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EXPERIMENTAL PAPER

Synthesis and Biological Activities of Novel Aryldiazo Substituted Heterocycles

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Interestingly, in some examples of bioactive heterocycles, a more pronounced effect is observed when two or more different heterocyclic moieties are incorporated within a single molecule.[1] In this context, recent attention is focused on construction of structures with multiple heterocycles, as well as on the creation of heterocyclic diversity from common precursors.

The benzopyran motif, for example, plays a vital role in pharmaceutical chemistry. The benzopyran core is considered to be responsible for most of significant biological activities such as Epicalyxin F exhibiting antiproliferative activity against HT-1080 fibrosarcoma and colon 26-L5 carcinoma,[2] tetrahydrocannabinol possessing an agonistic effect on cannabinoid receptors, CB 1 and CB 2[3], and rhododaurichromanic acid A showing phytotoxic properties[4]. Other valuable heterocycles, such as xanthenes[5–9] and 5-deaza-10-oxaflavins also incorporate the benzopyran skeleton. In particular, 1-oxo-hexahydroxanthenes have such pharmacological properties as antibacterial, anti-estrogenic, antithrombin and hypoglycemic activities.[10–14] Like xanthenes, 5-deaza-10-oxaflavins have received strong attention from organic chemists. They have been employed as intermediates for the preparation of other heterocycles[15–23] as well as acting as selective organic oxidants under mild conditions.[24] Moreover, they are known to display bioactivity as drugs.[25–27]

Such compounds have long been of interest because of their unique photochemical and photophysical properties.[28–30] But they are also well known for their medicinal significance.[31–38] Notably, they play a vital role in biological reactions such as the inhibition of DNA, RNA, carcinogenesis, protein synthesis and nitrogen fixation.[39,40] Interestingly, some arylazo compounds are found to exhibit anti-HIV,[41,42] anti-inflammatory and cytoprotective activities[43] (Figure 1).

In our own work, we hypothesized that, if benzopyran fused heterocycles were merged together with aryldiazo groups, the resulting molecular scaffolds might possess enhanced bioactivity. In continuation of our interest in ionic liquid catalyzed organic transformations,[44] we report herein the synthesis of 1-oxo-hexahydroxanthenes, 5-deaza-10-oxaflavins, 2,3-dihydroquinazolin-4(1H)-ones and 1,2,4-triazolidine-3-thiones incorporating aryldiazo groups. This was accomplished using catalysis by the ionic

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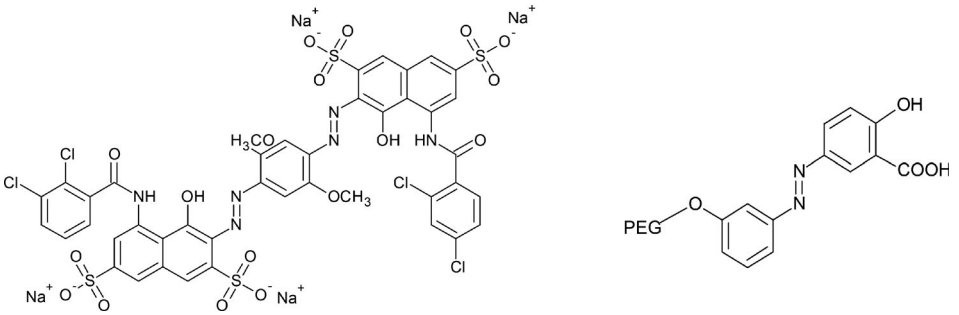


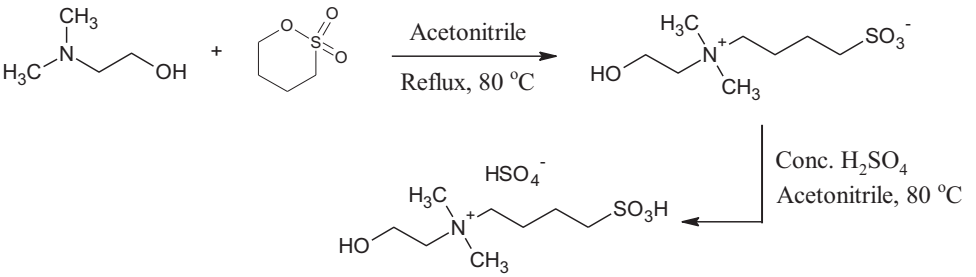
Figure 1. *bis*Azo compound exhibiting anti-HIV activity (left) and Azo compound exhibiting anti-inflammatory and cytoprotective activities (right).

liquid, [N-(2-hydroxyethyl)-N,N-dimethyl-4-sulfobutan-1-aminium] hydrogen sulfate. Remarkably, the synthesized ionic liquid [HDSA] HSO_4^- was found equally efficient for the synthesis of diverse kinds of molecular scaffolds from four different substrates having varied chemical reactivity.

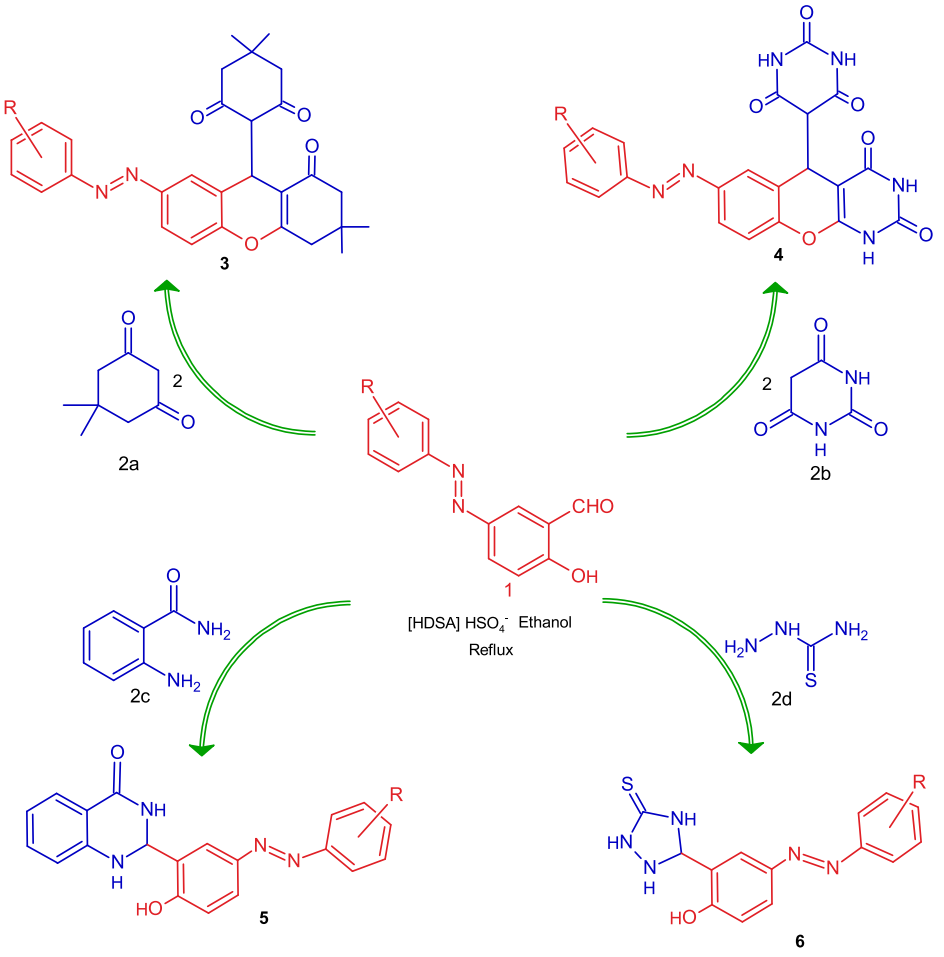
Earlier ionic liquids (ILs) were utilized as reaction media for organic synthesis. Nowadays, they have marched far beyond this border as mere solvents. Their eco--friendly credentials (nonvolatility, nonflammability, thermal stability, low vapor pressure, low toxicity and biodegradable nature) have increased their popularity for commercial use.[45–50] Remarkably, in many IL catalyzed reactions, enhancement of the rate is observed.[51] In this context, ionic liquids bearing task-specific functionalities have attracted the attention of researchers. Among these ILs, sulfate-functionalized Brønsted acidic ILs possesses such striking features as noncorrosivity, nonvolatility, air stability and easy recovery and reusability.[52–55] Hydroxyl functionalized ionic liquids are characterized by hydrophilicity, H-bonding ability and increased solubility of reagents. We thus decided to prepare task specific ILs with both acidic and hydroxyl functionalities to accomplish efficient catalytic activity.

