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Facile and efficient preparation of hybrid phenylthiazolyl-1,3,5-triazines and their antidepressant-like effect in mice

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ABSTRACT

High safety, robust efficacy and rapid onset of action remain the key challenges for improving antidepressant drug discovery. We report a facile and efficient synthetic strategy to structurally encompass mono-, di-, or tri-substituted derivatives using cyanuric chloride and various substituted phenylthiazole-2-amines. The predicted physicochemical property precisely state their specificity as CNS acting agent and antidepressant-like effect of the most promising compound **10** after oral administration significantly reduced immobility in mice behavior models, especially TST from 63 sec. In addition, good safety features of **10** highlights its ability to modulate hallmarks for antidepressant discovery. These insights are useful in generalization and systematization of CRF_1 antagonist design to develop future biological end points.

Depression affects more than 350 million people worldwide and impacts individuals regardless of their age, gender or socio-economic conditions.[1,2] Latest official figures reveal that by 2030 depression will be the leading cause of disease burden globally.[3] Nonetheless, despite impressive advances in the variety of therapeutics currently available, the major unmet clinical needs for antidepressant are (i) high safety, (ii) robust efficacy and (iii) rapid onset of action.[4,5] The above mentioned reasons have created a critical need to reinforce the discovery and development of novel antidepressant agents.[6]

In recent years, hybrid class pyrazole and 1,3,5-triazine derivatives are being studied as a next generation of CRF_1 antagonist for targeting depression.[7,8] In particular, a significant concern is that systemic administration of these 1,3,5-triazines leads to antidepressant effects in rodents.[9] Recent evidence also indicates that CRF_1 receptor antagonists may be identified by antidepressant-like activity in mice using tail suspension assay.[10] Unfortunately, in the face of impressive efforts no subsequent CRF_1 antagonist has successfully completed a definitive Phase III clinical trial.[11]

In our continued attempts to develop new, cost-effective and innovative entities from hybrid phenylthiazolyl-1,3,5-triazine derivatives[12-14], we herein report that oral administration of these agents exhibits significant antidepressant-like activity. Additionally, the assessment of toxicity using brine-shrimp methodology also ensures a good safety characteristic.

Cyanuric chloride was reacted with various substituted ~~phenylthi~~azoles[15] under similar set of conditions for constant period of time of 6 hours (Scheme 1). Triple molar quantity of diverse substituted phenylthiazoles as compared to cyanuric chloride was used. The spectroscopic approach and elemental analysis were applied to construct the structure of final compounds.

Antidepressant-like screening in a group of six mice (Albino, Swiss) of either sex, weighing 20–25 g, aged 6 to 8 weeks were conducted in accordance with the Institutional Animal Ethics Committee (SGRR/CPCSEA/2011/264) and fully complying with the CPCSEA guidelines. The behavioural Forced swimming test (FST)[16], Tail suspension test (TST)[17], and Open field test (OFT)[18] were investigated by acute oral administration at a dose 15 mg/kg and normal saline was used as a control. Brine shrimp lethality bioassay[19] was carried out to investigate the cytotoxicity of key compound **10**. The experimental data were expressed as mean along with standard error of mean (SEM) and evaluated by one-way analysis of variance (ANOVA) followed by Dunnet's test as post hoc. Differences between data sets were considered as significant when p value was less than 0.05.

The reaction was found to be facile and efficient for the preparation of various mono-, di-, or tri-substituted phenylthiazolyl-1,3,5-triazine derivatives (**1**-**12**). The reaction scheme involves nucleophillic substitution of chlorine atoms from cyanuric chloride by different substituted phenylthiazole-2-amines. As a matter of fact, electron-withdrawing groups[20] of phenylthiazole, for example nitro, bromo or chloro diminished electron density on triazine core and tends to slow down

