of reaction conditions for the synthesis of **4a**[a]

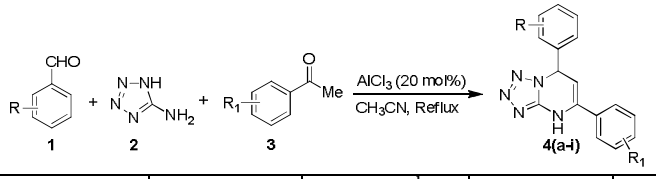


Entry	Catalyst (mol%)	Solvent	Temperature	Time (h)	Yield[b] (%)
1	$AlCl_3$ (10)	CH_3CN	Reflux	5	75
2	LiBr (10)	CH_3CN	Reflux	5	20
3	$FeCl_3$ (10)	CH_3CN	Reflux	5	34
4	Nano-YO (10)	CH_3CN	Reflux	5	40
5	nano-CuO (10)	CH_3CN	Reflux	5	38
6	$ZnCl_2$ (10)	CH_3CN	Reflux	5	25
7	$ZrOCl_2$ (10)	CH_3CN	Reflux	5	33
8	$AlCl_3$ (15)	CH_3CN	Reflux	4	85
9	$AlCl_3$ (20)	CH_3CN	Reflux	3	92
10	$AlCl_3$ (20)	$CHCl_3$	Reflux	5	75
11	$AlCl_3$ (20)	CH_2Cl_2	Reflux	5	77
12	$AlCl_3$ (20)	DMSO	Reflux	5	80

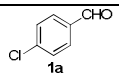
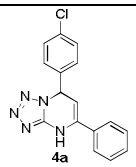
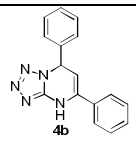
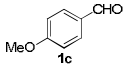
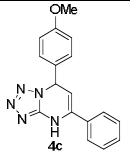
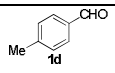
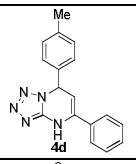
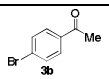
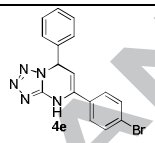
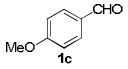
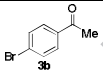
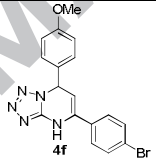
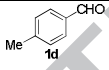
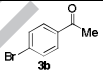
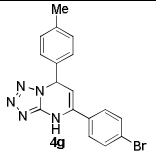
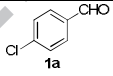
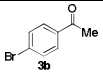
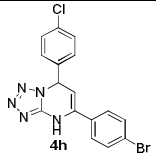
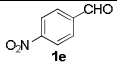
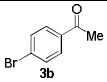
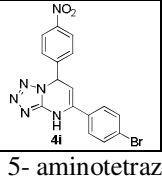
[a]Reactions were carried out using **1a**(1 mmol), **2** (1 mmol) and **3a**(1 mmol) and solvent (3 mL).
[b]Isolated yields.

Next, to explore the scope of current protocol optimal conditions were applied to wide-range of aromatic aldehyde and acetophenone. As summarized in Table 2 the aromatic aldehyde containing electron withdrawing group such as 4-NO_2, 4-Cl as well as electron releasing group such as 4-OMe, 4-Me were well tolerated and underwent three-component domino reaction smoothly to afford the anticipated product 5,7-diaryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidines, (**4a–i)** in high yields (Table 2, entries 1-9). On the other hand, replacement of acetophenone with *p*-Br-acetophenone was also found to be compatible under the optimal reaction conditions. All the reactions were completed in a duration of 3-5 h to afford the desired products.

