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# Molecular Properties Prediction, Synthesis and Bio-evaluation of Triazines glued Benzothiazole congeners.

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## ABSTRACT

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In the current investigation, some newer triazines merged benzothiazole hybrids were subjected to molecular properties prediction, drug-likeness, lipophilicity and solubility parameters determination using Molinspiration, Molsoft and ALOGPS 2.1 softwares. Amongst ten proposed analogues only seven therapeutic candidates were chosen on the basis of Lipinski's "Rule of Five". Selected title compounds were synthesized by cyclizing 3-chloroaniline and potassium thiocyanate in presence of bromine yielded the corresponding 2-amino benzothiazole synthon, which on further treatment with different substituted aromatic aldehydes afforded Schiff's bases. The later one condensed with phenyl isothiocyanate gave triazine merged benzothiazole analogues (**4a-4j**). The structural confirmation of the target compounds were established on the basis of IR, $^1$HNMR and Mass spectral analysis and subjected to *in-vitro* anti-inflammatory and anti-oxidant screening. Compound **4c** and **4g** showed pronounced antioxidant and ant-inflammatory activity respectively. The phenyl ring of triazine bearing –OH and –$OCH_3$ exhibited good biological activity and their predicted drug-likeness model score also found to be convincing among the series.

## INTRODUCTION

Heterocyclic annulated benzothiazole templates have received considerable attention owing to their synthetic accessibility and wide array of peculiar pharmacological versatility. The recapitulation of literature reveals that, when one biodynamic heterocyclic system coupled with another molecular framework displays impressive enhanced pharmacological profile like antitumor, anticonvulsant, antiviral[1], anti-diabetic, anti-tubercular, neuroprotective, and immunosuppressive activities[2]. Moreover triazines are privileged structural motif endowed with various types of pharmacological activities. This prompted us to synthesize some benzothiazole ring clamped with triazine entities could give entry to novel anti-inflammatory and anti-oxidant agents. Now-a-days about 30% of oral drugs development fails due to poor pharmacokinetics[3]. Among the pharmacokinetic properties, a low and highly variable bioavailability is indeed the main reason for stopping further development of the drugs[4]. Prediction of bioavailability and bioavailability related properties, such as solubility, lipophilicity are important before actual synthesis, in order to reduce enormous wastage of expensive chemicals and precious time. In the present investigation ten analogues were subjected to molecular properties prediction, drug-likeness by Molinspiration and Molsoft softwares. Lipophilicity and solubility parameters by using ALOGPS 2.1 program to filter the compounds for further synthesis and biological screening.

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## MATERIALS AND METHODS

***General:*** All the reagents and chemicals used were of analytical grade. Melting points were determined by open capillary tube method and are uncorrected. The progress of reaction and purity of the products were monitored by TLC and spots were located by UV chamber and iodine vapour. The $^1$HNMR spectra were recorded on BRUKER AVANCE II 400 NMR SPECTROMETER in DMSO with TMS as an internal standard and values are expressed in δ ppm. The infrared spectra were recorded on PERKIN ELMER FTIR using a thin film of potassium bromide pellets techniques and frequencies were expressed in $cm^{-1}$. Mass spectra were recorded on Matrix Assisted Laser Desorption Time of Flight Mass spectrometer (MALDI TOF MS) with voyagen version 5 software. Lipinski's parameters were predicted using Molsoft 2007. Lipophilicity and aqueous solubility were determined using ALOGPS 2.1 program.

***Molecular properties and drug-likeness:*** A molecular property is a complex balance of various structural features which determine whether a particular molecule is similar to the known drugs. Membrane permeability, hydrophobicity and bioavailabilty properties are always associated with some basic molecular descriptors such as log P (partition co-efficient), molecular weight, hydrogen bond acceptor and donors count in a molecule[5]. Lipinski's rule of five[6] is widely used as a filter for drug-like properties. Molecular polar surface area (PSA) is a very useful parameter for the prediction of drug transport properties. Absorption percent was calculated[7] using the expression %ABS=109-0.345PSA. PSA and volume are inversely proportional to %ABS. Number of rotatable bond is important for conformation changes of molecule under study and ultimately for the binding of receptors or channels. It is revealed that for passing

oral bioavailability criteria, number of rotatable bond[8] should be ⩽ 10.