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replacement of other chlorine atoms of triazine to afford merely mono-substituted triazines. On the other hand, optimal mobility was investigated in case of un-substituted phenylthiazole and strongly activating hydroxyl groups to report a simplistic synthetic pathway to tri-substituted triazines (**1, 2**). In the next instance, we might have observed that moderately activating groups like dimethylamino, acetoxy, butoxy, methoxy and weakly activating group like methyl releases electrons and tends to intensify the negative charge and accordingly, destabilize the carbanion to afford di- (**3-7**) and mono-substituted triazines (**8-12**) respectively. Notably, a moderate to weak activating characteristic of electron donating groups in substituted-phenylthiazole-triazine did not facilitate nucleophillic substitution and discouraged the formation of tri-substituted derivatives. Whereas deactivating nitro, carboxy, chloro and bromo groups by virtue of their delocalization by resonance release electrons and stabilize the carbanion to compensate merely mono substituted triazines. This clearly assigned that reactivity of cyanuric chloride follows –H, -OH> $(CH_3)_2NH$-, CH_3CO-, $-OC_4H_9$, $-OCH_3$> $-CH_3$> Br> Cl> NO_2 sequence substitution pattern on phenylthiazole.

The FTIR spectral interval 3835-3946 cm^{-1} mainly corresponds to the N-H stretching vibrations, in which the highest range of frequency was recorded in case of **2**.[20] The spectral interval 1542- 1783 cm^{-1} was formed by the bending vibrations of NH groups and in this range C=C, C-N groups vibration were also recorded. It was also seen from the spectra that absorption bands lower than 1000 cm^{-1} correspond to the bending vibrations of C-H. The assignment of structures was also elucidated by their proton nuclear spectrum. The singlet signal at δ 3.22- 3.90 ppm was a typical peak of bridged NH for these compounds, among them the most shielded protons were recorded in case of **2**, with 4-hydroxy substituent. Also, tri-substituted triazine (**1**) at δ 3.62 ppm exhibited broad singlet to state presence of three identical protons. The proton spectrum consists of all signals belonging to the thiazole hydrogen exhibited a singlet at δ 6.64-7.66 ppm and due to effect of 2,4-dichloro substitution, a hydrogen of later one was at maximum downfield shift. The aromaticity assignments of the protons to 2, 3 and 4 orientations were based on their coupling constant (J) values that range from 6.52- 8.72 Hz in case of ortho-substitutions and 1.45-1.72 Hz for meta-substitutions. A comparison of chemical shift of aromatic protons of nitro, bromo, chloro, methoxy, hydroxy, methyl substituents with un-substituted compound was a clear illustration of formation of these compounds. All electron-withdrawing groups in phenyl rings induce a deshielding of the protons, whereas electron donating hydroxyl, dimethy amino, acetoxy, butoxy, methoxy and methyl groups cause a shielding of the aromatic protons. Finally, carbon, hydrogen, and nitrogen concentrations were found within ±0.4%. These values were in good agreement with the proposed structures.

The Molinspiration study clearly depicts that calculated values of topological polar surface area (TPSA), total number of atoms(natoms), molecular weight(MW), number of hydrogen bond acceptors (nON) and donors (nOHNH) and number of rotatable bonds(nrotb) were in accord to Lipinski[21], lead likeness[22] and bioavailability rules[23] of oral bioavailability. Among them, the lowest degree of lipophilicity (log P 4.30 and 4.79) was exhibited by mono substituted compound **9** and **8** with polar, 4-nitro and short chain, 4-methyl functionalities respectively. All compounds excluding **2**, having TPSA values less than 140 $Å^2$ claims for good oral absorption. Most of them with mono substitution revealed minimal TPSA value at 63.60 and utmost permitted was achieved in case of **7**. The number of rotatable bonds count for these molecules were fewer than ten except for **5** and deemed to have satisfactory oral bioavailability. Additionally, hydrogen bond donors and acceptors count were found to be important predictors of good oral bioavailability. Hence, it was quite ambiguous that title compounds were devoid of violations except in case of logP, which already triggers key step during CNS drug development.