Table 2 Synthesis of 5,7-diaryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidines[a]



Entry	Aldehyde	Ketone	Product[b]	Time (h)	Yield[c] (%)

1	 1a	 3a	 4a	3	92
2	 1b	 3a	 4b	4	90
3	 1c	 3a	 4c	4	89
4	 1d	 3a	 4d	4	88
5	 1b	 3b	 4e	4	91
6	 1c	 3b	 4f	4	90
7	 1d	 3b	 4g	4	89
8	 1a	 3b	 4h	3	91
9	 1e	 3b	 4i	5	91

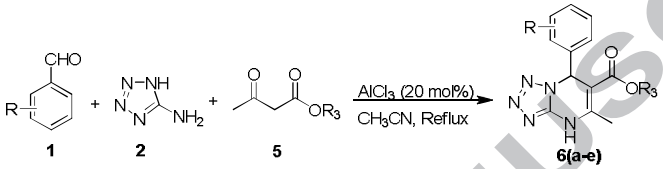
[a]Reaction condtions: Aldehyde **1**(1 mmol), 5- aminotetrazole **2**(1 mmol), acetophenone/ 4-Br-acetophenone **3**(1 mmol), CH_3CN (3 ml). [21(a)]

[b]All compounds gave C, H and N analysis within ± 0.4 % and satisfactory spectral (^{1}H NMR ^{13}C NMR) data.

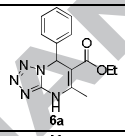
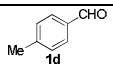
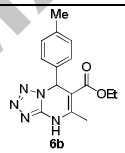
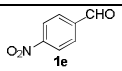
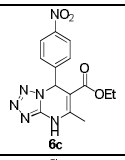
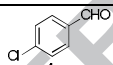
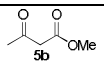
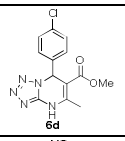
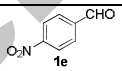
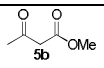
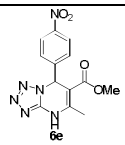
[c]Yield of isolated and purified products.

With the exceptional results with $AlCl_3$ in hand (Table 2), we tried to further expand the utility of this methodology, other three-component reaction of benzaldehydes (**1b, 1d and 1e**) 5-aminotetrazole (**2**) and ethylacetoacetate (**5a**) were reacted under optimized conditions and the results obtained are summarised in table 3. Fortunately, the reaction worked cleanly to deliver the corresponding products ethyl 5-methyl-7aryl-4,7-dihydrotetrazolo[1,5-a]pyrimidine-6-carboxylates, (**6a-c)** in excellent yields, however, the time required in this case was longer in comparison to substituted acetophenone. Interestingly, in this case also the reaction was compatible with both electron withdrawing and donating group on aromatic aldehyde furnishing products in high yields. Likewise, methylacetoacetate also reacted efficiently to afford the products, (**6d-e)** in very high yields (94-96%).

Table 3 Synthesis of alkyl 5-methyl-7aryl-4,7-dihydrotetrazolo[1,5-a]pyrimidine-6-carboxylates[a]



1 2 5 6(a-e)

Entry	Aldehyde	Ketone	Product[b]	Time (h)	Yield[c] (%)
1	 1b	 5a	 6a	4	94
2	 1d	 5a	 6b	6	91
3	 1e	 5a	 6c	5	92
4	 1a	 5b	 6d	5	96
5	 1e	 5b	 6e	5	94

[a]Reaction condtions: Aryl aldehyde **1**(1 mmol), 5-aminotetrazole **2**(1 mmol), ethylacetoacetate/ methylacetoacetate **5**(1 mmol), CH_3CN (3 ml). [21(a)]

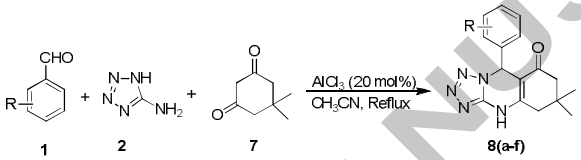
[b]All compounds gave C, H and N analysis within ± 0.4 % and satisfactory spectral (^1H NMR ^{13}C NMR) data.