Initially we focused our attention on the design and synthesis of [*N*-(2-hydroxyethyl)-*N*,*N*-dimethyl-4-sulfobutan-1-aminium] hydrogen sulfate (Figure 1). The synthesis of this IL is depicted in Scheme 1. In the first step, N,N-dimethylamino ethanol was reacted with 1,4-butane sultone to furnish a zwitterionic species. Further treatment with sulfuric acid afforded the target IL [HDSA] HSO_4^-. The structure was confirmed by ^{1}H-NMR, ^{13}C-NMR, IR and mass spectrometric analysis.

The catalytic activity of our newly synthesized IL was investigated for the model reaction of 5-phenyldiazo salicylaldehyde (1 mmol) and dimedone (2 mmol) in ethanol at reflux (Scheme 2). In order to optimize the catalyst, 20 mol % each of different Bronsted acids, Lewis acids and ionic liquids were examined (Table 1, entries 1-14). Low yields of product were observed in the presence of Lewis acids such as $AlCl_3$ and $ZnCl_2$ (Table 1, entries 1, 2) whereas moderate yields of product were found in the presence of Bronsted acids (*p*-TSA, acetic acid, sulfamic acid and ionic liquids containing Bronsted and Lewis acidic counterparts (Table 1, entries 3-11)). In the presence of a catalytic amount of the synthesized IL, ([HDSA] HSO_4^-) the reaction occurred smoothly, furnishing the desired product in 87% yield within 2.5 hour (Table 1, entry 12). The structure of the product was confirmed by ^{1}H NMR, ^{13}C NMR, IR and MS



Scheme 1. Synthesis of task specific ionic liquid, [HDSA] HSO_4^-.



Scheme 2. Synthesis of arylazo group linked diverse molecular scaffolds.

analysis. Thus, [HDSA] HSO_4^- was found to be the catalyst of choice for this transformation with respect to yield and reaction time.

To examine the impact of catalyst loading on the model reaction, the amount of [HDSA] HSO_4^- was varied from 10 to 30 mol % (Table 1, entries 12-15). From Table 1,

Table 1. Screening of catalyst for synthesis of 3[a].

Entry	Catalyst (mol %)	Time H	Yield[b] (%)
1	$AlCl_3$ (20)	5	23
2	$ZnCl_2$ (20)	5	17
3	PTSA (20)	5	66
4	Acetic acid (20)	5	25
5	Sulfamic acid (20)	5	64
6	Sulfuric acid (20)	5	79
7	[BMIM] Cl (20)	3	15
8	[BMIM] $AlCl_4$ (20)	3	40
9	[BMIM] HSO_4 (20)	2.5	76
10	[TESA] HSO_4^-	2.5	72
11	[HDSA] Cl^- (20)	2.5	77
12	[HDSA] HSO_4^- (20)	2.5	87
13	[HDSA] HSO_4^- (10)	2.5	80
14	[HDSA] HSO_4^- (30)	2.5	88

[a]Salicylaldehyde (1 mmol), Dimedone (2 mmol), catalyst (20 mol %), solvent (Ethanol, 7 mL), reflux.
[b]Isolated yield.

Table 2. Screening of solvent for synthesis of 3[a].

Entry	Solvent	Time H	Yield[b] (%)
1	Water	6	trace
2	Acetonitrile	4	36
3	DCM	5	25
4	Chloroform	4	30
5	Acetone	5	34
6	THF	4	55
7	DMF	4	70
8	Methanol	3	84
9	Ethanol	2.5	87

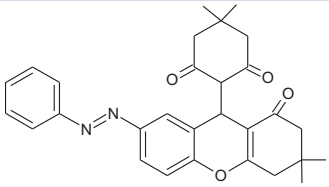
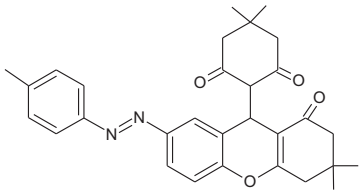
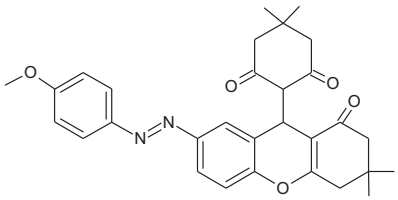
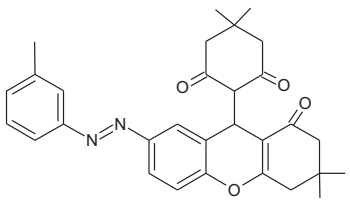
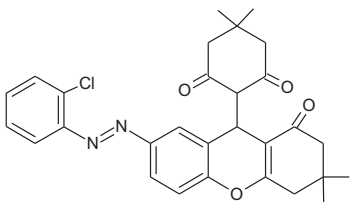
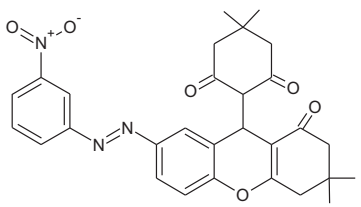
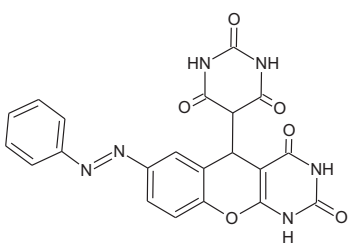
[a]Salicylaldehyde (1 mmol), Dimedone (2 mmol), [HDSA] HSO_4^-(20 mol %), solvent (7 mL), reflux.
[b]Isolated yield.

it can be concluded that 20 mol % of IL, [HDSA] HSO_4^- was sufficient to provide the product in 87% yield. No significant improvement in the yield was observed even when 30 mol % of IL was employed, whereas 10 mol % catalyst loading resulted in comparatively low yield (Table 1, entry 13). To investigate the effect of the acidic anion, the model reaction was carried out employing [HDSA] Cl^- (Table 1, entry 11) and this gave the desired product in 77% yield. This result suggested the significance of the acidic anion in the catalytic activity of synthesized ionic liquid [HDSA] HSO_4^-.