Encouraged by Molinspiration methodology, the synthesized compounds (**1**-**12**) were screened for antidepressant-like activity using forced swim test (FST), tail suspension test (TST) and locomotor activity by open field tests (OFT). It was quite apparent from Table 1 that **6**, **10** and **12** have demonstrated significant FST results in comparison to reference drug Imipramine. We were surprised to see that minor structural variation brought in by hybrid compounds were able to induce marked influence on biological activity. The structure activity relationship emphasized that 2,4-dichloro substitution pattern (**10**) was a requisite for optimal biological activity. The mean immobility time in case of **10** and control were 68 and 122 sec respectively. The administration of **10** significantly decreased immobility time by 54 sec in mice at 15 mg/kg doses tested. Similar dose of Imipramine administered under the same conditions clearly decreased the duration of immobility in comparison with control.

In next counterpart, disubstituted 4-methoxy (**6**) and mono-substituted, 4-bromo (**12**) also focus on escalating antidepressant activity. However, **8** and **11** with 4-methyl and 3-bromo substitutions respectively, were not well tolerated and have shown no activity even in comparison with control. Notably, two-fold amplified activity was disclosed by derivative **12**, with structural variation 4-bromo and 3-bromo by keeping all other fragments rigid. It was clearly evident that most active compound possess 2,4-dichloro groups, phenylthiazole and triazine functionalities. Hence, it seems that presence of the bulky halo groups at position 4 endowed with intermolecular bonds to establish good biological activity.

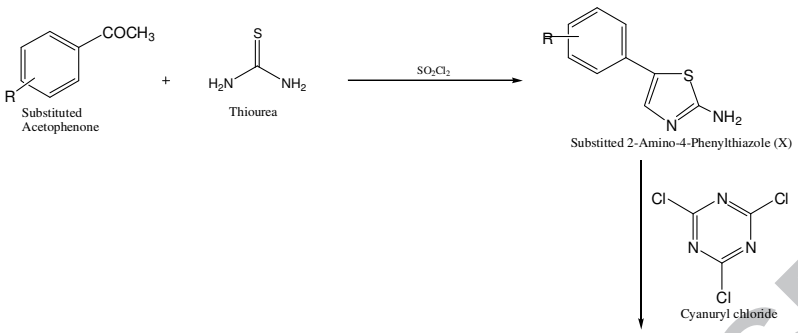
On inspection of data in Table 1, it was easy to analyze that **6**, **10** and **12** possess more potent intrinsic activity in TST than Imipramine with mean immobility time 74, 70 and 79 sec respectively. Once again, oral administration of **10** significantly decreased duration of immobility by 63 sec in comparison with control at 15 mg/kg dose tested. Therefore, once again it was of interest that appropriate placement of 2,4-dicholoro/4-methoxy or 4-bromo group on aromatic ring were significant for biological activity. Further, the biological effect of 4-substitutent followed that pattern as 2,4-di-Cl> 4-OMe> 4-Br. Nevertheless, one compound **10** was found almost equipotent to Imipramine in TST and this identified hit may have CRF_1 antagonistic activity.

In support of the above mentioned studies, OFT model also investigated the optimal pharmacological behavior as expressed by **10** in mice anxiety model. This compound reduces exit latency at a lower effective dose of 15 mg/kg. This suggests that 2,4-dicholoro substitution pattern, was important for suppression of locomotion effect. However, 4-methoxy/ 4-bromo substitutions have shown a greater shift to modify motor behaviour in comparison to Imipramine. Accordingly, structure activity relationship for these title analogs, summarizes that position of 2,4-dicholoro atoms was only the main determinant for escalation and generation of bio-activity. In the next counterpart, presence of 4-methoxy and 4-bromo would have its unique role, in regard of biological activity.

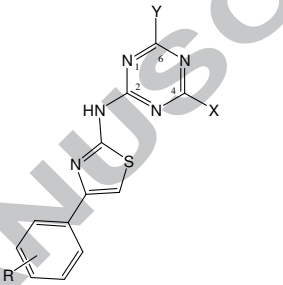
The brine shrimp lethality bioassay was considered as a useful tool for rapid and preliminary assessment of toxicity of the compounds. The hit compound **10** was analyzed for toxicity results and LC_{50} was calculated 1559.5µg/ml. This assay has exhibited overall a good safety profile of **10** (Table 2). The data from earlier study indicated that a total blood volume of a mouse was about 77-80 ml/kg.[24] This amounts to a maximum blood concentration 194.8- 187.5µg/ml in mice for **10** at a dose 15mg/kg. In particular, for **10** the difference between lethal

concentration and effective concentration has a high magnitude that is unprecedented in drug discovery.