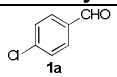
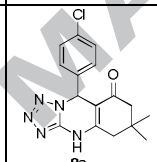
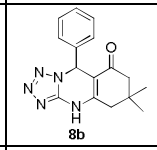
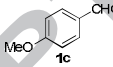
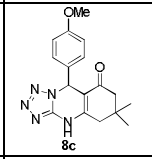
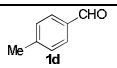
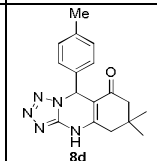
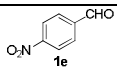
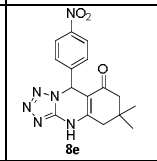
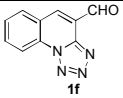
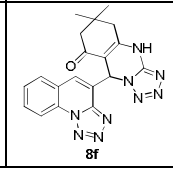
[c]Yield of Isolated and purified products.

A careful examination of literature reveals the limited records for the synthesis of tetrahydrotetrazolo[1,5-*a*]quinazolinones, a potential scaffold in drug development are available. Consequently, versatility of this three-component domino strategy was further explored with an aim to construct highly functionalized 6,6-dimethyl-9-aryl-5,6,7,9-tetrahydrotetrazolo[,5-

a]quinazolin-8(4*H*)-ones. In this context, we turned our attention to investigate the three component reaction of *p*-chlorobenzaldehyde, 5-aminotetrazole and dimedone as active methylene partner under established optimal reactions conditions. Indeed, dimedone successfully reacted in the presence of $AlCl_3$ to deliver entirely different scaffold, tetrahydrotetrazolo[1,5-*a*]quinazolinone, **8a** in 95% yield (Table 4, entry 1). Afterwards, the reaction was extended to differently substituted benzaldehydes. The maximum yield was obtained for (**8a**), 95% (Table 4, entry 1) and minimum yield was obtained for (**8d**), 90% (Table 4, entry 4). The reaction was further extended with fused heterocyclic aldehyde, tetrazoloquinolinecarbaldehyde, **1f**. Delightfully, the reaction gave a complex hybrid molecule incorporating two important scaffolds, tetrazoloquinoline and tetrahydrotetrazolo[1,5-a]quinazolinone in excellent yield (Table 4, entry 6).

Table 4 Synthesis of 6,6-dimethyl-9-aryl-5,6,7,9-tetrahydrotetrazolo[1,5-a]quinazolin-8(4*H*)-ones[a]

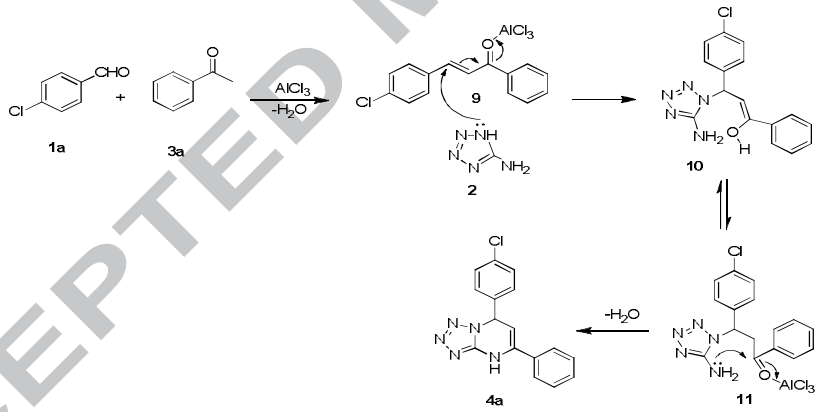


Entry	Aldehyde	Ketone	Product[b]	Time (h)	Yield[c] (%)
1				3	95
2				4	92
3				4	91
4				4	90
5				5	94
6				3	94

[a]Reaction condtions: Aryl aldehyde **1**(1 mmol), 5-aminotetrazole **2**(1 mmol), dimedone **7**(1 mmol), CH_3CN (2 ml). [21(b)]
[b]All compounds gave C, H and N analysis within ± 0.4 % and satisfactory spectral (^{1}H NMR ^{13}C NMR) data.
[c]Yield of Isolated and purified products.