The impact of reaction medium was also investigated using different solvents such as water, methanol, acetonitrile, chloroform, acetone, DCM and THF for the model reaction. With non-polar solvents, a lower yield of product was observed even after prolonged reaction time (Table 2, entries 2–5). The reaction failed in water which may be due to the poor solubility of reactants (Table 2, entry 1). In ethanol, the desired product was formed in 87% yield making it a good choice of solvent for the model transformation.

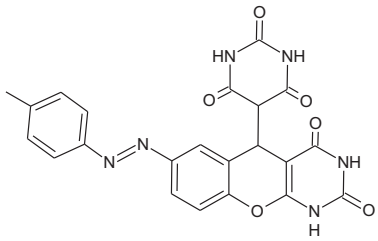
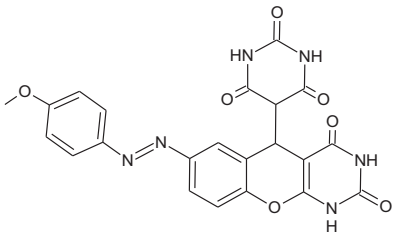
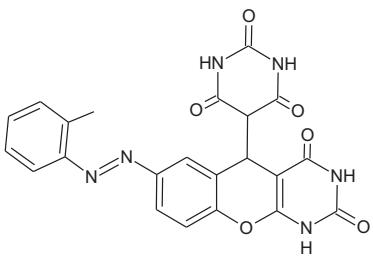
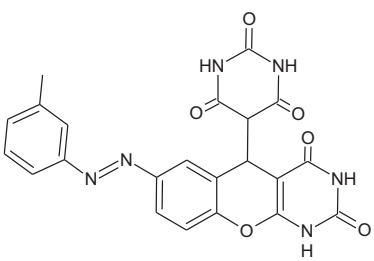
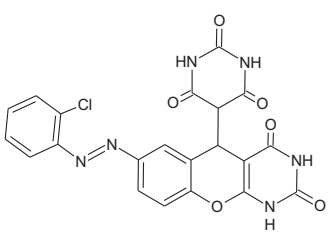
Having optimized reaction conditions in hand, a further exploration of the scope of substrate and functional group tolerance was carried out. We prepared a number of 1-oxo-hexahydroxanthenes by varying the 5-aryldiazosalicylaldehydes. Those having electron donating groups on the aryldiazo ring afforded the desired products in moderate to good yields (Table 3, entries 3a-e). However, in the case of 5-aryldiazosalicylaldehydes

Table 3. Synthesis of 1-oxo-hexahydroxanthenes and 5-deaza-10-oxaflavins.

Entry	R	Product	Time (h)	Yield (%)
3a	H		2.5	88
3b	4-Me		2.5	90
3c	4-OMe		3.2	84
3d	3-Me		2.4	89
3e	2-Cl		7.0	No reaction
3f	3-NO_2		7.0	No reaction
4a	H		2.7	88

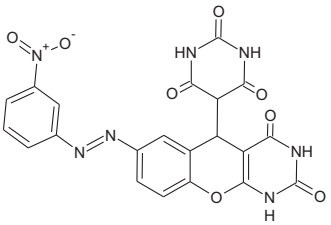
(*continued*)

Table 3. Continued.

Entry	R	Product	Time (h)	Yield (%)
4b	4-Me		2.5	90
4c	4-OMe		3.2	84
4d	2-Me		3	84
4e	3-Me		2.4	89
4f	2-Cl		7	No reaction

(*continued*)

Table 3. Continued.

Entry	R	Product	Time (h)	Yield (%)
4g	3-NO_2		7	No reaction

[a]Salicylaldehyde (1 mmol), 2a/2b (2 mmol), [HDSA] HSO_4^- (20 mol %), solvent (Ethanol,7 mL), reflux.
[b]Isolated yield.

substituted with electron withdrawing groups the reaction failed. This may be due to the poor solubility of substrates in the acidic medium.

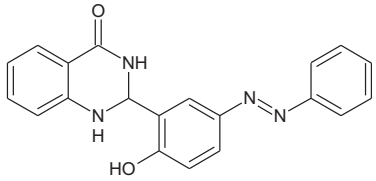
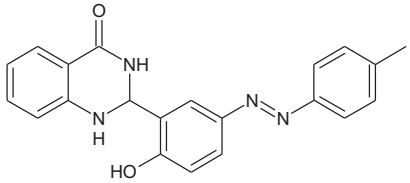
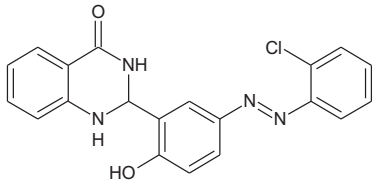
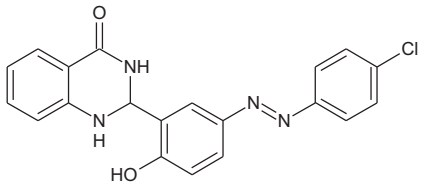
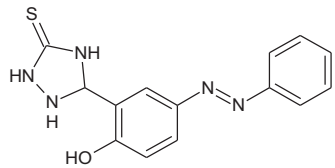
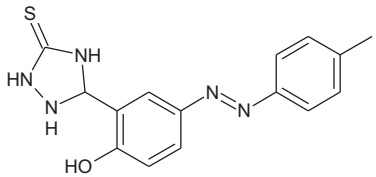
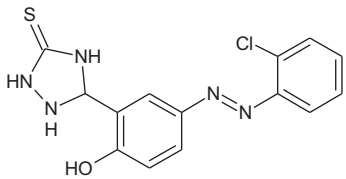
We next focused on the replacement of dimedone with barbituric acid and carried out the reaction of 5-phenyldiazo salicylaldehyde employing optimized reaction conditions. The corresponding 5-deaza-10-oxaflavin was obtained in good yield. A number of 5-aryldiazosalicylaldehydes possessing electron donating or electron withdrawing groups were allowed to react with barbituric acid. Those 5-aryldiaosalicylaldehydes possessing electron donating substituents smoothly furnished corresponding 5-deaza-10-oxaflavins (Table 3, entries 4a-4e). However, 5-aryldiazosalicylaldehydes with electron withdrawing groups failed to afford 5-deaza-10-oxaflavins (Table 3, entries 3e, 3f, 4f and 4g).