In summary, we report a simple, rapid and efficient synthesis strategy for preparation of mono-, di-, or tri-substituted phenylthiazolyl-1,3,5-triazine derivatives and offer well studied reactivity of cyanuric chloride with various substituted phenylthiazole-2-amines. These insights illustrate effectiveness of hybrid analogue **10** as a novel antidepressant agent and provide a molecular level insight that these identified entities may be a CRF_1 antagonist. Fortunately, the present work offers a guidance of future antidepressant lead building and prospective screens.



Compound	R	X	Y
1	4-H	-NH-phenylthiazole	-NH-phenylthiazole
2	4-OH	-NH-4-hydroxyphenylthiazole	-NH-4-hydroxyphenylthiazole
3	4-N(CH_3)$_2$	-NH-4-dimethylaminophenylthiazole	-Cl
4	4-$COCH_3$	-NH-4-acetoxyphenylthiazole	-Cl
5	4-OC_4H_9	-NH-4-butoxyphenylthiazole	-Cl
6	4-OCH_3	-NH-4-methoxyphenylthiazole	-Cl
7	3-CN	-NH-3-cynophenylthiazole	-Cl
8	4-CH_3	-Cl	-Cl
9	4-NO_2	-Cl	-Cl
10	2,4-Cl,Cl	-Cl	-Cl
11	3-Br	-Cl	-Cl
12	4-Br	-Cl	-Cl



Hybrid class substituted phenylthiazole 1,3,5-triazine

Scheme 1. Synthesis of substituted phenylthiazolyl-1,3,5-triazine derivatives. Reagents and conditions: (i) step 1: Acetophenone, thiourea, sulfuryl chloride 105 °C for 3-5hrs; (ii) step 2: 4-Substituted phenylthiazole-2-amine, $NaHCO_3$, dioxane 90°C for 6hrs.

Table 1. Antidepressant activity of compounds using FST, TST and OFT model

Compounds	FST Duration of immobility[#] (sec)	TST Duration of immobility[#] (sec)	OFT Number of crossings in the square
1	93±25	137±18	131±36
2	111±08	149±16	119±17
3	105±12	155±22	125±18
4	108±17	99±14	132±22
5	94±05	105±17	145±16
6	88±08*	74±12*	187±09*
7	99±18	109±19	136±21
8	136±22	175±39	53±26
9	102±15	108±19	162±26
10	68±03*	70±06*	136±05*
11	138±19	99±10	149±33
12	75±06*	79±07*	129±03*
Imipramine	61±12*	85±09*	128±02*
Control[§]	122±20	133±10	104±31

[#]Values represent the mean ±S.E.M. *Significant compared to control (Dunnet's test; $p < 0.05$). [§]Normal saline

Table 2. Brine-shrimp bioassay for hit compound **10.**

Concentration (µg/ml)	Mortality#
1000.00	3
Control	1
LC_{50}	1539.5 µg/ml
Toxicity	Non-toxic

