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DESIGNING AND BIOLOGICAL PREDICTION STUDY OF SOME 4-PHENYL-6 (SUBSTITUTED-PHENYL)-[1,3,5]TRIAZIN-2-YLAMINE/-OL/-THIOL DERIVATIVES AS POTENT PHOSPHODIESTERASE II INHIBITOR, UBIQUINOL-CYTOCHROME-C REDUCTASE INHIBITOR AND PTERINDE AMINASE INHIBITOR

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ABSTRACT
A series of 4-phenyl-6 (substituted-phenyl)-[1,3,5]triazin-2-ylamine/-ol/-thiol[4(a-l)] derivatives have been synthesized by one pot multicomponent reaction between aromatic ester or acid, urea/guanidine hydrochloride/thiourea, and benzonitrile by exposing to microwaves at 40% microwave power (280 W). The accomplishment of the reaction was checked by TLC. Its structure was elucidated by ^{1}H–NMR and the ^{13}C-NMR spectra. In addition, biological prediction study of some [1,3,5]triazin-2-ylamine/-ol/-thiol[4(a-l)] derivative having good activity against Phosphodiesterase II inhibitor, Ubiquinol-cytochrome-c reductase inhibitor and Pterindeaminase inhibitor.

KEYWORDS
Onepot multicomponent reaction, microwave, TLC, ^{1}H–NMR and the ^{13}C-NMR spectra.

INTRODUCTION
Triazines are six-membered heterocyclic compounds with three carbon and three nitrogen atoms. The three isomers namely, 1,2,3-triazine, 1,2,4-triazine, and 1,3,5-triazine. The 1,3,5-triazines are the primogenital and most widely studied of the isomeric forms[i,ii]. Given that 1,3,5-triazine is a symmetrical molecule, compounds of this type are frequently referred as *s*-triazines. In 1895 Nef accidently synthesized 1,3,5-Triazine from hydrogen cyanide and etheral solution saturated with hydrogen chloride in ethanol. The consequential salt was treated with base and distilled to give 1,3,5-triazine.
The most commonly used triazine derivatives are cyanuric acid and melamine. Cyanuric acid has been originated to naturally occur in nature in soil humus[ii]. Marketable applications of cyanuric acid embrace stabilizers of swimming pool disinfectants, industrial cleaners, household bleach, dishwasher detergents, and general sanitizers.

Naturally occurring melamine has been exposed in numerous meteorites which have reached earth[iii]. Nowadays melamine is produced in large amounts, regularly for the formation of resins. The resins have several applications containing coatings, molding compounds, laminates, glues and adhesives, paper and textiles[iv].

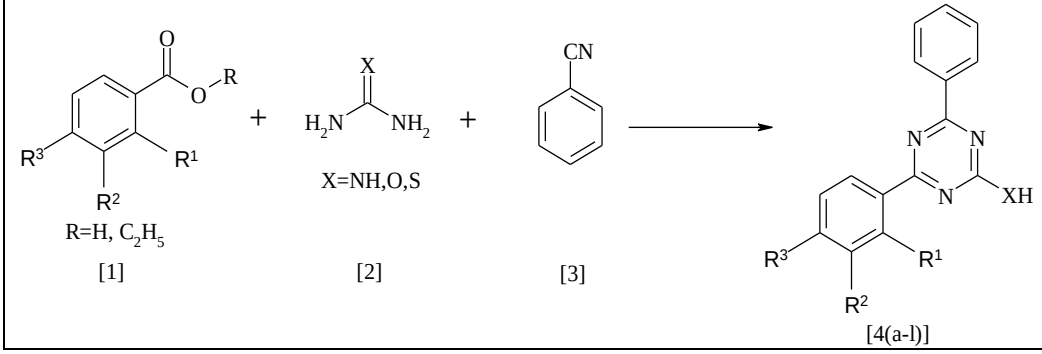
The 1,3,5-triazine derivatives are having wide applications in medical and agricultural field. Various triazine derivatives display various biological activities like anti-HIV[v], as promising agent in fibrosis treatment[vi], muscle relaxant[vii], hypoglycemic[viii], blood pressure depressant[ix], anti-diabetic[x] properties. They also showed anti-tumor[xi], anti-bacterial[xii], anti-inflammatory[xiii], anti-cancer[xiv], and anti-psychotic properties[xv]. Some of them are used in industries as finishing and brightening agents[xvi]. They are also been used as herbicidal[xvii-xviii], sea water algicidal[xix], fungicidal[xx], insecticidal[xxi]and pesticidals[xxii].