Due to their interesting pharmacological properties[56–60] and utility in agrochemicals as plant growth regulators,[61] our research group has investigated versatile strategies for the preparation of 1,2,4-triazoles. Recently, we reported novel routes for the synthesis of 1,2,4-triazolidine-3-thiones by the $[C_{16}MPy]AlCl_3Br$ catalyzed reaction of aldehydes and thiosemicarbazides,[62] multi-component assembly[63] and spirooxindole-embedded 1,2,4-triazolidine-3- thiones.[64]

This ongoing interest spurred us to investigate the use of the synthesized IL for the preparation of triazoles. We examined the reaction of 5-aryldiazo salicylaldehydes and thiosemicarbazide in ethanol employing 20 mol % of [HDSA] HSO_4^- under reflux conditions (Scheme 2, product 6). The reactions went smoothly to afford the corresponding aryldiazo substituted 1,2,4-triazolidine-3-thiones in excellent yield. Then several members of this new class of aryldiazo substituted triazolidine-3-thiones were prepared having both electron donating and electron withdrawing groups on the aryldiazo ring (Table 4, 6a-d).

The use of such drugs as Lapatinib,[65] Doxazosinmesylate,[66] and Gefitinib[67] for treatment of lung, breast and other kinds of cancers[67] points to the prominent place of quinazolines in pharmaceutical chemistry. In this context we extended our new catalyst for the synthesis of 5-aryldiazo 2,3-dihydroquinazolin-4(1H)-ones. Thus, 5-aryldiazo salicylaldehyde was treated with anthranilamide under optimized reaction conditions (Scheme 2, product 5). The corresponding 5-aryldiazo quinazolinone was formed in good yield (Table 3, entry 5a). Substituted 5-aryldiazo quinazolinones were synthesized employing 5-aryldiazo salicylaldehydes with electron donating or electron withdrawing substituents (Table 4, entry 5a-d).

Table 4. Synthesis of a new class of quinazolines and 1,2,4-triazolidine-3-thiones.

Entry	R	Product	Time (h)	Yield (%)
5a	H		1.5	92
5b	4-Me		1.3	94
5c	2-Cl		1.6	90
5d	4-Cl		1.5	89
6a	H		1.2	94
6b	4-Me		1.1	95
6c	2-Cl		1.2	92

[a]Salicylaldehyde (1 mmol), 2c/2d (1 mmol), [HDSA] HSO_4^- (20 mol %), solvent (Ethanol, 7 mL), reflux.
[b]Isolated yield.

It is well known that azo compounds possess antioxidant properties.[68] Hence, the *in vitro* antioxidant activities of all the newly prepared compounds were evaluated against 2,2'-diphenyl-1-picrylhydrazyl (DPPH) and superoxide radicals according to the literature method.[69–75] Thus the *in vitro* antioxidant activities of all derivatives were evaluated by the DPPH radical scavenging method and the results are summarized in Table 5.

The 1-oxo-hexahydroxanthenes (Table 5, entries 1-4) exhibited DPPH radical scavenging activity in the range of 36–66%. The 5-deaza-10-oxaflavins (Table 5, entries 5-9) exhibited excellent scavenging activity in the range of 74-84%. However, the new quinazolinones displayed poor DPPH scavenging activity in the range of 8-21% (Table 5,

Table 5. DPPH and superoxide radical scavenging activities of synthesized compounds[a].

Entry	Compound	Radical scavenging activity (%)	
		DPPH	Superoxide
1	3a	57.14	**57.14**
2	3b	58.09	**61.90**
3	3c	54.28	53.38
4	3d	65.71	28.57
5	4a	**80.95**	**57.14**
6	4b	**83.80**	52.38
7	4c	74.28	41.61
8	4d	**80.45**	19.04
9	4e	74.28	33.33
10	5a	68.57	33.33
11	5b	60.95	47.61
12	5c	65.71	42.85
13	5d	64.76	04.76
14	6a	14.28	14.28
15	6b	8.00	19.04
16	6c	14.28	04.76
17	Ascorbic acid	94.33	74.07

[a]1 mM of test sample used for evaluating activities.

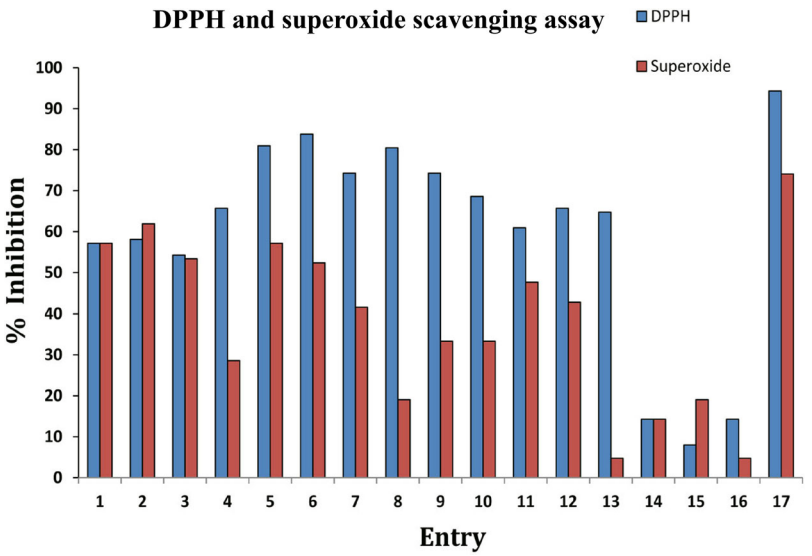


Figure 2. Comparison of antioxidant activity of **3a-6c** against standard.

entries 10-13). Moderate DPPH scavenging activity was observed for 1,2,4-triazolidine-3-thiones (Table 5, entries 14-16).

Although superoxide anion is a weak oxidant, it ultimately produces powerful and dangerous hydroxyl radicals as well as singlet oxygen, both of which contribute to oxidative stress. The superoxide anion scavenging activity of new compounds was measured and the results are summarized in Table 5. All the synthesized compounds exhibited moderate superoxide radical scavenging activities (5-62%) as compared to the standard at 1 mM concentration.

It has been noted that azo compounds exhibited excellent anti-inflammatory activity.[76] All compounds were screened for anti-inflammatory activity by the protein denaturation method. The results are summarized in Table 6. It was observed that the compounds of this report had only poor to moderate anti-inflammatory activity as compared to the standard drug (Table 6, entries 1-17).

In conclusion, we have explored the catalytic efficiency of the novel hydroxyl functionalized IL [*N*-(2-hydroxyethyl)-*N*,*N*-dimethyl-4-sulfobutan-1-aminium] hydrogen sulfate for the synthesis of new aryldiazo substituted 1-oxo-hexahydroxanthenes, 5-deaza-

Table 6. Anti-inflammatory activities of synthesized compounds[a].

Entry	Compound	Activity (%)	Entry	Compound	Activity (%)
1	3a	55.96	10	5a	**61.46**
2	3b	33.02	11	5b	21.10
3	3c	49.54	12	5c	33.02
4	3d	51.37	13	5d	**69.72**
5	4a	40.36	14	6a	54.12
6	4b	45.87	15	6b	55.04
7	4c	40.36	16	6c	**62.38**
8	4d	57.79	17	Standard	90.21
9	4e	58.71			

[a]1 mM of test sample used for evaluating activities, Standard = Diclofenac sodium.