***Lipophilicity and solubility:*** The ALOGPS method is part of the ALOGPS 2.1 program[9] used to predict lipophilicity and aqueous solubility[10] of compounds. The lipophilicity calculation within this program is based on the associative neural network approach and the efficient partition algorithm. The LogKow (Kow-WIN)[11] program estimates the log octanol/water partition coefficient (logP) of organic chemicals and drugs. An insufficient aqueous solubility is likely to impede bioavailability of the drugs. It is well known that, insufficient solubility of drugs can lead to poor absorption[12].

***In-vitro anti-inflammatory activity:*** The anti-inflammatory activity was evaluated by protein anti-denaturation method[13]. In this method, stock solution of 0.2%w/v of BSA was prepared in tris-buffer saline and pH was adjusted from 8.54 to 6.74 using glacial acetic acid. Many replicates of 500µl of the Bovine serum albumin stock solution were pipetted out and the test compounds and standard Diclofenac sodium was dissolved in ethanol and added to the BSA solution to make various concentrations like 50, 100, 150, and 200µg/ml. The control consists of 500µl BSA with 5µl methanol. The samples were then heated to 72°C for 5 mins in 2.0 ml Eppendrof tubes in metal racks then cooled for 20 mins under laboratory conditions and absorbances were read using spectrophotometer at 660nm. The percentage inhibition of precipitation (stabilization of the protein) was determined on a percentage basis relative to the control as in equation shown below. The results are given in Table 6.

$$\% \text{ Inhibition} = \frac{\text{Abs of control} - \text{Abs of test}}{\text{Abs of control}} \times 100$$

***In-vitro antioxidant activity:*** Free radical scavenging activity of the test compound was studied by the nitric oxide assay[14]. 1ml of sodium nitroprusside (5mM) in phosphate-buffer saline (PBS) was mixed with 3ml of various concentrations (50 to 200µg/ml) sample dissolved in distilled water. In an identical manner the procedure was repeated for standard Ascorbic acid. The assay mixture was then incubated at 25°C for 150 mins. These incubated mixtures were treated with Griess reagent (sulphanilamide 1% w/v, O-phosphoric acid 2% w/v and naphthyl ethylene diamine dihydrochloride 0.1% w/v) and the optical density of the resultant chromophores were determined spectrophotometrically at 546nm and compared with standard Ascorbic acid. Simultaneously run the identical assay units. The experiment was run in triplicate. The assay mixture without sample or Ascorbic acid was used as blank.

$$\% \text{ Inhibition} = \frac{\text{Abs of control} - \text{Abs of test}}{\text{Abs of control}} \times 100$$

## EXPERIMENTAL

***Procedure for synthesis of 7-Chlorobenzo [d] thiazol-2-amine(2)*:** To the precooled glacial acetic acid (20 ml), potassium thiocyanate (8g, 0.08mol) and 3-chlorobenzamine (1.45g, 0.01mol) were mixed and placed in freezing mixture of ice and salt and mechanically stirred while bromine (1.6ml) in glacial acetic acid (6ml) was added from dropping funnel at such a rate that the temperature does not rise beyond 0°C. After all bromine has been added (105 min) the solution was stirred for further 2hours at 0°C followed by room temperature for 10 hours. It was then allowed to stand overnight. During this period an orange precipitate was settled at the bottom. To this water (6ml) was added quickly and slurry was heated at 85°C on a steam bath and filtered hot. The orange residue was placed in a reaction flask and treated with 10ml of glacial acetic acid, heated again to 85°C and filtered hot[15]. The combined filterate was cooled and neutralized with concentrated ammonia solution to pH 6 when a dark yellow precipitate was collected. Recrystallised from benzene. Yield : 73-77%, MP: 85-87°C, $R_f$ value: 0.642, **IR(KBr)**: 723(C-Cl), 3085(Ar C-H), 1314(C-N), 1633(C=N), 1173(C-S), 1623(C=C), 3427(N-H).