Looking to the importance, we intended to synthesize new 4-phenyl-6 (substituted-phenyl)-[1,3,5]triazin-2-ylamine/-ol/-thiol derivatives like, 4-(2-nitro-phenyl)-6-phenyl-[1,3,5]-triazin-2-ylamine [4(a)], 4-(4-nitro-phenyl)-6-phenyl-[1,3,5]-triazin-2-ylamine [4(b)], 4-(4-chloro-phenyl)-6-phenyl-[1,3,5]-triazin-2-ylamine [4(c)], 4,6-diphenyl-[1,3,5]-triazin-2-ylamine [4(d)], 4,6-diphenyl-[1,3,5]-triazin-2-ylamine [4(e)], 4-(2-nitro-phenyl)-6-phenyl-[1,3,5]-triazin-2-ol [4(f)], 4-(4-nitro-phenyl)-6-phenyl-[1,3,5]-triazin-2-ol [4(g)], 4-(4-chloro-phenyl)-6-phenyl-[1,3,5]-triazin-2-ol [4(h)], 4,6-diphenyl-[1,3,5]-triazin-2-ol [4(i)], 4,6-diphenyl-[1,3,5]-triazin-2-ol [4(j)], 4,6-diphenyl-[1,3,5]-triazin-2-thiol [4(k)], 4,6-diphenyl-[1,3,5]-triazin-2-thiol [4(l)].

RESULT AND DISCUSSION

Library of such triazin-2-ylamine/-ol/-thiol derivatives has been generated. **(SCHEME)** The structures of the products [4(a-l)] were confirmed on the base of IR, ^{1}H NMR, ^{13}C NMR, Mass spectral and elemental analyses. And confirmed structures were subjected to computer programme 'PASS' for biological predictions. The probabilities for being active (Pa) are compared with the structures to find out most active molecules for the predicted biological activity. Based on the biological prediction study the derivatives [4(i)], [4(j)] and [4(g)] are recommended for the screening of both phosphodiesterase II inhibitorand 2 ubiquinol-cytochrome-c reductase inhibitor activities.

(SCHEME 1)



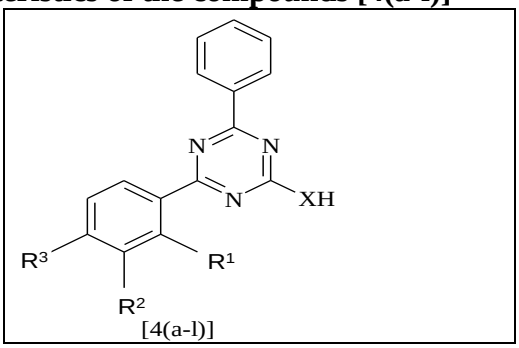
EXPERIMENTAL WORK

Synthetic procedure for the triazin-2-ylamine/-ol/-thiolderivatives [4(a-l)]:

In 50 mL RB flask aromatic ester or acid (0.01 mole), urea/guanidine hydrochloride/thiourea (0.01 mole), and benzonitrile (0.01 mole) are taken, further absolute ethanol was added in RB flask, which was exposed to microwaves at 40% microwave power (280 W). The reaction mixture was irradiated for the showed time required for the completion of the reaction **(Table**

1). The accomplishment of the reaction was checked by TLC. The reaction mixture was transferred on ice contained a beaker to obtain the product. The solidified product was filtered and recrystallized from ethanol. TLC Elution done by a mixture of Ethyl acetate and Hexane (3:7)

Table-1: General Characteristics of the compounds [4(a-l)]



[4(a-l)]