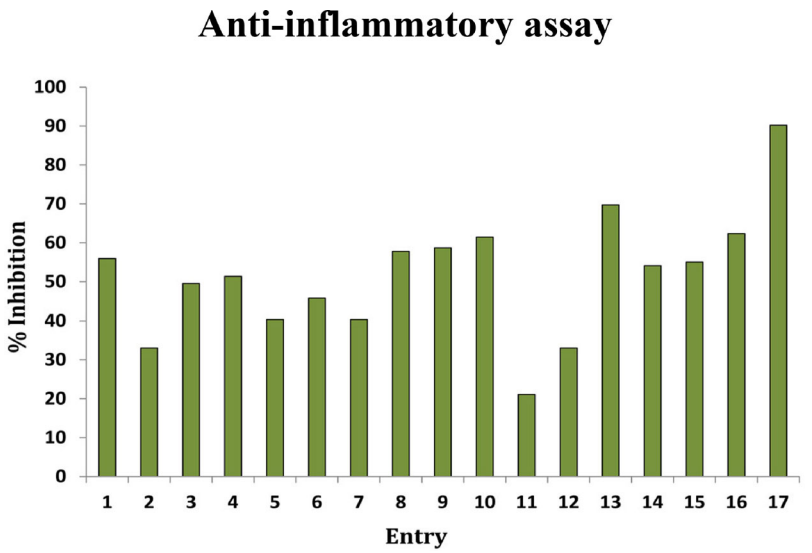


Figure 3. Comparison of anti-inflammatory activity of 3a-6c against standard.

10-oxaflavins, 2,3-dihydroquinazolin-4(1*H*)-ones and 1,2,4-triazolidine-3-thiones. We have reported on the biological activities of our products. It is our hope that the ease with which our new IL may be used will encourage greater research on the important compounds forming the nucleus of our study.

Experimental section

Salicylaldehydes (Sigma-Aldrich), dimedone (Alfa Aesar), thiosemicarbazide (Alfa Aesar), and barbituric acid (Spectrochem) were used as received. Melting points were recorded by the open capillary method and are uncorrected. IR spectra were recorded on a Bruker Alfa 100508 FTIR spectrometer; NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) or AC-400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) spectrometers. DMSO-d_6 or $CDCl_3$ was employed as solvent for scanning the NMR using TMS as internal standard. The δ values are expressed in ppm. Mass spectra were recorded on a Shimadzu LCMS 2020 and GCMS QP 2010. Elemental analysis was done on an Exeter CE440 model instrument.

Procedure for synthesis of [N-(2-hydroxyethyl)-N,N-dimethyl-4-sulfobutan-1-aminium] hydrogen sulfate

In a 50 ml round bottom flask, N,N-dimethylamino ethanol was reacted with 1,4-butane sultone in acetonitrile at 80 °C for 8 hours. An equimolar amount of conc. H_2SO_4 was then added and the resulting mixture was refluxed at 80 °C for 6 hours to afford the desired ionic [HDSA] HSO_4^-. It was then washed with ethyl acetate (20 ml X 3) to get pure product.

[N-(2-Hydroxyethyl)-N,N-dimethyl-4-sulfobutan-1-aminium]hydrogen sulfate

Viscous liquid,^{1}H NMR (300 MHz, DMSO-d_6): δ 1.63-1.78 (m, 2H) , 1.78-1.89 (m, 2H), 2.83-2.88 (t, 2H), 3.02 (s, 6H), 3.27-3.39 (m, 4H), 3.92 (d, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): 20.96, 50.03, 51.36, 51.41, 51.46, 55.36, 64.68, 65.04 ppm; MS: (m/z)= 226 (cation), 97 (anion).

Procedure for synthesis of 7-aryldiazo-9-(2-hydroxy-6-oxocyclohex-1-en-1-yl)-2,3,4,9-tetrahydro-1H- xanthen- 1-ones (3)

In a 25 mL round bottom flask, a mixture of a 5-aryldiazosalicylaldehyde (1 mmol), dimedone (2 mmol) and [HDSA] HSO_4 (20 mol %) in ethanol (95%, 7 mL) was stirred at reflux temperature until completion of reaction. The progress of reaction was monitored by TLC (silica gel 60 F_{254}, ethyl acetate 40%:n-hexane 60%). After completion of the reaction, the reaction mixture was filtered and washed with ethyl acetate to furnish the corresponding substituted-5-deaza-10-oxaflavins.

7-Phenyldiazo-9-(2-hydroxy-6-oxocyclohex-1-en-1-yl)-2,3,4,9-tetrahydro-1H-xanthen-1-one (3a)

mp 250-252 ^{0}C; IR (ATR): 3290, 2956, 2884, 1625, 1575, 1485, 1372, 1269, 1236, 1028, 822 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.00 (s, 3H), 1.02 (s, 3H) 1.06 (s, 3H), 1.17

(s 3H), 1.99 (s, 2H), 2.35-2.61 (m, 6 H), 4.76 (s, 1H), 7.16-7.28 (m, 1H, Ar-H), 7.46-7.54 (m, 3H, Ar-H), 7.64-7.65 (m, 1H, Ar-H), 7.78-7.88 (m, 3H, Ar-H) ^{13}C NMR (75 MHz, DMSO-d_6): 26.67, 27.10, 27.99, 29.24, 29.71, 31.14, 32.33, 41.44, 43.21, 49.94, 50.65, 111.04, 116.37, 118.21, 122.41, 122.71, 122.97, 125.21, 129.04, 130.75,149.61, 152.63, 152.98, 168.59, 171.10, 196.69, 200.98 ppm; MS(EI) $m/z = 471[M]^+$.

Anal. Calcd for $C_{29}H_{30}N_2O_4$: C, 74.02; H, 6.43; N, 5.95. Found: C, 73.72; H, 6.33; N, 5.94.

7-(4-Methyl-phenyldiazo)-9-(2-hydroxy-6-oxocyclohex-1-en-1-yl)-2,3,4,9-tetrahydro-1H-xanthen- 1-one (3b)

mp 272-274 ^{0}C, ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.00 (s, 3H) , 1.01 (s, 3H), 1.06 (s, 3H), 1.16 (s, 3H), 1.99 (d, 2H), 2.38 (s, 4H), 2.40 (s, 3H), 2.56-2.61 (d, 2H), 4.76 (s, 1H), 7.15-7.18 (d, 1H, Ar-H, $J = 9$Hz), 7.28-7.32 (t, 1H, Ar-H, $J = 9$Hz), 7.62 (s, 1H, Ar-H), 7.76-7.79 (d, 4H, Ar-H, $J = 12$Hz); ^{13}C NMR (75MHz, DMSO-d_6): 21.46, 26.70, 27.08, 27.98, 29.24, 29.68, 31.15, 32.31, 41.45, 43.21, 49.94, 50.66, 111.03, 116.33, 118.22, 122.30, 122.71, 125.14, 129.69, 141.30, 149.69, 150.75, 152.77, 168.60, 171.03, 196.66, 200.94 ppm; MS(EI) $m/z = 485[M]^+$.

Anal. Calcd for $C_{30}H_{32}N_2O_4$: C, 74.36; H, 6.66; N, 5.78. Found: C, 73.98; H, 6.60; N, 5.77.