***Synthesis of N - ( 4 - ( Dimethylamino ) arylidene ) – 7–chlorobenzo [d]thiazol –2–amine(3 ) :*** Compound 2 (3.15g, 0.015mol) was dissolved in methanol (25ml), different aromatic aldehyde (1.65g, 0.015mol) and 2-3 drops of glacial acetic acid was added and then refluxed for 4.5 hours. The solvent was recovered under reduced pressure and the residue was recrystallized from ethanol. Yield : 80 - 82%, MP: 95-97°C, $R_f$ value: 0.673, **IR(KBr)**: 720(C-Cl), 3105(Ar C-H), 1620(Ar C=C), 1302(C-N), 1623(C=N)

***Synthesis of title compound (4a-4g): 10 - chlorobenzo - 2 - aryl (substituted) – 3 –phenyl - 3, 4, 5, 6 – tetrahydro - 2H – triazolo [3, 2 - a] [ 1, 3, 5 ] triazin – 4 - thione:*** An equimolar mixture of compound (3) and appropriate isothiocyanate was refluxed for 4-6 hours in dry toluene and the solvent was distilled off under reduced pressure. The residue was washed with small amount of ethanol followed by water and product was recrystallized from ethanol.

## RESULTS AND DISCUSSION

Extensive literature survey spurred the benzothiazole and triazine moieties for synthesis of series of compounds (**4a-4j**) which were subjected to drug-likeness using Lipinski's "Rule of Five" by customized softwares. This provides insight into ADME properties of the synthesized compounds. Computed

partition co-efficient (XLOGP2 method) for drugs studied varied between 4.51-5.96. The XLOGP2 method is best supported for most of the compounds on the basis of lipophilicity ($\leqslant 5$) to consider on oral drug/lead. Investigation of the rate-limited steps of human oral absorption of 238 drugs[12] showed that the absorption of a drug is usually very low if the calculated solubility is <0.0001mg/l. As per this criterion compounds of series (**4a-4j**) almost fulfill the requirement of solubility (ALOGPS) and could be considered as the candidate drugs. All the compounds showed better oral bioavailability. The lipophilicity and solubility values are depicted in Table 1. The compounds in this series (**4a-4j**) in general possess moderate number of rotatable bonds and therefore exhibit moderate conformational flexibility and oral bioavailability. The series under investigation portrayed that almost all the compounds possess zero number of hydrogen bond donors but do possess considerable number of acceptors. The Lipinski's parameters data are elicited in Table2.

Drug-likeness model score (a combined effect of physico-chemical properties, pharmacokinetics and pharmacodynamics of a compound and is represented by a numerical value) was computed by Molsoft (Molsoft 2007) software for the ten molecules under study. As shown in the fig. 1 the dotted line graph indicates non drug-like behavior and those fall under thickest line graph are considered as drug-like. Computed drug-likeness scores are presented in Table 2. Compounds having zero or negative value should not be considered as drug-like. Maximum drug-likeness score was found out to be 0.45 for compound **4e**. On the basis of drug-likeness model score it was observed that compound having nitro substitution on phenyl ring in triazine moiety are failed to be treated as candidate molecules (**4h, 4i, 4j**) even though it complies with Lipinski's parameters.

The synthesis of triazine merged benzothiazole congeners {(**4a-4g**)}, described in this study are outlined in scheme 1 and physical data are presented in Table 3. The 7-Chloro-2-amino benzothiazole was prepared by reacting 3-