[#]Ten larvae (*Artemia salina*) for each test concentration

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20. *Spectra data for* **1:** Physical state: yellowish green solid; % Yield: 89; Melting Range: 141-142°C; Rf Value: (Benzene. ethylacetate. 0.1M alcoholic KOH= 3:3:4): 0.4214; FTIR (IRPrestige-21 KBr, cm^{-1}): 780 C-H bending, 991 ar C-H bending, 1366 C-N amine, 1413 ar C=C, 1608 N-H bending, 3445 broad N-H (sec. amine); ^{1}H-NMR (Bruker Avance II 400 MHz $CDC1_3$ δ ppm): 3.62(s, 3H, bridge NH), 6.70(s, 3H, thiazole), 7.22(m, 3H, J = 7.36 & 1.46 Hz, ar-H), 7.33(m, 6H, J = 7.68 & 1.45 Hz, ar-H), 7.91(d, 6H, J = 7.32 Hz, ar-H); Anal. Calc. (Vario EL III) for $C_{30}H_{21}N_9S_3$: Calculated C: 59.68, H: 3.51, N: 20.88% Found C: 59.37, H: 3.14, N: 20.65%. **2:** Physical state: orange solid; % Yield: 75; Melting Range: 138-139°C; Rf Value: (Benzene. ethylacetate. 0.1M alcoholic KOH= 3:3:4): 0.5234; FTIR (IRPrestige-21 KBr, cm-1): 875 C-H bending, 995 C-H ar bending, 1364 C-H amine, 1663 N-H bending, 3946 NH (sec. amine); ^{1}H-NMR (Bruker Avance II 400 MHz $CDC1_3$ δ ppm): 3.22(s, 3H, bridge NH), 6.64(s, 3H, thiazole), 7.34(s, 3H, ar-OH), 8.02(d, 6H, J = 8.22 Hz, ar-H), 8.11(d, 6H, J = 8.14 Hz, ar-H); Anal. Calc. (Vario EL III) for $C_{30}H_{21}N_9O_3S_3$: Calculated C: 55.29, H: 3.25, N: 19.34 Found C: 55.67, H: 3.55, N: 19.64. **3:** Physical state: red purple solid; % Yield: 82; Melting Range: 151-153°C; Rf Value: (Benzene. ethylacetate. 0.1M alcoholic KOH= 3:3:4): 0.6541; FTIR (IRPrestige-21 KBr, cm-1): 869 C-H bending, 989 C-H ar bending, 1360 C-H amine, 1382 dimethylamino, 1659 N-H bending, 3940 NH (sec. amine); ^{1}H-NMR (Bruker Avance II 400 MHz $CDC1_3$ δ ppm): 2.84(s, 12H, $-CH_3$), 3.34(s, 2H, bridge NH), 6.76(s, 2H, thiazole), 8.10(d, 4H, J = 8.15 Hz, ar-H), 8.19(d, 4H, J = 8.19 Hz, ar-H); Anal. Calc. (Vario EL III) for $C_{25}H_{24}ClN_9S_2$: Calculated C: 54.58, H: 4.40, N: 22.92 Found C: 54.64, H: 4.68, N: 22.64. **4:** Physical state: reddish purple oil; % Yield: 69; Boiling Range: 286-288°C; Rf Value: (Benzene. ethylacetate. 0.1M alcoholic KOH= 3:3:4): 0.6275; FTIR (IRPrestige-21 KBr, cm-1): 858 C-H bending, 987 C-H ar bending, 1355 C-H amine, 1650 N-H bending, 3934 NH (sec. amine); ^{1}H-NMR (Bruker Avance II 400 MHz $CDC1_3$ δ ppm): 2.07(s, 6H, $-CH_3$), 3.42(s, 2H, bridge NH), 6.85(s, 2H, thiazole), 7.11(d, 4H, J = 8.13 Hz, ar-H), 7.18(m, 4H, J = 8.14 Hz, ar-H); Anal. Calc. (Vario EL III) for $C_{25}H_{18}ClN_7O_4S_2$: Calculated C: 51.77, H: 3.13, N: 16.90 Found C: 51.45, H: 3.05, N: 16.58. **5:** Physical state: orange solid; % Yield: 59; Melting Range: 187-189°C; Rf Value: (Benzene. ethylacetate. 