Product	**R**	**R^1**	**R^2**	**R^3**	**Time (min.)**	**Yield**	**M.P. °C**	**Mol. Formula (Molar Mass)**
[4(a)]	C_2H_5	NO_2	H	H	2.30	60	180	$C_{15}H_{13}N_5O_2$ (295)
[4(b)]	C_2H_5	H	H	NO_2	3.00	65	210	$C_{15}H_{13}N_5O_2$ (295)
[4(c)]	H	H	H	Cl	4.00	67	208	$C_{15}H_{11}N_4Cl$ (282)
[4(d)]	H	H	H	H	3.10	60	240	$C_{15}H_{12}N_4$ (248)
[4(e)]	C_2H_5	H	H	H	5.00	55	240	$C_{15}H_{12}N_4$ (248)
[4(f)]	C_2H_5	NO_2	H	H	2.00	62	160	$C_{15}H_{12}N_4O_3$ (296)
[4(g)]	C_2H_5	H	H	NO_2	3.20	68	188	$C_{15}H_{12}N_4O_3$ (296)
[4(h)]	H	H	H	Cl	3.40	70	190	$C_{15}H_{10}N_3OCl$ (283)
[4(i)]	H	H	H	H	4.50	70	222	$C_{15}H_{11}N_3O$ (249)
[4(j)]	C_2H_5	H	H	H	5.00	58	222	$C_{15}H_{11}N_3O$ (249)
[4(k)]	H	H	H	H	4.20	70	235	$C_{15}H_{11}N_3S$ (265)
[4(l)]	C_2H_5	H	H	H	5.10	60	235	$C_{15}H_{11}N_3S$ (265)

SPECTRAL ANALYSIS AND ELEMENTAL ANALYSIS DATA

4-(2-Nitro-phenyl)-6-phenyl-[1,3,5]-triazin-2-ylamine[4(a)]:

Nature and color: Off- White Solid.

Molecular Formula: $C_{15}H_{13}N_5O_2$,

Melting Point: 180 ºC,

IR (KBr) ν_{max}: 3311.78(NH_2), 3051.13(Ar-H), 1593.86 (CH=N), 1503.06 (Ar-NO_2) cm^{-1}.

^{1}H-NMR (DMSO-d_6, 300MHz): δ 5.256(s, 2H, NH_2), 7.630-7.656(d, 1H, Ar-H), 7.669-7.692(dd, 1H, Ar-H), 7.818-7.891(m, 5H, Ar-H), 8.323-8.361(dd, 2H, Ar-H) ppm.

^{13}C-NMR (DMSO-d_6, 100 MHz): δ 112.10, 116.63, 124.40, 124.54, 125.48, 127.41, 130.53, 134.93, 135.19, 139.67, 143.54, 148.14, and 148.42 ppm.

GCMS *m/z* (%): 295.2 (M+)

Elemental Analysis Data

Calcd.: C(61.43%), H(3.78%), N(23.88%), O(10.20%).

Found: C(61.39%), H(3.75%), N(23.84%), O(10.10%).

4-(4-Nitro-phenyl)-6-phenyl-[1,3,5]-triazin-2-ylamine[4(b)]:

Nature and color: Off- White Solid.

Molecular Formula: $C_{15}H_{13}N_5O_2$,

Melting Point: 210 ºC,

IR (KBr) ν_{max}: 3313.38(NH_2), 3053.33(Ar-H), 1593.86(CH=N), 1503.06 (Ar-NO_2) cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ 4.305(s, 2H, NH_2), 7.521-7.535(d, 3H, Ar-H), 7.546-7.706(t, 2H, Ar-H), 7.862-7.891(d, 2H, Ar-H), 7.950-7.981(m, 2H, Ar-H) ppm.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 126.92, 127.41, 128.15, 128.83, 129.71, 130.46, 131.67, 134.56, 135.32, 137.63, 140.06, and 143.65 ppm.

GCMS *m/z* (%):295.2 (M+)

Elemental Analysis Data

Calcd.:C(61.43%), H(3.78%), N(23.88%), O(10.20%).

Found: C(61.39%), H(3.70%), N(23.83%), O(10.18%).

4-(4-Chloro-phenyl)-6-phenyl-[1,3,5]-triazin-2-ylamine[4(c)]:

Nature and color: Off- White Solid.

Molecular Formula: $C_{15}H_{11}N_4Cl$,

Melting Point: 208 ºC,

IR (KBr) ν_{max}: 3300.56(NH_2), 3021.24, 3012.04(Ar-H), 1600.35(CH=N), 700(Ar-Cl) cm^{-1}.