**Table 1: Calculated partition coefficient and solubilities of the Benzothiazole merged triazines**

| Compounds | ALOGPS | KoW-WIN | XLOGP2 |
|---|---|---|---|
| 4a | -5.44(1.50mg/l) | 8.01 | 5.17 |
| 4b | -5.60(1.22mg/l) | 8.90 | 5.96 |
| 4c | -5.10(3.55mg/l) | 8.19 | 5.38 |
| 4d | -5.38(1.97mg/l) | 7.65 | 4.73 |
| 4e | -5.39(1.90mg/l) | 8.17 | 5.00 |
| 4f | -5.38(2.07mg/l) | 7.52 | 4.51 |
| 4g | -4.90(5.66mg/l) | 7.35 | 4.68 |
| 4h | -5.44(1.63mg/l) | 7.83 | 5.60 |
| 4i | -5.43(1.68mg/l) | 7.83 | 5.06 |
| 4j | -5.45(1.62mg/l) | 7.83 | 5.06 |

**Fig.1: Drug likeness model score graph**

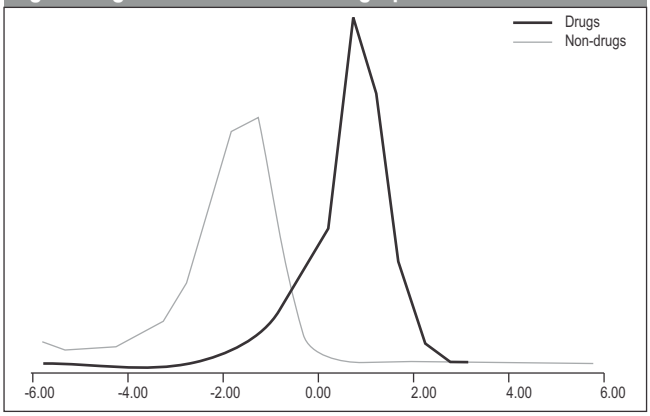


**Table 2: Results of calculated absorption (%ABS), Polar surface area(PSA), Lipinski's parameters and Drug-likeness model score of series of compounds investigated**

| Compound | %ABS | Volume(A3) | PSA(A2) | NROTB | HBA | HBD | logP, calcd. | Formula weight | Drug-likeness model score |
|---|---|---|---|---|---|---|---|---|---|
| 4a | 103.06 | 364.04 | 17.23 | 2 | 3 | 0 | 4.84 | 407.951 | 0.27 |
| 4b | 103.06 | 385.97 | 17.23 | 2 | 3 | 0 | 5.76 | 486.847 | 0.14 |
| 4c | 102.03 | 413.55 | 20.19 | 3 | 3 | 0 | 5.10 | 451.02 | 0.10 |
| 4d | 97.50 | 427.49 | 33.32 | 4 | 5 | 0 | 4.57 | 468.003 | 0.45 |
| 4e | 97.41 | 427.49 | 33.58 | 4 | 5 | 0 | 4.95 | 468.003 | 0.16 |
| 4f | 94.69 | 459.33 | 41.19 | 5 | 6 | 0 | 4.36 | 498.029 | 0.43 |
| 4g | 94.44 | 406.33 | 42.19 | 3 | 5 | 1 | 4.45 | 453.976 | 0.30 |
| 4h | 91.27 | 390.80 | 51.37 | 3 | 5 | 0 | 4.63 | 452.948 | -0.55 |
| 4i | 91.53 | 389.03 | 50.63 | 3 | 5 | 0 | 4.74 | 452.948 | -0.52 |
| 4j | 91.53 | 389.11 | 50.63 | 3 | 5 | 0 | 4.78 | 452.948 | -0.60 |

Chloroaniline and appropriate potassium thiocyanate in the presence of bromine by conventional cyclisation. The Schiff's reaction between newly synthesized 7-Chloro-2-aminobenzothiazole and different aromatic aldehydes resulted in various novel Schiff's bases. On condensation of Schiff's bases with phenyl isothicyanate results in triazine merged benzothiazole analogues.