7-(4-Methoxy-phenyldiazo)-9-(2-hydroxy-6-oxocyclohex-1-en-1-yl)-2,3,4,9-tetrahydro-1H-xanthen- 1-one (3c)

mp 275-277 ^{0}C; IR (ATR): 2961, 2941, 1653, 1596, 1498, 1240, 1139, 1029, 837 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.00 (s, 3H), 1.02 (s, 3H), 1.05 (s, 3H), 1.16 (s, 3H), 1.99 (s, 2H) 2.37-2.60 (m, 6H), 3.89 (s, 3H), 4.75 (s, 1H), 6.99-7.16 (m, 3H, Ar-H), 7.59-7.87 (m, 4H, Ar-H), 10.45 (s, 1H, -OH) ^{13}C NMR (75 MHz, DMSO-d_6) : 26.73, 27.07, 27.98, 29.25, 29.67, 31.16, 32.30, 41.45, 43.22, 49.95, 50.66, 111.01, 114.18, 116.30, 118.24, 122.13, 122.52,123.97, 124.57, 125.10, 129.28, 146.99, 146.73, 152.50, 161.90, 168.62, 171.02, 196.67, 200.90 ppm; MS(EI) $m/z = 500[M]^+$.

Anal. Calcd for $C_{30}H_{32}N_2O_5$: C, 71.98; H, 6.44; N, 5.60. Found: C, 71.70; H, 6.33; N, 5.58.

7-(3-Methyl-phenyldiazo)-9-(2-hydroxy-6-oxocyclohex-1-en-1-yl)-2,3,4,9-tetrahydro-1H-xanthen- 1-one (3d)

mp 255-257 ^{0}C; IR (ATR): 2942, 2863, 1643, 1604, 1585, 1484, 1372, 1313, 1256, 1237 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.00 (s, 3H), 1.01 (s, 3H), 1.06 (s, 3H), 1.17 (s, 3H), 1.61 (s, 3H Ar-CH_3), 2.37- 2.62 (m, 8H), 4.76 (s, 1H), 7.16-7.19 (d, 1H, Ar-H), 7.30-7.40 (m, 1H, Ar-H), 7.63-7.67 (t, 3H, Ar-H), 7.73-7.80 (m, 2H, Ar-H), 10.43 (s, 1H, -OH) ^{13}C NMR (75 MHz, DMSO-d_6) : 21.33, 26.71, 27.09, 28.00, 29.23, 29.66, 31.15, 32.32, 41.45, 43.23, 49.95, 50.68, 111.09, 116.35, 118.20, 120.32, 122.37, 122.82, 122.88, 125.18, 128.85, 131.54, 138.92, 149.67, 152.74, 152.93, 168.59, 171.06, 196.66, 200.94 ppm; MS(EI) $m/z = 485[M]^+$.

Anal. Calcd for $C_{30}H_{32}N_2O_4$: C, 74.36; H, 6.66; N, 5.78. Found: C, 74.10; H, 6.64; N, 5.71.

Procedure for synthesis of 5-(2,4-Dioxo-7-aryldiazo-2,3,4,5-tetrahydro-1H-chromeno[2,3-d]pyrimidin-5-yl)pyrimidine-2,4,6(1H,3H,5H)-triones (4)

In a 25 mL round bottom flask, a mixture of 5-aryldiazosalicylaldehyde (1 mmol), barbituric acid (2 mmol) and [HDSA] HSO_4^- (20 mol %) in ethanol (95%, 7 mL) was stirred at reflux temperature until completion of reaction for a period mentioned in Table 3. The progress of reaction was monitored by TLC (silica gel 60 F_{254}, ethyl acetate 50%: n-hexane 50%). After completion of the reaction, the reaction mixture was just filtered and washed with ethyl acetate to furnish corresponding substituted-5-deaza-10-oxaflavins in high yield.

5-(2,4-Dioxo-7-phenyldiazo-2,3,4,5-tetrahydro-1H-chromeno[2,3-d]pyrimidin-5-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (4a)

mp 265-267 ^{0}C; IR (ATR): 3280, 3202, 3105, 3000, 1698, 1690,1632 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.00 (s, 1H) , 4.84 (s, 1H) 6.77-6.84 (m, 2H, Ar-H) , 7.31-7.90 (m, 8H, Ar-H), 11.08 (br. s, 1H, -NH), 11.25 (br. s, 1H, -NH), 11.36 (br. s, 1H, -NH), 12.12 (br. s, 1H, -NH); ^{13}C NMR (75 MHz, DMSO-d_6) : 33.82, 54.05, 85.53, 118.18, 123.09, 123.35, 123.64, 129.97, 132.21, 149.49, 149.93, 150.98, 151.46, 152.22, 155.52, 163.95, 169.39, 169.92 ppm; MS(EI) $m/z = 318[M - 128]^+$.

Anal. Calcd for $C_{21}H_{14}N_6O_6$: C, 56.51; H, 3.16; N, 18.83. Found: C, 56.17; H, 3.11; N, 18.77.

5-(2,4-Dioxo-7-{4-methyl-phenyldiazo}-2,3,4,5-tetrahydro-1H-chromeno[2,3-d]pyrimidin-5-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (4b)

mp 280-282 ^{0}C; IR (ATR): 3220, 3200, 3108, 1695, 1690, 1632 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.42 (s, 3H) , 4.00 (d, 1H, $J = 3$Hz) , 4.84 (d, 2H, $J = 3$Hz) , 7.69-7.70 (d, 1H, Ar-H, $J = 3$Hz), 7.82-7.86 (m, 3H, Ar-H), 11.07 (br. s, 1H, -NH), 11.24 (br. s, 1H, -NH), 11.36 (br. s, 1H, -NH), 12.10 (br. s, 1H, -NH); ^{13}C NMR (75 MHz, DMSO-d_6) :21.11, 21.51, 33.83, 54.05, 85.52, 118.10, 120.61, 122.90, 123.13, 123.41, 129.94, 130.46, 137.76, 142.52, 149.55, 149.93, 150.34, 150.97, 151.25, 155.53, 163.81, 163.95, 169.38, 169.91ppm; MS(EI) $m/z = 332[M - 128]^+$.

Anal. Calcd for $C_{22}H_{16}N_6O_6$: C, 57.39; H, 3.50; N, 18.25. Found: C, 56.99; H, 3.46; N, 18.21.

5-(2,4-Dioxo-7-{4-methoxy-phenyldiazo}-2,3,4,5-tetrahydro-1H-chromeno[2,3-d]pyrimidin-5-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (4c)

mp 288-290 ^{0}C; IR (ATR): 3394, 3173, 3075, 2988, 1827, 1703, 1661, 1524, 1355, 1247 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.8 (s, 3H, OMe), 3.96 (d, 1H, J=1.6Hz), 4.91(s, 1H), 6.98-7.00 (d, 2H, Ar-H, J=8.8Hz), 7.13-7.15 (d, 1H, Ar-H, J=8.8Hz), 7.72-7.75 (q, 2H, Ar-H, J=8.8Hz), 7.81-7.83 (d, 2H, Ar-H, J=9.2Hz), 11.05 (s, 2H, -NH), 11.09 (s, 1H, -NH), 11.35 (s, 1H, -NH). ^{13}C NMR (100 MHz, DMSO-d_6) : 33.67, 53.56, 55.76, 85.41, 114.49, 117.61, 122.56, 123.23, 124.94, 146.48, 149.77, 150.06, 150.72, 150.90, 151.59, 152.39, 164.05, 168.82, 169.34 ppm; MS(EI) $m/z = 348[M - 128]^+$.