^{1}H-NMR (DMSO-d_6, 300MHz): δ 4.350(s, 2H, NH_2), 7.001-7.029(t, 3H, Ar-H), 7.072-7.078(d, 2H, Ar-H), 7.210-7.237(d, 2H, Ar-H), 7.373-7.402 (dd, 2H, Ar-H) ppm.

^{13}C-NMR (DMSO-d_6, 100 MHz): δ 111.06, 118.21, 124.36, 125.65, 126.36, 141.31, 145.27, 147.46, 149.67, and 152.50 ppm.

GCMS *m/z* (%):282.5 (M+)

Elemental Analysis Data

Calcd.: C(63.72%), H(3.92%), N(19.82%), Cl(12.54%).

Found: C(63.65%), H(3.90%), N(19.80%), Cl(12.44%).

4,6-Diphenyl-[1,3,5]-triazin-2-ylamine[4(d)]:

Nature and color: Off- White Solid.

Molecular Formula: $C_{15}H_{12}N_4$,

Melting Point: 240 ºC,

IR (KBr) ν_{max}: 3300.56(NH_2), 3021.24, 3012.04(Ar-H), 1600.35(CH=N) cm^{-1}.

^{1}H-NMR (DMSO-d_6, 300MHz): δ 4.224(s, 2H, NH_2), 7.486-7.577(m, 4H, Ar-H), 7.663-7.740(m, 2H, Ar-H), 7.800-7.862(m, 4H, Ar-H) ppm.

^{13}C-NMR (DMSO-d_6, 100 MHz): δ 123.65, 126.21, 131.36, 149.27, 150.46 and 152.07 ppm.

GCMS (m/z): 248.2 (M+)

Elemental Analysis Data
Calcd.: C(72.56%), H(4.87%), N(22.57%).
Found: C(72.51%), H(4.86%), N(22.50%).

4,6-Diphenyl-[1,3,5]-triazin-2-ylamine[4(e)]:
Nature and color: Off- White Solid.
Molecular Formula: $C_{15}H_{12}N_4$,
Melting Point: 240 ^oC,
IR (KBr) ν_{max}: 3300.56(NH_2), 3021.24, 3012.04(Ar-H), 1600.35(CH=N) cm^{-1}.
^{1}H-NMR (DMSO-d_6, 300MHz): δ 4.224(s, 2H, NH_2), 7.486-7.577(m, 4H, Ar-H), 7.663-7.740(m, 2H, Ar-H), 7.800-7.862(m, 4H, Ar-H) ppm.
^{13}C-NMR(DMSO-d_6, 100 MHz): δ 123.65, 126.21, 131.36, 149.27, 150.46 and 152.07 ppm.
GCMS *m/z* (%): 248.2 (M+)
Elemental Analysis Data
Calcd.:C(72.56%), H(4.87%), N(22.57%).
Found: C(72.55%), H(4.84%), N(22.55%).

4-(2-Nitro-phenyl)-6-phenyl-[1,3,5]-triazin-2-ol[4(f)]:
Nature and color: Off- White Solid.
Molecular Formula: $C_{15}H_{12}N_4O_3$,
Melting Point: 160 ^oC,
IR (KBr) ν_{max}: 3508.29(OH), 3186.79(Ar-H), 1635.34(Ar-NO_2), 1508.06(CH=N), cm^{-1}.
^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.330 (s, 1H, OH), 7.409-7.495 (m, 2H, Ar-H), 7.626-7.698 (d, 3H, Ar-H), 7.809-7.881 (m, 4H, Ar-H) ppm.
^{13}C-NMR (DMSO-d_6, 100 MHz): δ 124.42, 124.80, 127.97, 128.34, 130.98, 134.85, 135.61, 136.11, 138.28, 144.38, 147.45, 148.75 and 149.02 ppm.
GCMS *m/z* (%): 296.8 (M+)
Elemental Analysis Data
Calcd.: C(61.22%), H(3.43%), N(19.04%), O(16.31%).
Found: C(61.15%), H(3.40%), N(19.01%), O(16.25%).