The IR spectra of synthesized compounds displayed strong absorption bands from 3095 to 3040 $cm^{-1}$ for Ar-H Str, from 1684 to 1649 $cm^{-1}$ for C=N Str, from 1383 to 1304 $cm^{-1}$ for C-N Str, from 1268 to 1073 $cm^{-1}$ for C=S Str, and from 880 to 686 $cm^{-1}$ for C-Cl Str forms substantial evidence for the reaction that has taken place. The $^{1}$H-NMR spectrum of compounds in general showed multiplet in the region of δ 7.15-6.15 due to aromatic proton. At δ 3.9-3.5 appeared as singlet due to –CH in triazine moiety. Similarly a singlet appeared at δ 3.52-3.62 owing to the three protons of the methoxy group and the aromatic –OH protons resonated as a singlet between δ 5.1-5.3. The mass spectra of synthesized compounds showed molecular ion peak $M^{+}$ at m/z corresponding to their respective molecular masses which is in agreement with their respective molecular formula. The spectral data are presented in Table 4.

***Antioxidant Activity***

The *In-vitro* antioxidant activity of all selected compounds at four concentrations are given in Table 5. On intense

**Scheme**

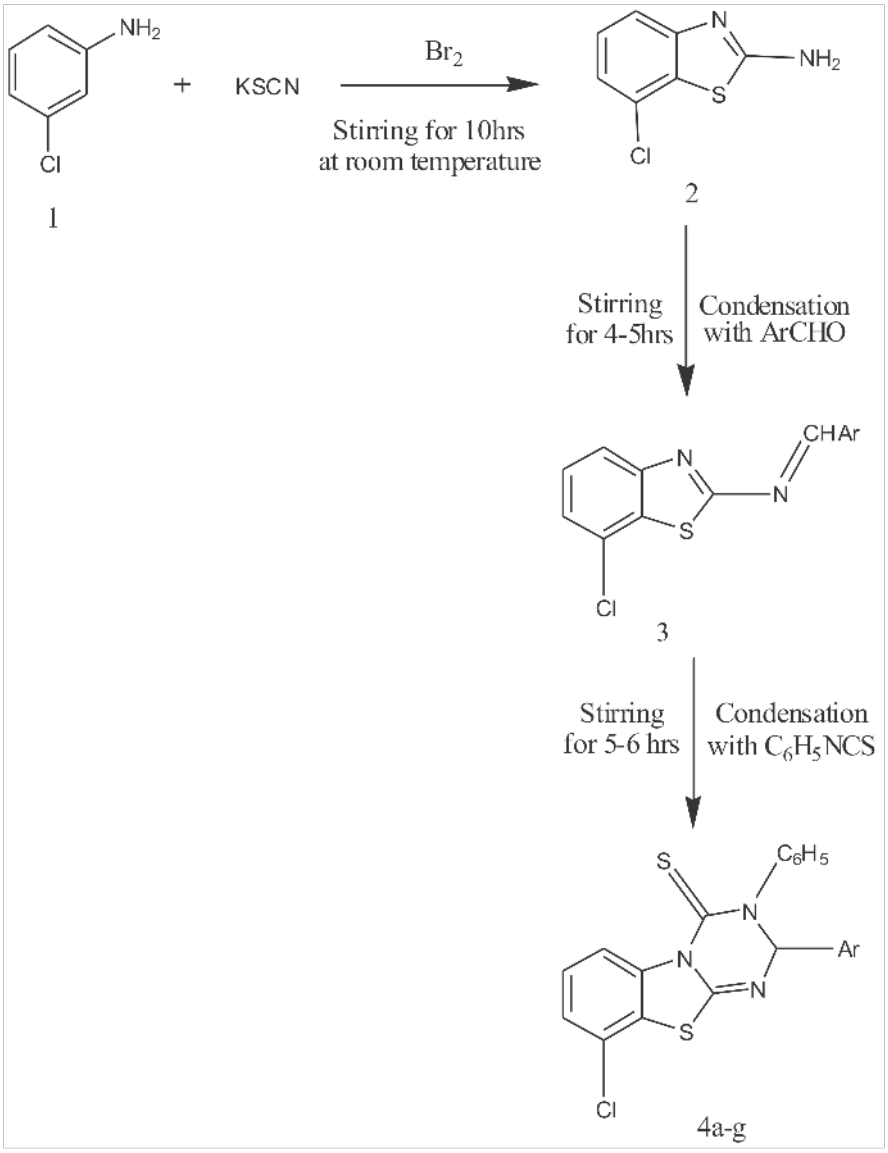

**Table 3: Physicochemical data of synthesized compounds**

| Compounds | R | Mol. Formula | Mol. Wt. | M.P. °C | Yield % | $R_f$ Value |
|---|---|---|---|---|---|---|
| 4a | Phenyl | $C_{21}H_{14}N_3S_2Cl$ | 407.951 | 105-107 | 86 | 0.671 |
| 4b | 3-Bromophenyl | $C_{21}H_{13}N_3S_2BrCl$ | 486.847 | 108-110 | 82 | 0.720 |
| 4c | 4-Dimethyl aminophenyl | $C_{23}H_{19}N_4S_2Cl$ | 451.02 | 115-117 | 81 | 0.705 |
| 4d | 3,4-Dimethoxy phenyl | $C_{23}H_{18}N_3O_2S_2Cl$ | 468.003 | 102-104 | 76 | 0.654 |
| 4e | 2,5- Dimethoxy phenyl | $C_{23}H_{18}N_3O_2S_2Cl$ | 468.003 | 100-102 | 71 | 0.701 |