Anal. Calcd for $C_{22}H_{16}N_6O_7$: C, 55.47; H, 3.39; N, 17.64. Found: C, 55.16; H, 3.34; N, 17.62.

5-(2,4-Dioxo-7-{2-methyl-phenyldiazo}-2,3,4,5-tetrahydro-1H-chromeno[2,3-d]pyrimidin-5-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (4d)

mp 275-277 ^{0}C; IR (ATR): 3430, 3198, 3062, 3024, 2851, 2803, 1716, 1691, 1624, 1528, 1484, 1421, 1364, 1298, 1238 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.66 (s, 3H), 4.01 (d, 1H, *J*=2.1Hz), 4.84-4.85 (d, 1H, *J*= 1.8Hz), 7.30-7.33 (d, 2H, Ar-H, *J*=8.7Hz), 7.44 (s, 2H, Ar-H), 7.53-7.56 (d, 1H, Ar-H, *J*=7.8Hz), 7.7 (s, 1H, Ar-H) , 7.85-7.88 (d, 1H, Ar-H, *J*=8.7Hz), 11.08 (s, 1H, -NH), 11.19 (s, 1H, -NH), 11.25 (s, 1H, -NH), 11.37 (s, 1H, -NH). ^{13}C NMR (75 MHz, DMSO-d_6) : δ 17.58, 33.71, 53.88, 85.59, 115.53, 118.20, 123.36, 123.59, 127.12, 131.97, 138.36, 149.95, 150.22, 150.96, 151.33, 155.53, 163.94, 169.34, 169.90 ppm; MS(EI) $m/z = 332[M - 128]^+$.

Anal. Calcd for $C_{22}H_{16}N_6O_6$: C, 57.39; H, 3.50; N, 18.25. Found: C, 56.99; H, 3.45; N, 18.23.

5-(2,4-Dioxo-7-{3-methyl-phenyldiazo}-2,3,4,5-tetrahydro-1H-chromeno[2,3-d]pyrimidin-5-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (4e)

mp 287-289 ^{0}C; IR (ATR): 3411, 3186, 3060, 3017, 2862, 2804, 1745, 1717, 1658, 1371 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.43 (s, 3H Me), 3.99 (s, 1H), 4.88 (s, 1H,) , 7.24-7.26 (d, 1H ArH, *J*=8.4Hz), 7.32-7.34 (d, 1H, Ar-H, *J*= 7.6Hz), 7.41-7.45 (t, 1H, Ar-H, *J*=7.2Hz), 7.66-7.68 (d, 1H, Ar-H, *J*=7.6Hz), 7.74 (s, 1H, Ar-H), 7.81-7.84 (q, 1H, Ar-H, *J*=8.6Hz), 8.16 (s, 1H, Ar-H), 11.08 (s, 1H, -NH), 11.20 (s, 1H, -NH), 11.36 (s, 1H, -NH), 12.02 (bs, 1H, -NH). ^{13}C NMR (100 MHz, DMSO-d_6) : δ 21.39, 33.74, 85.46, 117.36, 120.62, 123.15, 123.55, 129.39, 132.17, 132.49, 149.58, 149.98, 150.87, 151.39, 152.29, 155.54, 163.97, 169.66 ppm; MS(EI) $m/z = 332[M - 128]^+$.

Anal. Calcd for $C_{22}H_{16}N_6O_6$: C, 57.39; H, 3.50; N, 18.25. Found: C, 57.10; H, 3.41; N, 18.21.

Procedure for synthesis of 2-{2-Hydroxy-5-[(E)-aryldiazenyl]phenyl}-2,3-dihydroquinazolin-4(1H)-ones (5)

To a mixture of 5-aryldiazo salicylaldehyde (1 mmol), and anthranilamide (1 mmol) in ethanol (95%, 7 mL), [HDSA] HSO_4^- (20 mol %) was added. The reaction mixture was stirred at reflux temperature for the time mentioned in Table 4, until completion of reaction. Progress of reaction was monitored by TLC. (silica gel 60 F_{254}, ethyl acetate 30%: n-hexane 70%) After completion of reaction, the precipitated product was just filtered to obtain the desired product.

2-{2-Hydroxy-5-[(E)-phenyldiazenyl]phenyl}-2,3-dihydroquinazolin-4(1H)-one (5a)

mp 295-297 ^{0}C; IR (ATR): 3257, 3100, 3052, 1651,1598, 1445, 1386, 1281, 1253, 1148, 1097, 929, 826, 754, 683 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.08 (s, 1H) , 6.81 (m, 1H, Ar-H) , 6.91 (m, 1H, Ar-H) , 7.07 (m, 1H, Ar-H) , 7.25 (m, 1H, Ar-H), 7.54 (m, 1H, Ar-H) , 7.65 (m, 5H, Ar-H) , 7.79-7.82 (m, 3H, Ar-H) , 8.01 (s, 1H, -NH), 8.14 (s,

1H,-NH), 10.88 (s, 1H,-OH); ^{13}C NMR (75 MHz, DMSO-d_6) : 61.58, 115.05, 115.22, 116.52, 117.71, 122.60, 122.70, 125.35, 127.84, 128.53, 129.84, 131.11, 133.78, 145.25, 148.46, 152.46, 158.69, 164.36 ppm; MS(ESI) $m/z = 344$[M + 1].

Anal. Calcd for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.37; H, 4.60; N, 16.25.

2-{2-Hydroxy-5-[(E)-(4-methylphenyl)diazenyl]phenyl}-2,3-dihydroquinazolin-4(1H)-one (5b)

mp 314-317 ^{0}C; IR (KBr): 3243, 1649, 1596, 1507, 1459, 1431, 1381, 1279, 1252, 1155, 1099, 827, 748, 701 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.22 (s, 3H) , 6.11 (s, 2H), 6.68-6.74 (m, 2H, Ar-H) , 6.95-6.97 (m, 1H, Ar-H), 7.16-7.22 (m, 3H, Ar-H), 7.28 (s, 1H, -NH), 7.58 (s, 1H), 7.63-7.98 (m, 3H), 7.99 (s, 1H, -NH), 10.20 (s, 1H, -OH); ^{13}C NMR (75MHz, DMSO-d_6): 21.40, 62.84, 114.92, 115.11, 116.24, 118.20, 122.42, 122.62, 124.36, 127.50, 127.94, 129.70, 133.66, 140.73, 145.69, 147.88, 150.56, 157.82, 164.85; MS(ESI) $m/z = 358$[M + 1].

Anal. Calcd for $C_{21}H_{18}N_4O_2$: C, 70.38; H, 5.06; N, 15.63. Found: C, 69.98; H, 4.98; N, 15.61.