4-(4-Nitro-phenyl)-6-phenyl-[1,3,5]-triazin-2-ol[4(g)]:
Nature and color: Off- White Solid.
Molecular Formula: $C_{15}H_{12}N_4O_3$,
Melting Point: 188 ^oC,
IR (KBr) ν_{max}: 3508.29(OH), 3487.21(Ar-H), 1634.38(Ar-NO_2), 1519.63(CH=N), cm^{-1}.
^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.512 (s, 1H, OH), 7.018-7.124(m, 2H, Ar-H), 7.362-7.391(d, 2H, Ar-H), 7.423-7.540 (m, 1H, Ar-H), 7.737-7.807 (m, 2H, Ar-H), 8.042-8.070 (d, 2H, Ar-H) ppm.
^{13}C-NMR (DMSO-d_6, 100 MHz): δ 117.40, 122.99, 123.37, 125.67, 125.87, 127.26, 128.21, 129.29, 131.77, 135.97 and 142.67 ppm.
GCMS *m/z* (%): 296.8 (M+)
Elemental Analysis Data
Calcd.:C(61.22%), H(3.43%), N(19.04%), O(16.31%).
Found: C(61.15%), H(3.40%), N(19.00%), O(16.24%).

4-(4-Chloro-phenyl)-6-phenyl-[1,3,5]-triazin-2-ol[4(h)]:
Nature and color: Off- White Solid.
Molecular Formula: $C_{15}H_{10}N_3OCl$,
Melting Point: 190 ^oC,
IR (KBr) ν_{max}: 3518.31(OH), 3497.91(Ar-H), 1589.06(CH=N), 670(Ar-Cl) cm^{-1}.
^{1}H-NMR (DMSO-d_6, 300MHz): δ 6.410 (s, 1H, OH), 7.042-7.154(m, 2H, Ar-H), 7.399-7.501(m, 5H, Ar-H), 7.704-8.805(m, 2H, Ar-H) ppm.

^{13}C-NMR (DMSO-d_6, 100 MHz): δ 124.64, 125.61, 127.55, 128.03, 128.24, 129.53, 135.45, 137.41, 143.30, 158.69, 161.19 ppm.
GCMS *m/z* (%):283.4 (M+)
Elemental Analysis Data
Calcd.: C(63.50%), H(3.55%), N(14.81%), Cl(12.50%), O(5.64%).
Found: C(63.46%), H(3.54%), N(14.78%), Cl(12.44%), O(5.59%).
4,6-Diphenyl-[1,3,5]-triazin-2-ol[4(i)]:
Nature and color: Off- White Solid.
Molecular Formula: $C_{15}H_{11}N_3O$,
Melting Point: 222^{0}C,
IR (KBr) ν_{max}: 3298.74(OH), 3100.00(Ar-H), 1492.63(CH=N) cm^{-1}.
^{1}H-NMR (DMSO-d_6, 300MHz): δ 5.454 (s, 1H, OH), 7.006-7.107(m, 4H, Ar-H), 7.163-7.240(m, 4H, Ar-H), 7.350-7.402(t, 2H, Ar-H) ppm.
^{13}C-NMR (DMSO-d_6, 100 MHz): δ 126.85, 132.96, 137.76, 142.51, 144.71, and 156.29 ppm.
GCMS *m/z* (%):249.4 (M+)
Elemental Analysis Data
Calcd.: C(72.28%), H(4.45%), N(16.86%), O(6.42%).
Found: C(72.24%), H(4.41%), N(16.84%), O(6.40%).
4,6-Diphenyl-[1,3,5]-triazin-2-ol[4(j)]:
Nature and color: Off- White Solid.
Molecular Formula: $C_{15}H_{11}N_3O$,
Melting Point: 222 ^{o}C,
IR (KBr) ν_{max}: 3298.74(OH), 3100.00(Ar-H), 1492.63 (CH=N) cm^{-1}.
^{1}H-NMR (DMSO-d_6, 300MHz): δ 5.454(s, 1H, OH), 7.006-7.107(m, 4H, Ar-H), 7.163-7.240(m, 4H, Ar-H), 7.350-7.402(t, 2H, Ar-H) ppm.
^{13}C-NMR(DMSO-d_6, 100 MHz): δ 126.85, 132.96, 137.76, 142.51, 144.71, and 156.29 ppm.
GCMS *m/z* (%):249.4 (M+)
Elemental Analysis Data
Calcd.:C(72.28%), H(4.45%), N(16.86%), O(6.42%).
Found: C(72.20%), H(4.38%), N(16.82%), O(6.41%).
4,6-Diphenyl-[1,3,5]-triazin-2-thiol[(4k)]:
Nature and color: Off- White Solid.
Molecular Formula: $C_{15}H_{11}N_3S$,
Melting Point: 235 ^{o}C,
IR (KBr) ν_{max}: 2550(SH), 3100.00(Ar-H), 1500.00(CH=N) cm^{-1}.
^{1}H-NMR (DMSO-d_6, 300MHz): δ 7.006-7.107(m, 4H, Ar-H), 7.163-7.240(m, 4H, Ar-H), 7.350-7.402(t, 2H, Ar-H) ppm.
^{13}C-NMR (DMSO-d_6, 100 MHz): δ 126.85, 132.96, 137.76, 142.51, 144.71, and 156.29 ppm.
GCMS *m/z* (%):234.2 (M+)
Elemental Analysis Data
Calcd.: C(67.90%), H(4.18%), N(15.84%), S(12.08%).
Found: C(67.79%), H(4.08%), N(15.82%), S(12.04%).
4,6-Diphenyl-[1,3,5]-triazin-2-thiol[(4l)]:
Nature and color: Off- White Solid.
Molecular Formula: $C_{15}H_{11}N_3S$,
Melting Point: 235^{0}C,
IR (KBr) ν_{max}: 2550(SH), 3100.00(Ar-H), 1500.00(CH=N) cm^{-1}.
^{1}HNMR (DMSO-d_6, 300MHz): δ 7.006-7.107(m, 4H, Ar-H), 7.163-7.240(m, 4H, Ar-H), 7.350-7.402(t, 2H, Ar-H) ppm.