| 4f | 3,4,5-Trimethoxy phenyl | $C_{24}H_{20}N_3O_3S_2Cl$ | 498.029 | 113-115 | 69 | 0.743 |
| 4g | 3-Methoxy- 4-hydroxy phenyl | $C_{22}H_{16}N_3O_2S_2Cl$ | 453.976 | 111-113 | 74 | 0.725 |

**Table 4: Spectral data of Synthesized Compounds**

| Compounds | I $R_t$,($cm^{-1}$) | $^1$H-NMR, δ ppm | MS, m/z |
|---|---|---|---|
| 4a | 686(C-Cl Str),3095(Ar C-H Str),1304(C-N Str), 1653(C=N Str),1073(C=S Str),1183(C-S Str), 1633(Ar C=C Str) | 7.15-6.18(m,13H, Ar), 3.9(s,1H,-CH) | 407 $M^+$ |
| 4b | 718(C-Cl Str),3056(Ar C-H Str),1343(C-N Str), 1649(C=N Str),1123(C=S Str),1104(C-S Str), 1625(Ar C=C Str),657(C-Br Str) | 7.2-6.15(m,12H,Ar), 3.5(s,1H,-CH) | 486 $M^+$ |
| 4c | 754(C-Cl Str),3040(Ar C-H Str),1325(C-N Str), 1664(C=N Str),1268(C=S Str),1083(C-S Str), 1617( Ar C=C Str),2906(C-H Aliphatic Str) | 7.04-6.12(m,12H,Ar), 3.2(s,1H,-CH), 2.85(s,6H,$CH_3$) | 451 $M^+$ |
| 4d | 728(C-Cl Str),3072( Ar C-H Str),1340(C-N Str), 1684(C=N str),1168(C=S Str),1149(C-S Str), 1543(Ar C=C Str),2830(C-O-$CH_3$ Str), 2916(C-H Aliphatic Str) | 7.11-6.14(m,11H Ar), 3.5(s,1H,-CH), 3.52(s,6H,-$CH_3$) | 467 $M^+$ |
| 4e | 718(C-Cl Str),3060(Ar C-H Str),1383(C-N Str), 1649(C=N Str),1146(C-S Str),1500(Ar C=C Str), 2834(C-O-$CH_3$ Str),2907(C-H Aliphatic Str) | 7.01-6.17(m,11H,Ar), 3.7(s,1H,-CH), 3.71(s,6H,-$CH_3$) | 467 $M^+$ |
| 4f | 683(C-Cl Str),3055(Ar C-H Str),1325(C-N Str), 1665(C=N Str),1229(C=S Str),1065(C-S Str), 1630(Ar C=C Str),2916(C-O-$CH_3$ Str), 2819(C-H Aliphatic Str) | 7.11-6.19(m,10H,Ar), 3.5(s,1H,-CH), 3.79(s,9H,-$CH_3$) | 498 $M^+$ |
| 4g | 880(C-Cl Str),3104(Ar C-H Str),1340(C-N Str), 1653(C=N Str),1186(C=S Str),1104(C-S Str), 1450(Ar C=C Str),2830(C-O-$CH_3$ Str), 2996(C-H Aliphatic Str),3490(O-H Str) | 7.09-6.13(m,1H,Ar), 3.9(s,11H,-CH), 5.0(s,1H,Ar,C-OH), 3.70(s,3H,-$CH_3$) | 453 $M^+$ |