0.1M alcoholic KOH= 3:3:4): 0.5814; FTIR (IRPrestige-21 KBr, cm-1): 728 methylene rocking, 821 C-H bending, 1389 C-N amine, 1470 methylene bending, 1654 C=C(ar-H), 1783 N-H bending, 2920 methylene stret., 3885 broad N-H (sec. amine); ^{1}H-NMR (Bruker Avance II 400 MHz $CDC1_3$ δ ppm): 1.06(s, 6H, $-CH_3$), 1.42(s, 4H, $-CH_2$), 1.96(s, 4H, $-CH_2$), 3.71(s, 2H, bridge NH), 3.98(s, 4H, $-OCH_2$), 6.92(s, 2H, thiazole), 6.69(d, 4H, J = 8.45 Hz, ar-H), 7.39(d, 4H, J = 8.34 Hz, ar-H); Anal. Calc. (Vario EL III) for $C_{29}H_{30}ClN_7O_2S_2$: Calculated C: 57.27, H: 4.97, N: 16.12 Found C: 57.01, H: 4.64, N: 15.88. **6:** Physical state: yellowish orange solid; % Yield: 40; Melting Range: 148-150°C; Rf Value: (Benzene. ethylacetate. 0.1M alcoholic KOH= 3:3:4): 0.5778; FTIR (IRPrestige-21 KBr, cm-1): 781 C-H bending, 1368 C-N amine, 1651 C=C(ar-H), 1741 N-H bending, 3835 broad N-H (sec. amine); ^{1}H-NMR (Bruker Avance II 400 MHz $CDC1_3$ δ ppm): 3.62(s, 6H, $-OCH_3$), 3.79(s, 2H, bridge NH), 6.99(s, 2H, thiazole), 6.92(d, 4H, J = 8.44 Hz, Ar-H), 7.68(d, 4H, J = 8.32 Hz, Ar-H); Anal. Calc. (Vario EL III) for $C_{23}H_{18}ClN_7O_2S_2$: Calculated C: 52.72, H: 3.46, N: 18.71 Found C: 52.72, H: 3.46, N: 18.71. **7:** Physical state: red orange oil; % Yield: 65; Boiling Range: 256-258°C; Rf Value: (Benzene. ethylacetate. 0.1M alcoholic KOH= 3:3:4): 0.4885; FTIR (IRPrestige-21 KBr, cm-1): 575 C- Cl, 805 C-H bending, 1325 C-N amine, 1538 C=C ar., 1644 N-H bending, 2232 Ar C≡N, 3939 broad N-H(sec. amine); ^{1}H-NMR (Bruker Avance II 400 MHz $CDC1_3$ δ ppm): 3.76(s, 2H, bridge NH), 6.87(s, 2H, thiazole), 7.48(m, 2H, J = 7.52 & 1.49 Hz, ar-H), 7.50(d, 2H, J = 7.75 Hz, ar-H), 7.74(m, 2H, J = 1.61 Hz, ar-H), 7.78(m, 2H, J = 8.13, 1.58 & 1.62 Hz, ar-H); Anal. Calc. (Vario EL III) for $C_{23}H_{12}ClN_9S_2$: Calculated C: 53.75, H: 2.35, N: 24.53 Found C: 53.49, H: 2.75, N: 24.86. **8:** Physical state: yellow solid; % Yield: 78; Melting Range: 135-136°C; Rf Value: (Benzene. ethylacetate. 0.1M alcoholic KOH= 3:3:4): 0.3113; FTIR (IRPrestige-21 KBr, cm-1): 564 C- Cl, 794 C-H bending, 1309 C-N amine, 1513 C=C ar., 1637 N-H bending, 2870 sym. methyl stret., 2955 asym. methyl stret., 3447 broad N-H(sec. amine); ^{1}H-NMR (Bruker Avance II 400 MHz $CDC1_3$ δ ppm): 2.36(s, 3H, $-CH_3$), 3.81(s, 1H, bridge NH), 7.10(s, 1H, thiazole), 7.20(d, 2H, J = 7.04 Hz, ar-H), 7.67(d, 2H, J = 8.12 Hz, ar-H); Anal. Calc. (Vario EL III) for $C_{13}H_9Cl_2N_5S$: Calculated C: 46.17, H: 2.68, N: 20.71 Found C: 45.87, H: 2.42, N: 20.50. **9:** Physical state: purple solid; % Yield: 89; Melting Range: 261-263°C; Rf Value: (Benzene. ethylacetate. 