^{13}C NMR (DMSO-d_6, 100 MHz): δ 126.85, 132.96, 137.76, 142.51, 144.71, and 156.29 ppm.
GCMS *m/z* (%):234.2 (M+)
Elemental Analysis Data
Calcd.:C(67.90%), H(4.18%), N(15.84%), S(12.08%).
Found: C(67.85%), H(4.15%), N(15.80%), S(12.00%).

RESULTS AND DISCUSSION: BIOLOGICAL PREDICTION STUDY

The confirmed structures were subjected to free online computer software PASS to obtain the prediction of their biological activities. Compounds[4(a-l)] showed three activities predicted with top probability.
1 Phosphodiesterase II inhibitor
2 Ubiquinol-cytochrome-c reductase inhibitor
3 Pterindeaminase inhibitor

Table-2 Biological Prediction Analysis of Activities with PASS of derivatives [4(a-l)]

Activity Comp.	Phosphodiesterase II inhibitor	Ubiquinol-cytochrome-c reductase inhibitor	Pterindeaminase inhibitor
	Pa	Pa	Pa
[4(a)]	0.000	0.692	0.696
[4(b)]	0.000	0.786	0.729
[4(c)]	0.000	0.629	0.753
[4(d)]	0.000	0.658	0.864
[4(e)]	0.000	0.658	0.864
[4(f)]	0.655	0.823	0.472
[4(g)]	0.683	0.876	0.515
[4(h)]	0.745	0.786	0.550
[4(i)]	**0.973**	0.803	0.738
[4(j)]	**0.973**	0.803	0.738
[4(k)]	0.000	0.593	0.572
[4(l)]	0.000	0.593	0.572

CONCLUSION

In short, we have established well-organized protocol for the selective synthesis of novel triazin-2-ylamine/-ol/-thiol derivatives with excellent yield under microwave irradiation, which attains completion in 2.30-5.10 min in an organic medium and may provide a useful route for the rapid drug discovery.

Based on the biological prediction study; the compound 4-(4-nitro-phenyl)-6-phenyl-[1,3,5]-triazin-2-ol [4(g)] is probably significant as ubiquinol-cytochrome-c reductase inhibitor and 4,6-diphenyl-[1,3,5]-triazin-2-ylamine [4(e)] is predicted to be moderate to good as Pterindeaminase inhibitor agent.Whereas, 4,6-diphenyl-[1,3,5]-triazin-2-ol [4(i)] and 4,6-diphenyl-[1,3,5]-triazin-2-ol [4(j)] are predicted commendable and hence recommended for the phosphodiesterase II inhibitor activity as they are having highest probability of being active.

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