investigation of the data given in table revealed that compound **4c** which is 4-dimethyl amino derivative has better activity than standard. The analogues **4e** and **4g** which are methoxy derivatives are equipotent as standard. All the other compounds has moderate to good activity.

### *Anti-inflammatory Activity*

Anti-inflammatory screening data indicates that all the compounds showed good activity at 50µg/ml concentration. Among the screened compounds **4g** which is a methoxy derivative showed similar potential as standard. The congeners **4c** and **4e** which are dimethyl amino and dimethoxy derivative has good activity.

## CONCLUSION

In present study novel benzothiazole merged triazines were synthesized with the assumption of good anti-inflammatory and antioxidant activities. A series of benzothiazole annealed triazines were subjected for the prediction of molecular properties and drug-likeness by different softwares in order to find suitable molecules for the synthesis and biological screening. Among the series only seven compounds were selected on the basis of molecular properties and drug-likeness score for oral bioavailability. Selected compounds (**4a-4g**) were designed for synthesis. All the synthesized compounds were screened for anti-inflammatory and antioxidant activities by adopting standard protocol.

**Table 5: Antioxidant Activity of Synthesized Compound**

| S.No. | Compound | Percentage Inhibition | | | |
|---|---|---|---|---|---|
| | | 50µg/ml | 100µg/ml | 150µg/ml | 200µg/ml |
| 1 | 4a | 41.17 | 50.08 | 66.98 | 83.631 |
| 2 | 4b | 40.51 | 54.70 | 67.84 | 82.272 |
| 3 | 4c | 49.67 | 53.64 | 69.62 | 85.023 |
| 4 | 4d | 42.24 | 51.23 | 65.92 | 82.543 |
| 5 | 4e | 48.24 | 52.97 | 68.76 | 84.400 |
| 6 | 4f | 43.09 | 59.54 | 65.65 | 82.650 |
| 7 | 4g | 48.20 | 52.30 | 68.87 | 84.340 |
| 8 | Ascorbic acid (Std) | 48.45 | 52.14 | 68.54 | 84.674 |

**Table 6:Anti-inflammatory activity of synthesized Compound**

| S.No. | Compound | Percentage Inhibition | | | |
|---|---|---|---|---|---|
| | | 50µg/ml | 100µg/ml | 150µg/ml | 200µg/ml |
| 1 | 4a | 21.56 | 30.89 | 40.01 | 47.31 |
| 2 | 4b | 20.23 | 29.54 | 38.06 | 46.13 |
| 3 | 4c | 23.85 | 33.37 | 42.20 | 50.85 |
| 4 | 4d | 21.33 | 31.58 | 41.12 | 49.42 |
| 5 | 4e | 23.01 | 33.23 | 42.02 | 50.27 |
| 6 | 4f | 22.34 | 32.39 | 39.43 | 48.67 |
| 7 | 4g | 24.20 | 34.92 | 43.29 | 51.50 |
| 8 | Diclofenac sodium (Std) | 23.34 | 33.34 | 42.34 | 50.34 |

Examining closely on substitution it may be concluded that, role of electron withdrawing group (-$OCH_3$ and –OH) on the phenyl ring of triazine has great influence on anti-inflammatory and antioxidant activities. The amino substitution on phenyl ring of triazine influence the antioxidant activity. The orientation of methoxy group is important for anti-inflammatory activity. Maximum activity is observed, when methoxy groups are in para position to each other which has less steric hindrance. This result is further supported by the fact that, their drug-likeness model score were maximum among the series. Finally it is conceivable that further derivatization of such compounds will be of great interest with the hope to get more selective anti-inflammatory and antioxidant agents.

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