2-{5-[(E)-(2-Chlorophenyl)diazenyl]-2-hydroxyphenyl}-2,3-dihydroquinazolin-4(1H)-one (5c)

mp > 330 ^{0}C; IR (KBr): 3385, 3348, 1658, 1596, 1465, 1283, 1253, 1147, 1095, 823, 748, 589 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.07 (s, 1H) , 6.69 (m, 1H), 6.79.-6.82 (m, 1H, Ar-H) , 6.93-7.07 (m, 1H, Ar-H), 7.25 (m, 1H, Ar-H), 7.44-7.50 (m, 1H, Ar-H), 7.60-7.65(m, 2H, Ar-H), 7.68-7.81(m, 1H, Ar-H), 7.82-8.01 (m, 1H, Ar-H), 8.02 (s, 1H, -NH), 8.12 (s, 1H, -NH), 11.00 (s, 1H, -OH); ^{13}C NMR (75MHz, DMSO-d_6): 61.49, 115.05, 115.26, 116.63, 117.70, 117.90, 122.99, 125.93, 127.83, 128.48, 128.93, 131.07, 132.21, 133.72, 133.79, 145.63, 148.36, 148.41, 159.27, 164.27 ppm; MS(ESI) $m/z = 377$ [M - 1].

Anal. Calcd for $C_{20}H_{15}ClN_4O_2$: C, 63.41; H, 3.99; N, 14.79. Found: C, 63.04; H, 3.92; N, 14.77.

2-{5-[(E)-(4-Chlorophenyl)diazenyl]-2-hydroxyphenyl}-2,3-dihydroquinazolin-4(1H)-one (5d)

mp 330 ^{0}C; IR (ATR): 3300, 3175, 3058, 2878, 1678, 1608, 1482, 1375, 1257 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.09 (s, 1H), 6.43 (s, 1H), 6.62- 6.67 (t, 1H, J= 3.2Hz) , 6.74-6.76 (d, 1H, Ar-H, J= 8Hz), 6.96-7.00 (t, 1H, Ar-H, J= 8Hz), 7.15-7.19 (t, 1H, Ar-H, J= 8Hz), 7.41-7.43 (t, 2H, Ar-H, J= 8Hz), 7.66-7.75 (m, 4H, Ar-H), 7.84 (s, 1H), 8.00 (s, 1H), 10.51 (s, 1H, -OH). ^{13}C NMR (100 MHz, DMSO-d_6) : δ 62.31, 114.91, 115.06, 116.29, 117.91, 122.99, 123.85, 124.74, 127.84, 129.30, 133.61, 135.73, 145.36, 148.06, 150.92, 158.55, 167.74 ppm; MS(ESI) $m/z = 377$ [M - 1].

Anal. Calcd for $C_{20}H_{15}ClN_4O_2$: C, 63.41; H, 3.99; N, 14.79. Found: C, 63.06; H, 3.95; N, 14.77.

Procedure for synthesis of 5-{2-Hydroxy-5-[(E)-aryldiazenyl]phenyl}-1,2,4-triazolidine-3-thiones (6)

In a 25 mL round-bottom flask, to a mixture of 5-aryldiazo salicylaldehyde (s) (1 mmol), and thiosemicarbazide (1 mmol) in ethanol (7 mL), [HDSA] HSO_4^- (20 mol %) was added. The reaction mixture was stirred at reflux temperature for the time specified in Table 4. The progress of reaction was monitored by TLC (silica gel 60 F_{254}, ethyl acetate 40%:n-hexane 60%). After completion of the reaction, the reaction mixture was filtered to furnish the corresponding product.

5-{2-Hydroxy-5-[(E)-phenyldiazenyl]phenyl}-1,2,4-triazolidine-3-thione (6a)

mp 244-247 ^{0}C; IR (ATR): 3425, 3300, 3237, 3149, 1600, 1506, 1361,1270, 1107, 824, 773, 683 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.04-7.07 (d, 1H, Ar-H, $J = 9$Hz) , 7.51-7.60 (m, 3H, Ar-H) , 7.77-8.45 (m, 3H, Ar-H) 8.10 (s, 1H) , 8.56 (s, 1H, -NH), 8.57 (s, 1H, -NH), 10.84 (s, 1H,-NH), 11.49 (s, 1H,-OH); ^{13}C NMR (75 MHz, DMSO-d_6) : 117.33, 121.55, 122.66, 123.55, 124.53, 129.81, 131.20, 139.03, 145.87, 152.53, 159.84, 178.34 ppm; MS(ESI) $m/z = 298$ [M - 1].

Anal. Calcd for $C_{14}H_{13}N_5OS$: C, 56.17; H, 4.38; N, 23.40. Found: C, 55.95; H, 4.30; N, 23.37.

5-{2-Hydroxy-5-[(E)-4-methylphenyldiazenyl]phenyl}-1,2,4-triazolidine-3-thione (6b)

mp 249-251 ^{0}C; IR (ATR): 3412, 3255, 3170, 1606, 1520, 1479, 1355, 1279, 1116, 1056, 946, 829, 664 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.37 (s, 3H), 6.98-7.00 (d, 1H, Ar-H, $J = 6$Hz), 7.30-7.37 (m, 2H, Ar-H), 7.48-7.51 (m, 2H, Ar-H), 7.58-7.61 (m, 2H, Ar-H), 7.76-7.81 (m, 2H, Ar-H), 8.26 (s, 1H, -NH), 8.39 (s, 1H, -NH), 10.39 (s, 1H, -NH) 11.41 (s, 1H, -OH); ^{13}C NMR (75 MHz, DMSO-d_6): 21.43, 117.29, 121.50, 122.68, 123.45, 124.31, 130.31, 139.13, 141.29, 145.86, 150.60, 159.60, 178.34 ppm; MS(ESI) $m/z = 313$[M - 1].

Anal. Calcd for $C_{15}H_{15}N_5OS$: C, 57.49; H, 4.82; N, 22.35. Found: C, 57.14; H, 4.75; N, 22.33.

5-{2-Hydroxy-5-[(E)-2-chlorophenyldiazenyl]phenyl}-1,2,4-triazolidine-3-thione (6c)

mp 273-275 ^{0}C; IR (ATR): 3428, 3246, 3151, 2875, 1604, 1511, 1356, 1269, 1105 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.00-7.03 (q, 1H, Ar-H, J=8.8Hz), 7.34-7.42 (m, 2H), 7.53-7.63 (m, 2H, Ar-H), 7.76-7.78 (d, 2H, Ar-H, J=8.8Hz), 8.00-8.03 (d, 1H, Ar-H J=10Hz), 8.41 (s, 1H), 8.42 (s, 1H) , 10.56 (s, 1H, -NH), 11.46 (s, 1H, -NH) . ^{13}C NMR (100 MHz, DMSO-d_6) : δ 117.36, 117.74, 120.85, 123.46, 126.29, 127.45, 130.75, 131.61, 134.17, 140.09, 146.11, 148.52, 160.30, 178.33 ppm; MS(ESI) $m/z = 332$ [M - 1].

Anal. Calcd for $C_{14}H_{12}ClN_5OS$: C, 50.38; H, 3.62; N, 20.98. Found: C, 49.98; H, 3.57; N, 20.95.

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