It is remarkable that the current method can be efficiently applied for the preparation of diverse dihydrotetrazolo[1,5-*a*]pyrimidines and tetrahydrotetrazolo[1,5-*a*]quinazolinones using wide range of easily available starting materials. Importantly, purification of all these products was done without using column chromatography and recrystallization techniques except for compound, **8f** which was purified by column chromatography.[21b] After completion of reaction, the mixture was cooled at room temperature, solid was filtered, followed by washing with cold acetonitrile to deliver the pure product. Hence, the current method avoided the traditional purification steps of recrystallization and column chromatography thus reducing unwanted waste generated from silica and solvents during the course of column chromatography.

A plausible reaction mechanism for the formation of 4a in presence of $AlCl_3$ is depicted in scheme 3. In this typical tandem reaction *p*-chlorobenzalaldehyde, (**1a)** and acetophenone, (**2a)** reacts to form benzylideneacetophenone, (**9)** a strong Michael acceptor. Subsequently, 5-aminotetrazole readily attacks Michael acceptor to give an intermediate, 10 which undergoes imine-enamine tautomerism to form intermediate, (**11)** which finally undergoes intramolecular nucleophilic attack at the keto-carbonyl site followed by elimination of water to afford the desired cyclic product (**4a)**.



Scheme 3

Conclusion:

In conclusion, this study has expanded the applicability of $AlCl_3$ as an effective catalyst for the synthesis of diverse dihydrotetrazolo[1,5-*a*]pyrimidines and tetrahydrotetrazolo[1,5-*a*]quinazolinones *via* one pot, convergent and expedient multi-component domino strategy utilizing 5-aminotetrazole as key a component. The prominent features associated with this novel protocol are the use of readily available starting materials, operationally convenient conditions, mild reactions conditions, high yields. In addition, this method showed great tolerance towards diverse substrates and the products were purified without using column chromatography thus reducing the generation of waste in the form of silica and toxic solvents.

Further extension of this protocol with varied quinolinecarbaldehyde and quinolinecarbaldehyde are underway and will be reported in due course of time.

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21. **(a) General procedure for the synthesis of 5,7-diaryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidines (4a-i) and alkyl 5-methyl-7aryl-4,7-dihydrotetrazolo[1,5-a]pyrimidine -6-carboxylates (6a-e)**

To a mixture of substituted aldehydes (1mmol), 5-aminotetrazole (1 mmol) and acetophenones /alkylacetoacetates (1 mmol) in CH_3CN (3 mL), was added 20 mol% $AlCl_3$. The contents of reaction mixture were heated under reflux for appropriate time (Table 2 and 3). After completion of the reaction as monitored by TLC, the reaction mixture was cooled at room temperature and the solid was filtered followed by washing with cold acetonitrile to afford the pure product.

(b) General procedure for the synthesis of 6,6-dimethyl-9-aryl-5,6,7,9-tetrahydrotetraz-olo[1,5-b]quinazolin-8(4*H*)-ones (8a-f)

To a mixture of substituted aldehydes (1 mmol), 5-aminotetrazole (1 mmol) and dimedone (1 mmol) in CH_3CN (3 mL), was added 20 mol% $AlCl_3$. The contents of reaction mixture were heated under reflux for appropriate time (Table 4). After completion of the reaction as monitored by TLC, the reaction mixture was cooled at room temperature and the solid was filtered followed by washing with cold acetonitrile to afford the pure product, however **8f** is purified by column chromatography using ethyl acetate/hexane (70:30).

❖ **Highlights of the research work:**

- Synthesis of dihydrotetrazolo[1,5-*a*]pyrimidines and related quinazolinones.
- One-pot, Multi-component domino strategy with good to excellent yield (88-96%).
- Great toleration towards broad substrates of the devised protocols.
- Developed methodology avoided column chromatography and recrystallization steps.

Graphical Abstract:

Al(III) Chloride catalyzed Multi-Component Domino Strategy: Synthesis of Library of Dihydrotetrazolo[1,5-*a*]pyrimidines and Tetrahydrotetrazolo[1,5-*a*]quinazolinones