0.1M alcoholic KOH= 3:3:4): 0.6995; FTIR (IRPrestige-21 KBr, cm-1): 719 C-Cl, 1108 C-N amine, 1342 C-N amine, 1641 C=N, 1741 N-H bending, 3400 broad N-H (sec. amine); ^{1}H-NMR (Bruker Avance II 400 MHz $CDC1_3$ δ ppm): 3.90(s, 1H, bridge NH), 7.08(s, 1H, thiazole), 8.13(d, 2H, J = 8.56 Hz, ar-H), 8.23(d, 2H, J = 8.72 Hz, ar-H); Anal. Calc. (Vario EL III) for $C_{21}H_{13}ClN_8O_4S_2$: Calculated C: 46.63, H: 2.42, N: 20.71 Found C: 46.87, H: 2.49, N: 20.89. **10:** Physical state: yellow solid; % Yield: 47; Melting Range: 120-121°C; Rf Value: (Benzene. ethylacetate. 0.1M alcoholic KOH= 3:3:4): 0.4771; FTIR (IRPrestige-21 KBr, cm-1): 771 C-Cl, 1234 C-N amine, 1365 C=C(ar-H), 1542 N-H bending, 3436 broad N-H (sec. amine); ^{1}H-NMR (Bruker Avance II 400 MHz $CDC1_3$ δ ppm): 3.59(s, 1H, bridge NH), 7.51(m, 1H, J = 7.52 Hz, ar-H), 7.66(s, 1H, thiazole), 7.84(m, 1H, J = 8.40 & 1.72 Hz, ar-H), 8.12(d, 1H, J = 1.56 Hz, ar-H); Anal. Calc. (Vario EL III) for $C_{12}H_5Cl_4N_5S$: Calculated C: 36.67, H: 1.28, N: 17.82 Found C: 36.45, H: 1.04, N: 17.68. **11:** Physical state: yellow solid; % Yield: 80; Melting Range: 141-143°C; Rf Value: (Benzene. ethylacetate. 0.1M alcoholic KOH= 3:3:4): 0.5345; FTIR (IRPrestige-21 KBr, cm-1): 629 C-Cl, 830 C-H bending, 1365 C-N amine, 1542 C=C ar, 1601 N-H bending, 3442 broad N-H (sec. amine); ^{1}H-NMR (Bruker Avance II 400 MHz $CDC1_3$ δ ppm): 3.62(s, 1H, bridge NH), 7.31(s, 1H, thiazole), 7.49(m, 1H, J = 8.48 & 1.68 Hz, ar-H), 7.55 (d, 1H, J = 8.24 Hz, ar-H), 7.85(m, 1H, J = 1.61 Hz, ar-H), 7.91(m, 2H, J = 8.13, 1.62 & 1.65 Hz, ar-H); Anal. Calc. (Vario EL III) for $C_{12}H_6BrCl_2N_5S$: Calculated C: 35.76, H: 1.50, N: 17.37 Found C: 35.87, H: 1.41, N: 17.43. **12:** Physical state: orange solid; % Yield: 69; Melting Range: 145-146°C; Rf Value: (Benzene. ethylacetate. 0.1M alcoholic KOH= 3:3:4): 0.6116; FTIR (IRPrestige-21 KBr, cm-1): 779 C-Cl, 1243 C-N(Amine), 1367 C-N amine, 1364 C-H amine, 1638 C=N, 1708 N-H bending, 3449 broad N-H (sec. amine); ^{1}H-NMR (Bruker Avance II 400 MHz $CDC1_3$ δ ppm): 3.68(s, 1H, bridge NH), 7.37(s, 1H, thiazole), 7.50(d, 2H, J = 6.92 Hz, ar-H), 7.86(d, 2H, J = 8.00 Hz, ar-H); Anal. Calc. (Vario EL III) for $C_{12}H_6BrCl_2N_5S$: Calculated C: 35.76, H: 1.50, N: 17.37 Found C: 35.44, H: 1.42, N: 17.21.
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Graphical Abstract

Facile and efficient preparation of hybrid phenylthiazolyl-1,3,5-triazines and their antidepressant-like effect in mice.

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